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(71) Applicant: CAMBRIDGE ENTERPRISE LIMITED [GB/GB]; The Old Schools, Trinity Lane, Cambridge, Cambridgeshire, CB2 1TN (GB).

(72) Inventors: HYVONEN, Marko Juhana; Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge, Cambridgeshire, CB2 1GA (GB). **BREAK, Paul**; Department of Biochemistry, University of Cambridge, 80 Tennis Court Road, Cambridge, Cambridgeshire, CB2 1GA (GB). **SPRING, David Robert**; Yusuf Hamied Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, Cambridgeshire, CB2 1EW (GB). **GLOSSOP, Paul**; Sandexis Medicinal Chemistry, Innovation House, Discovery Park, Sandwich, Kent, CT13 9FF (GB).

(74) Agent: **HGF Limited**; Doument Handling - HGF (Manchester), 1 City Walk, Leeds, Yorkshire, LS11 9DX+ (GB).

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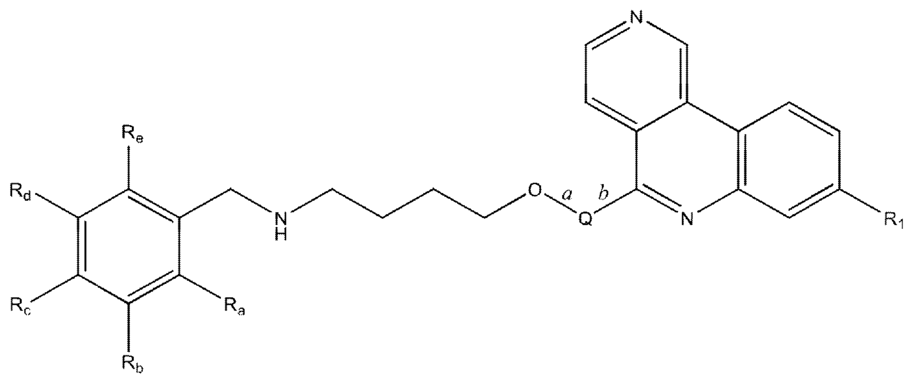

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(57) Abstract: Provided are compounds of the Formula I, and salts, hydrates and solvates thereof: wherein R1, Q, Ra, Rb, Rc, Rd and Re are each as defined in the specification. The compounds are inhibitors of Casein Kinase 2 alpha (CK2α) and are useful for the treatment and/or prevention of diseases and conditions in which CK2α activity is implicated, such as, for example, but not limited to, the treatment and/or prevention of proliferative disorders (e.g. cancer), viral infections, inflammation, diabetes, vascular and ischemic disorders, neurodegeneration and the regulation of circadian rhythm. The present invention also relates to pharmaceutical compositions comprising the compounds defined herein, to processes for synthesising these compounds and to their use for the treatment of diseases and/or conditions in which CK2α activity is implicated.

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BENZO[C][2,6]NAPHTHYRIDINE DERIVATIVES, COMPOSITIONS AND THERAPEUTIC USES THEREOF

INTRODUCTION

[001] The present invention relates to novel therapeutic compounds. More specifically, the present invention relates to novel therapeutic compounds that inhibit Casein Kinase 2 alpha subunit (CK2α (CSNK2A1) and/or CK2α' (CSNK2A2)) and as part of the CK2 holoenzyme. The novel therapeutic compounds are therefore useful for the treatment and/or prevention of diseases and conditions in which CK2α activity is implicated, such as, for example but not limited to, the treatment and/or prevention of proliferative disorders (e.g. cancer), viral infections, inflammation, diabetes, vascular and ischemic disorders, neurodegeneration and the regulation of circadian rhythm.

[002] The present invention also relates to pharmaceutical compositions comprising the novel therapeutic compounds defined herein, to processes for synthesising these compounds and to their use for the treatment of diseases and/or conditions in which CK2α activity is implicated.

BACKGROUND OF THE INVENTION

[003] CK2α is a serine/threonine kinase that is a key regulator of many cellular processes and is involved in cellular proliferation and anti-apoptotic mechanisms (Battistutta & Lolli, Mol. Cell. Biochem. 2011). It mainly exists as a holoenzyme composed of two catalytic (α and/or α') and a dimer of regulatory (β) subunits, but it can also be found as the isolated subunits (Niefind *et al*, EMBO *J* 2001). Unlike most other kinases, it is constitutively active and more than 300 proteins have been identified as putative CK2α substrates, making it one of the most pleiotropic proteins in eukaryotic systems (Meggio & Pinna, FASEB 2003).

[004] CK2α is a pro-survival kinase that operates across multiple signaling pathways to convey a proliferative and anti-apoptotic phenotype to cells. Consequently, cancer cells are often described as being addicted to CK2α activity and a high-profile genome-wide CRISPR-Cas9 screen highlighted CK2α as a top tier, high priority drug target for Colorectal Cancer (CRC) (Behan *et al*, Nature 2019). The target is well validated by human data that correlates poor patient survival in numerous tumor types, including CRC, with increased CK2α expression (Lin *et* al, PLoS ONE 2011). Additionally, data from clinical samples shows CK2α expression is upregulated in numerous tumor types (Ortega *et al*, PLoS ONE 2014; Di Maira *et al*, 2019).

[005] The human genetics of CRC are well characterized and approximately 80% tumors are identified as being wnt pathway mutation driven (e.g. APC, β-catenin) (Zhan *et al*, Oncogene 2017). The wnt pathway is known to be sensitive to and amplified by CK2α activity and can be inhibited by loss of CK2α function (Gao & Wang, JBC 2006). For example, in animal models, CK2α inhibition prevents tumor growth that is driven by different mutations in the wnt pathway (Dowling *et al*, ACS 2016).

[006] CK2α also contributes to the malignant phenotype in cholangiocarinoma (CCA), which is known to be a wnt-dysregulated tumor type (Zhan *et al*, Oncogene 2017). CK2α is over-expressed in human CCA samples and CCA tumor cell lines (Di Maira *et al*, Oncogenesis 2019); and disruption of CK2α activity in CCA cell models is reported to inhibit tumorigenic properties. (Zakharia *et al*, Translational Oncology 2019).

[007] It is hypothesised that a CK2α inhibitor given either as a monotherapy, in combination with standard of care chemotherapy or in combination with other targeted therapies in development, such as, but not limited to, KRAS inhibitors, will inhibit CRC tumor growth by reversing aberrant mutation-driven upregulation of wnt signaling to the restore normal balance of apoptosis and proliferation.

[008] Existing CK2α inhibitors target the highly conserved ATP binding site. This design strategy often leads to a poor selectivity profile for such inhibitors over other kinases. There is therefore a need for potent and more selective CK2α inhibitors that bind to the catalytic ATP site of CK2α (to drive potent enzyme inhibition) but also interact with other areas of CK2α, such as the αD site (to drive high levels of selectivity over other kinases).

[009] The present invention was devised with the foregoing in mind.

SUMMARY OF THE INVENTION

[0010] In one aspect, the present invention provides a compound of Formula I as defined herein, and/or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0011] In another aspect, the present invention provides a pharmaceutical composition which comprises a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and one or more pharmaceutically acceptable excipients.

[0012] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in therapy.

[0013] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a disease or condition in which CK2α activity is implicated.

[0014] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a disease or condition associated with aberrant activity of CK2α.

[0015] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of proliferative disorders (e.g. cancer or benign neoplasms), viral infections, an inflammatory disease or condition, diabetes, vascular and ischemic disorders, neurodegenerative disorders and/or the regulation of circadian rhythm.

[0016] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a cancer.

[0017] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a viral infection.

[0018] In another aspect, the present invention provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of a disease or condition in which CK2α activity is implicated.

[0019] In another aspect, the present invention provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of a disease or condition associated with aberrant activity of CK2α.

[0020] In another aspect, the present invention provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of proliferative disorders (e.g. cancer or benign neoplasms), viral infections, an inflammatory disease or condition, diabetes, vascular and ischemic disorders, neurodegenerative disorders and/or the regulation of circadian rhythm.

[0021] In another aspect, the present invention the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of a cancer.

[0022] In another aspect, the present invention provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of a viral infection.

[0023] In another aspect, the present invention provides a method of treating a disease or condition in which CK2α activity is implicated, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0024] In another aspect, the present invention provides a method of treating a disease or condition associated with aberrant activity of CK2α, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0025] In another aspect, the present invention provides a method of treating a proliferative disorder (e.g. cancer or benign neoplasms), a viral infection, an inflammatory disease or condition, diabetes, vascular and ischemic disorders, neurodegenerative disorders and/or regulating cardiac rhythm, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0026] In another aspect, the present invention provides a method of treating cancer, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0027] In another aspect, the present invention provides a method of treating a viral infection, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0028] In another aspect, the present invention provides a combination treatment comprising a compound of Formula I, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein, with one or more additional therapeutic agents.

[0029] In another aspect, the present invention provides processes for preparing compounds of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein, with one or more additional therapeutic agents.

[0030] Preferred, suitable, and optional features of any one particular aspect of the present invention are also preferred, suitable, and optional features of any other aspect.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0031] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0032] It is to be appreciated that references to "treating" or "treatment" include prophylaxis as well as the alleviation of established symptoms of a condition. "Treating" or "treatment" of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

[0033] A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0034] References to "Casein Kinase 2 alpha" or "CK2α" herein include CK2α (CSNK2A1) and/or CK2α' (CSNK2A2). Where reference is made to the compounds of the present invention defined herein inhibiting CK2α or being CK2α inhibitors, we mean that the compounds function as inhibitors of CK2α (CSNK2A1) and/or CK2α' (CSNK2A2) and the CK2 holoenzyme. In a particular embodiment, the compounds of the invention inhibit CK2α (CSNK2A1). In another embodiment, the compounds of the invention inhibit CK2α' (CSNK2A2).

[0035] The compounds and intermediates described herein may be named according to either the IUPAC (International Union for Pure and Applied Chemistry) or CAS (Chemical Abstracts Service) nomenclature systems. It should be understood that unless expressly stated to the contrary, the terms “compounds of Formula I”, “compounds of the invention” and the more general term “compounds” refer to and include any and all compounds described by and/or with reference to Formula I herein. It should also be understood that these terms encompasses all stereoisomers, i.e. cis and trans isomers, as well as optical isomers, i.e. R and S enantiomers, of such compounds, in substantially pure form and/or any mixtures of the foregoing in any ratio. This understanding extends to pharmaceutical compositions and methods of treatment that employ or comprise one or more compounds of the Formula I, either by themselves or in combination with additional agents.

[0036] Unless specified otherwise, atoms are referred to herein by their chemical symbol as appearing in the IUPAC periodic table of the Elements. For example, “C” refers to a carbon atom.

[0037] The term "(m-nC)" or "(m-nC) group" used alone or as a prefix, refers to any group having m to n carbon atoms.

[0038] In this specification the term “alkyl” includes both straight and branched chain alkyl groups. References to individual alkyl groups such as “propyl” are specific for the straight chain version only and references to individual branched chain alkyl groups such as “isopropyl” are specific for the branched chain version only. For Example, “(1-6C)alkyl” includes (1-4C)alkyl, (1-3C)alkyl, propyl, isopropyl and *t*-butyl. A similar convention applies to other radicals, for example “phenyl(1-6C)alkyl” includes phenyl(1-4C)alkyl, benzyl, 1-phenylethyl and 2-phenylethyl.

[0039] An “alkylene” group is an alkyl group that is positioned between and serves to connect two other chemical groups. Thus, “(1-6C)alkylene” means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, for example, methylene, ethylene, propylene, 2-methylpropylene, pentylene, and the like.

[0040] “(3-6C)cycloalkyl” means a hydrocarbon ring containing from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl.

[0041] The term “halo” or “halogeno” refers to fluoro, chloro, bromo and iodo.

[0042] As used herein by themselves or in conjunction with another term or terms, “haloalkyl” and “haloalkyl group” refer to alkyl groups in which one or more hydrogen atoms are replaced by halogen atoms. Representative examples include, but are not limited to, $–CF_3$, $–CHF_2$, $–CH_2F$, $–CF_2CF_3$, $–CHFCF_3$, and $–CH_2CF_3$. Suitably, a haloalkyl group is selected from $–CHF_2$ and $–CF_3$, suitably $–CF_3$.

[0043] As used herein by themselves or in conjunction with another term or terms, "haloalkoxy" and "haloalkoxy group" refer to alkoxy groups (i.e. O-alkyl groups) in which one or more hydrogen atoms are replaced by halogen atoms. Representative examples include, but are not limited to, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, and $-OCF_2CF_3$. Suitably, a haloalkyoxy group is selected from $-OCHF_2$ and $-OCF_3$, suitably $-OCF_3$.

[0044] The term "heterocyclyl", "heterocyclic" or "heterocycle" means a non-aromatic saturated or partially saturated monocyclic, fused, bridged, or spiro bicyclic heterocyclic ring system(s). Monocyclic heterocyclic rings contain from about 3 to 12 (suitably from 3 to 7) ring atoms, with from 1 to 5 (suitably 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur in the ring. Bicyclic heterocycles contain from 7 to 17 member atoms, suitably 7 to 12 member atoms, in the ring. Bicyclic heterocyclic(s) rings may be fused, spiro, or bridged ring systems. Examples of heterocyclic groups include cyclic ethers such as, but not limited to, oxiranyl, oxetanyl, tetrahydrofuranyl, dioxanyl, and substituted cyclic ethers. Heterocycles containing nitrogen include, for example, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrotriazinyl, tetrahydropyrazolyl, and the like. Typical sulfur containing heterocycles include tetrahydrothienyl, dihydro-1,3-dithiol, tetrahydro-2*H*-thiopyran, and hexahydrothiepine. Other heterocycles include dihydrooxathiolyl, tetrahydrooxazolyl, tetrahydro-oxadiazolyl, tetrahydrodioxazolyl, tetrahydrooxathiazolyl, hexahydrotriazinyl, tetrahydrooxazinyl, morpholinyl, thiomorpholinyl, tetrahydropyrimidinyl, dioxolinyl, octahydrobenzofuranyl, octahydrobenzimidazolyl, and octahydrobenzothiazolyl. For heterocycles containing sulfur, the oxidized sulfur heterocycles containing SO or SO_2 groups are also included. Examples include the sulfoxide and sulfone forms of tetrahydrothienyl and thiomorpholinyl such as, but not limited to, tetrahydrothiene 1,1-dioxide and thiomorpholinyl 1,1-dioxide. A suitable value for a heterocyclyl group which bears 1 or 2 oxo (=O) or thioxo (=S) substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl. Particular heterocyclyl groups are saturated monocyclic 3 to 7 membered heterocyclyls containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulfur, for example azetidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, thiomorpholinyl, thiomorpholinyl 1,1-dioxide, piperidinyl, homopiperidinyl, piperazinyl or homopiperazinyl. As the skilled person would appreciate, any heterocycle may be linked to another group via any suitable atom, such as via a carbon or nitrogen atom. However, reference herein to piperidino or morpholino refers to a piperidin-1-yl or morpholin-4-yl ring that is linked via the ring nitrogen.

[0045] By "bridged ring systems" is meant ring systems in which two rings share more than two atoms, see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley

Interscience, pages 131-133, 1992. Examples of bridged heterocyclyl ring systems include, aza-bicyclo[2.2.1]heptane, 2-oxa-5-azabicyclo[2.2.1]heptane, aza-bicyclo[2.2.2]octane, aza-bicyclo[3.2.1]octane and quinuclidine.

[0046] By "spiro bicyclic ring systems" we mean that the two ring systems share one common spiro carbon atom, i.e. the heterocyclic ring is linked to a further carbocyclic or heterocyclic ring through a single common spiro carbon atom. Examples of spiro ring systems include 6-azaspiro[3.4]octane, 2-oxa-6-azaspiro[3.4]octane, 2-azaspiro[3.3]heptanes, 2-oxa-6-azaspiro[3.3]heptanes, 7-oxa-2-azaspiro[3.5]nonane, 6-oxa-2-azaspiro[3.4]octane, 2-oxa-7-azaspiro[3.5]nonane and 2-oxa-6-azaspiro[3.5]nonane.

[0047] The term "heteroaryl" or "heteroaromatic" means an aromatic mono-, bi-, or polycyclic ring incorporating one or more (for example 14, particularly 1, 2 or 3) heteroatoms selected from nitrogen, oxygen or sulfur. The term heteroaryl includes both monovalent species and divalent species. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring, for example a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulfur and oxygen. Typically, the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general, the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

[0048] Examples of heteroaryl include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, isoindolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzothiazolyl, indazolyl, purinyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl, pteridinyl, naphthyridinyl, carbazolyl, phenazinyl, benzisoquinolinyl, pyridopyrazinyl, thieno[2,3b]-furanyl-, 2H-furo[3,2b]-pyranyl-, 5H-pyrido[2,3-d]-ooxazinyl-, 1H-pyrazolo[4,3-d]-oxazolyl, 4H-imidazo[4,5d]thiazolyl, pyrazino[2,3d]pyridazinyl, -imidazo[2,1b]thiazolyl, -imidazo[1,2b][1,2,4]-triazinyl. "Heteroaryl" also covers partially aromatic bi- or polycyclic ring systems wherein at least one ring is an aromatic ring and one or more of the other ring(s) is a nonaromatic, saturated or partially saturated ring, provided at least one ring contains one or more heteroatoms selected from nitrogen, oxygen or -sulfur-. Examples of partially aromatic heteroaryl groups include for example, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 2-oxo-1,2,3,4-tetrahydroquinolinyl, dihydrobenzthienyl, dihydrobenzfuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzo[1,3]dioxolyl, 2,2-dioxo-1,3-dihydro-2-benzothienyl, 4,5,6,7-tetrahydrobenzofuranyl, indolinyl, 1,2,3,4-tetrahydro-1,8-naphthyridinyl, 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazinyl, 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl and 6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazinyl.

[0049] Examples of five membered heteroaryl groups include but are not limited to pyrrolyl, furanyl, thienyl, imidazolyl, furazanyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl and tetrazolyl groups.

[0050] Examples of six membered heteroaryl groups include but are not limited to pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl and triazinyl.

[0051] A bicyclic heteroaryl group may be, for example, a group selected from:

a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a pyridine ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a pyrimidine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a pyrrole ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a pyrazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a pyrazine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an imidazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an oxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an isoxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a thiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

an isothiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

a thiophene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a furan ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

a cyclohexyl ring fused to a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 ring heteroatoms; and

a cyclopentyl ring fused to a 5- or 6-membered heteroaromatic ring containing 1, 2 or 3 ring heteroatoms.

[0052] Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuranyl, benzthiophenyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, benzisothiazolyl, isobenzofuranyl, indolyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl, purinyl (e.g., adeninyl, guaninyl), indazolyl, benzodioxolyl and pyrazolopyridinyl groups.

[0053] Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinolinyl, isoquinolinyl, chromanyl, thiochromanyl, chromenyl, isochromenyl, chromanyl, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl groups.

[0054] The term “aryl” means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. In particular embodiment, an aryl is phenyl.

[0055] This specification also makes use of several composite terms to describe groups comprising more than one functionality. Such terms will be understood by a person skilled in the art. For Example heterocyclyl(m-nC)alkyl comprises (m-nC)alkyl substituted by heterocyclyl.

[0056] The term “aryl(1-2C)alkyl” means an aryl group covalently attached to a (1-2C)alkylene group, both of which are defined herein. Examples of aryl-(1-2C)alkyl groups include benzyl, phenylethyl, and the like.

[0057] “Heteroaryl(1-3C)alkyl” means a heteroaryl group covalently attached to a (1-3C)alkylene group, both of which are defined herein. Examples of heteroaryl-alkyl groups include pyridin-3-ylmethyl, 2-(benzofuran-2-yl)ethyl, and the like.

[0058] “Heterocyclyl(1-2C)alkyl” means a heterocyclyl group covalently attached to a (1-2C)alkylene group, both of which are defined herein.

[0059] “(3-6C)cycloalkyl-(1-2C)alkyl” means a (3-6C)cycloalkyl group covalently attached to a (1-2C)alkylene group, both of which are defined herein.

[0060] The term "optionally substituted" refers to either groups, structures, or molecules that are substituted and those that are not substituted. The term “wherein a/any CH, CH_2, CH_3 group or heteroatom (i.e. NH) within a R^1 group is optionally substituted” suitably means that (any) one of the hydrogen radicals of the R^1 group is substituted by a relevant stipulated group.

[0061] Where optional substituents are chosen from “one or more” groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

[0062] A wavy bond () is used herein to show a point of attachment.

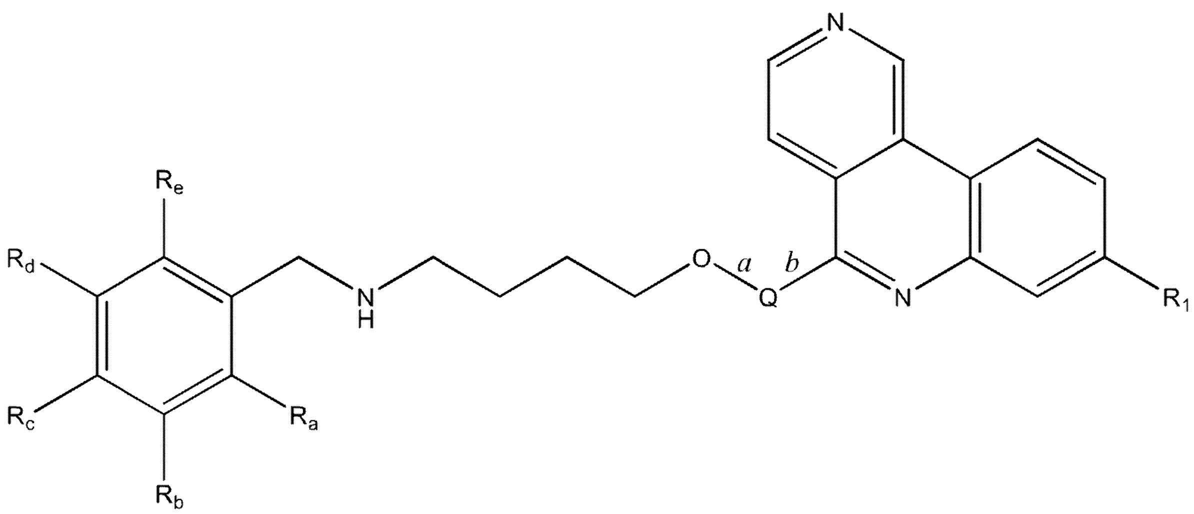
[0063] The phrase "compound of the invention" means those compounds which are disclosed herein, both generically and specifically.

[0064] As used herein by itself or in conjunction with another term or terms, "pharmaceutically acceptable" refers to materials that are generally chemically and/or physically compatible with other ingredients (such as, for example, with reference to a formulation), and/or are generally physiologically compatible with the recipient (such as, for example, a subject) thereof.

[0065] As used herein by themselves or in conjunction with another term or terms, "subject(s)" and "patient(s)", suitably refer to mammals, in particular humans.

Compounds of the invention

[0066] In a first aspect, the present invention relates to a compound, or pharmaceutically acceptable salt, hydrate or solvate thereof, having the structural formula I shown below:

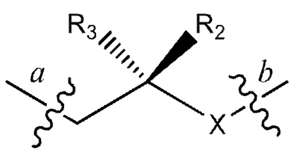


I

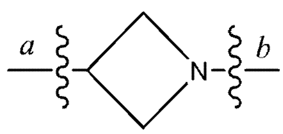
wherein:

R_1 is selected from -C(O)OH or -C(O)NH_2;

Q is selected from formula Ia or Ib:



Ia



Ib

wherein:

bond *a* in formulae Ia and Ib corresponds with bond *a* in formula I and bond *b* in formulae Ia and Ib corresponds with bond *b* in formula I;

R_2 and R_3 are each independently selected from hydrogen or methyl; and

X is NH or O;

R_a and R_e are both independently selected from hydrogen, methyl or halo;

R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

$-[CH_2]_{0-3}$-(1-4C)alkoxy,

$-[CH_2]_{0-3}-C(O)NH_2$,

$-[CH_2]_{0-3}$-C(O)NH(1-4C)alkyl,

$-[CH_2]_{0-3}$-C(O)N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-3}$-NH(1-4C)alkyl,

$-[CH_2]_{0-3}$-N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-3}-S(O)_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

$-[CH_2]_{0-3}$-C(O)(1-4C)alkyl,

$-[CH_2]_{0-3}$-C(O)O-(1-4C)alkyl,

$-[CH_2]_{0-3}-N(R_f)C(O)$-(1-4C)alkyl (wherein R_f is hydrogen or methyl),

$-[CH_2]_{0-3}-S(O)_2$NH(1-4C)alkyl,

$-[CH_2]_{0-3}-S(O)_2$N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-3}-N(R_g)SO_2$-(1-4C)alkyl (wherein R_g is hydrogen or methyl),

a group of the formula:

$$-Y_1-[CH_2]_{0-3}-Z_1$$

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or $-S(O)_2-$; and

Z_1 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, $-C(O)NH_2$, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -S(O)$_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -S(O)$_2$NH(1-2C)alkyl, -S(O)$_2$N[(1-2C)alkyl]$_2$, or -$NHSO_2$-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl;

R_c is selected from hydrogen, halo, cyano, -C(O)NH_2, (1-4C)alkyl,

-[CH_2]$_{0-3}$-(1-4C)alkoxy,

-[CH_2]$_{0-3}$-(3-6C)cycloalkoxy,

-[CH_2]$_{0-3}$-C(O)NH_2,

-[CH_2]$_{0-3}$-C(O)NH(1-4C)alkyl,

-[CH_2]$_{0-3}$-C(O)N[(1-4C)alkyl]$_2$,

-[CH_2]$_{0-3}$-NH(1-4C)alkyl,

-[CH_2]$_{0-3}$-N[(1-4C)alkyl]$_2$,

-[CH_2]$_{0-3}$-S(O)$_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

-[CH_2]$_{0-3}$-C(O)(1-4C)alkyl,

-[CH_2]$_{0-3}$-C(O)O-(1-4C)alkyl,

-[CH_2]$_{0-3}$-N(R_h)C(O)-(1-4C)alkyl (wherein R_h is hydrogen or methyl),

-[CH_2]$_{0-3}$-S(O)$_2$NH(1-4C)alkyl,

-[CH_2]$_{0-3}$-S(O)$_2$N[(1-4C)alkyl]$_2$,

-[CH_2]$_{0-3}$-N(R_i)SO_2-(1-4C)alkyl (wherein R_i is hydrogen or methyl),

a group of the formula:

-Y_2-[CH_2]$_{0-3}$-Z_2

wherein Y_2 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -S(O)$_2$-; and

Z_2 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_c substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

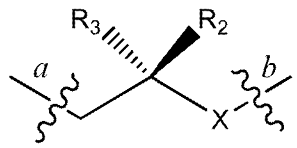
Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -S(O)$_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -S(O)$_2$NH(1-2C)alkyl, -S(O)$_2$N[(1-2C)alkyl]$_2$, or -NHSO_2-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl.

[0067] Particular compounds of the invention include, for example, compounds of the formula I, or pharmaceutically acceptable salts, hydrates and/or solvates thereof, wherein, unless otherwise stated, each of R_1, Q, R_a, R_b, R_c, R_d and R_e each have any of the meanings defined hereinbefore or are as defined in any one of paragraphs (1) to (60) hereinafter:-

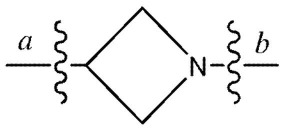
(1) R_1 is -C(O)OH;

(2) R_1 is -C(O)NH_2;

(3) Q is selected from formula Ia or Ib:



Ia



Ib

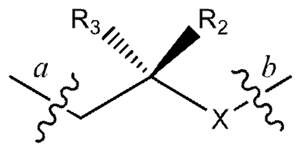
wherein:

bond *a* in formulae Ia and Ib corresponds with bond *a* in formula I and bond *b* in formulae Ia and Ib corresponds with bond *b* in formula I;

R_2 and R_3 are each independently selected from hydrogen or methyl; and

X is O;

(4) Q is selected from formula Ia or Ib:



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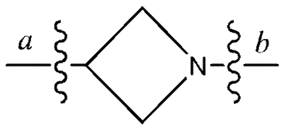


Ib

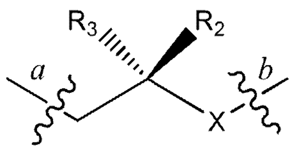
wherein:

bond *a* in formulae Ia and Ib corresponds with bond *a* in formula I and bond *b* in formulae Ia and Ib corresponds with bond *b* in formula I;

R_2 and R_3 are both hydrogen or one of R_2 and R_3 is hydrogen and the other is methyl;

X is O;

(5) Q is selected from formula Ia or Ib:



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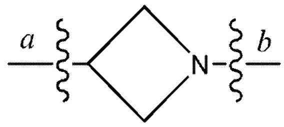


Ib

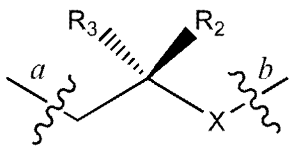
wherein:

bond *a* in formulae Ia and Ib corresponds with bond *a* in formula I and bond *b* in formulae Ia and Ib corresponds with bond *b* in formula I;

R_2 and R_3 are both hydrogen;

X is O;

(6) Q is selected from formula Ia or Ib:



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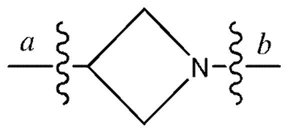


Ib

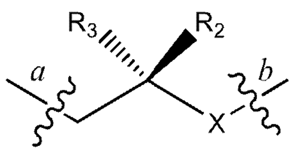
wherein:

bond *a* in formulae Ia and Ib corresponds with bond *a* in formula I and bond *b* in formulae Ia and Ib corresponds with bond *b* in formula I;

R_2 and R_3 are each independently selected from hydrogen or methyl;

X is NH;

(7) Q is selected from formula Ia or Ib:



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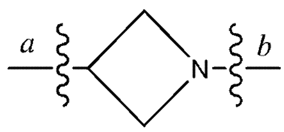


Ib

wherein:

bond *a* in formulae Ia and Ib corresponds with bond *a* in formula I and bond *b* in formulae Ia and Ib corresponds with bond *b* in formula I;

R_2 and R_3 are both hydrogen or one of R_2 and R_3 is hydrogen and the other is methyl;

X is NH; or

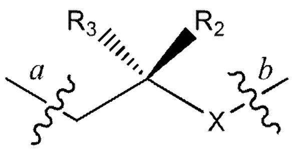
Q is selected from formula Ia or Ib above, wherein:

bond *a* in formulae Ia and Ib corresponds with bond *a* in formula I and bond *b* in formulae Ia and Ib corresponds with bond *b* in formula I;

R_2 and R_3 are both hydrogen;

X is NH;

(8) Q is selected from formula Ia:



Ia

wherein:

bond *a* in formula Ia corresponds with bond *a* in formula I and bond *b* in formula Ia corresponds with bond *b* in formula I;

R_2 and R_3 are each independently selected from hydrogen or methyl; and

X is NH or O;

(9) Q is a group of formula Ia as defined in paragraph (3) above;

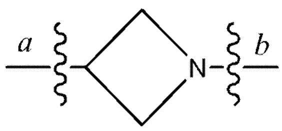
(10) Q is a group of formula Ia as defined in paragraph (4) above;

(11) Q is a group of formula Ia as defined in paragraph (5) above;

(12) Q is a group of formula Ia as defined in paragraph (6) above;

(13) Q is a group of formula Ia as defined in paragraph (7) above;

(14) Q is a group of formula Ib:



Ib

wherein:

bond *a* in formula Ib corresponds with bond *a* in formula I and bond *b* in formula Ib corresponds with bond *b* in formula I;

(15) R_a and R_e are each independently selected from hydrogen, methyl, fluoro, chloro or bromo;

(16) R_a and R_e are each independently selected from hydrogen, fluoro, chloro or bromo;

(17) R_a and R_e are each independently selected from hydrogen, methyl, fluoro or chloro;

(18) R_a and R_e are each independently selected from hydrogen, fluoro or chloro;

(19) R_a and R_e are each independently selected from hydrogen or chloro;

(20) R_a and R_e are both hydrogen;

(21) one of R_a and R_e is hydrogen and the other is hydrogen, methyl or halo;

(22) one of R_a and R_e is hydrogen and the other is hydrogen, methyl, fluoro, chloro or bromo;

(23) one of R_a and R_e is hydrogen and the other is hydrogen, methyl, fluoro or chloro;

(24) one of R_a and R_e is hydrogen and the other is hydrogen or methyl;

(25) one of R_a and R_e is hydrogen and the other is hydrogen or fluoro;

(26) one of R_a and R_e is hydrogen and the other is hydrogen or chloro;

(27) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

-$[CH_2]_{0-2}$-(1-4C)alkoxy,

-$[CH_2]_{0-2}$-C(O)NH_2,

-$[CH_2]_{0-2}$-C(O)NH(1-4C)alkyl,

-$[CH_2]_{0-2}$-C(O)N[(1-4C)alkyl$]_2$,

-$[CH_2]_{0-2}$-NH(1-4C)alkyl,

-$[CH_2]_{0-2}$-N[(1-4C)alkyl$]_2$,

-$[CH_2]_{0-2}$-$S(O)_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

-$[CH_2]_{0-2}$-C(O)(1-4C)alkyl,

-$[CH_2]_{0-2}$-C(O)O-(1-4C)alkyl,

-$[CH_2]_{0-2}$-NHC(O)-(1-4C)alkyl,

-$[CH_2]_{0-2}$-$S(O)_2$NH(1-4C)alkyl,

-$[CH_2]_{0-2}$-$S(O)_2$N[(1-4C)alkyl$]_2$,

-$[CH_2]_{0-2}$-$NHSO_2$-(1-4C)alkyl,

a group of the formula:

-Y_1-$[CH_2]_{0-2}$-Z_1

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -$S(O)_2$-; and Z_1 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl$]_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl$]_2$, -$S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -$S(O)_2$NH(1-2C)alkyl, -$S(O)_2$N[(1-2C)alkyl$]_2$, or -$NHSO_2$-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl;

(28) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

-$[CH_2]_{0-1}$-(1-4C)alkoxy,

-$[CH_2]_{0-1}$-C(O)NH_2,

-$[CH_2]_{0-1}$-C(O)NH(1-4C)alkyl,

-$[CH_2]_{0-1}$-C(O)N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-1}$-NH(1-4C)alkyl,

-$[CH_2]_{0-1}$-N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-1}$-S(O)$_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

-$[CH_2]_{0-1}$-C(O)(1-4C)alkyl,

-$[CH_2]_{0-1}$-C(O)O-(1-4C)alkyl,

-$[CH_2]_{0-1}$-NHC(O)-(1-4C)alkyl,

-$[CH_2]_{0-1}$-S(O)$_2$NH(1-4C)alkyl,

-$[CH_2]_{0-1}$-S(O)$_2$N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-1}$-$NHSO_2$-(1-4C)alkyl,

a group of the formula:

-Y_1-$[CH_2]_{0-1}$-Z_1

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -S(O)$_2$-; and Z_1 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -S(O)$_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -S(O)$_2$NH(1-2C)alkyl, -S(O)$_2$N[(1-2C)alkyl]$_2$, or -$NHSO_2$-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl;

(29) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

-$[CH_2]_{0-2}$-(1-2C)alkoxy,

-$[CH_2]_{0-2}$-C(O)NH_2,

-$[CH_2]_{0-2}$-C(O)NH(1-2C)alkyl,

-$[CH_2]_{0-2}$-C(O)N[(1-2C)alkyl$]_2$,

-$[CH_2]_{0-2}$-NH(1-2C)alkyl,

-$[CH_2]_{0-2}$-N[(1-2C)alkyl$]_2$,

-$[CH_2]_{0-2}$-S$(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2),

-$[CH_2]_{0-2}$-C(O)(1-2C)alkyl,

-$[CH_2]_{0-2}$-C(O)O-(1-2C)alkyl,

-$[CH_2]_{0-2}$-NHC(O)-(1-2C)alkyl,

-$[CH_2]_{0-2}$-S$(O)_2$NH(1-2C)alkyl,

-$[CH_2]_{0-2}$-S$(O)_2$N[(1-2C)alkyl$]_2$,

-$[CH_2]_{0-2}$-NHSO_2-(1-2C)alkyl,

a group of the formula:

-Y_1-$[CH_2]_{0-2}$-Z_1

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -S$(O)_2$-; and

Z_1 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl$]_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl$]_2$, -S$(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -S$(O)_2$NH(1-2C)alkyl, -S$(O)_2$N[(1-2C)alkyl$]_2$, or -NHSO_2-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl;

(30) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

-$[CH_2]_{0-1}$-(1-2C)alkoxy,

-$[CH_2]_{0-1}$-C(O)NH_2,

-$[CH_2]_{0-1}$-C(O)NH(1-2C)alkyl,

-$[CH_2]_{0-1}$-C(O)N[(1-2C)alkyl$]_2$,

-$[CH_2]_{0-1}$-NH(1-2C)alkyl,

-$[CH_2]_{0-1}$-N[(1-2C)alkyl$]_2$,

-$[CH_2]_{0-1}$-S$(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2),

$-[CH_2]_{0-1}$-C(O)(1-2C)alkyl,

$-[CH_2]_{0-1}$-C(O)O-(1-2C)alkyl,

$-[CH_2]_{0-1}$-NHC(O)-(1-2C)alkyl,

$-[CH_2]_{0-1}-S(O)_2NH$(1-2C)alkyl,

$-[CH_2]_{0-1}-S(O)_2N$[(1-2C)alkyl]$_2$,

$-[CH_2]_{0-1}-NHSO_2$-(1-2C)alkyl,

a group of the formula:

$-Y_1-[CH_2]_{0-1}-Z_1$

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or $-S(O)_2-$; and

Z_1 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, $-C(O)NH_2$, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, $-C(O)NH_2$, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, $-S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, $-N(R_f)C(O)$-(1-2C)alkyl, $-S(O)_2NH$(1-2C)alkyl, $-S(O)_2N$[(1-2C)alkyl]$_2$, or $-NHSO_2$-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl;

(31) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

$-[CH_2]_{0-2}$-(1-4C)alkoxy,

$-[CH_2]_{0-2}-C(O)NH_2$,

$-[CH_2]_{0-2}$-C(O)NH(1-4C)alkyl,

$-[CH_2]_{0-2}$-C(O)N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-2}$-NH(1-4C)alkyl,

$-[CH_2]_{0-2}$-N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-2}-S(O)_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

$-[CH_2]_{0-2}$-C(O)(1-4C)alkyl,

$-[CH_2]_{0-2}$-C(O)O-(1-4C)alkyl,

$-[CH_2]_{0-2}-N(R_f)C(O)$-(1-4C)alkyl,

$-[CH_2]_{0-2}-S(O)_2NH$(1-4C)alkyl,

$-[CH_2]_{0-2}-S(O)_2N$[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-2}$-$NHSO_2$-(1-4C)alkyl,

a group of the formula:

-Y_1-$[CH_2]_{0-2}$-Z_1

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -$S(O)_2$-; and

Z_1 is (3-6C)cycloalkyl, phenyl, or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)NH_2 or (1-2C)alkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, (1-2C)alkoxy, (1-2C)alkyl, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -$S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, or -C(O)O-(1-2C)alkyl, and wherein any (1-2C)alkoxy or (1-2C)alkyl group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, or (1-2C)alkoxy;

(32) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

-$[CH_2]_{0-1}$-(1-4C)alkoxy,

-$[CH_2]_{0-1}$-C(O)NH_2,

-$[CH_2]_{0-1}$-C(O)NH(1-4C)alkyl,

-$[CH_2]_{0-1}$-C(O)N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-1}$-NH(1-4C)alkyl,

-$[CH_2]_{0-1}$-N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-1}$-$S(O)_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

-$[CH_2]_{0-1}$-C(O)(1-4C)alkyl,

-$[CH_2]_{0-1}$-C(O)O-(1-4C)alkyl,

-$[CH_2]_{0-1}$-N(R_f)C(O)-(1-4C)alkyl,

-$[CH_2]_{0-1}$-$S(O)_2$NH(1-4C)alkyl,

-$[CH_2]_{0-1}$-$S(O)_2$N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-1}$-$NHSO_2$-(1-4C)alkyl,

a group of the formula:

-Y_1-$[CH_2]_{0-1}$-Z_1

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -$S(O)_2$-; and

Z_1 is (3-6C)cycloalkyl, phenyl, or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)NH_2 or (1-2C)alkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, (1-2C)alkoxy, (1-2C)alkyl, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -S(O)$_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, or -C(O)O-(1-2C)alkyl, and wherein any (1-2C)alkoxy or (1-2C)alkyl group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, or (1-2C)alkoxy;

(33) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

-[CH$_2$]$_{0-1}$-(1-4C)alkoxy,
-[CH$_2$]$_{0-1}$-C(O)NH$_2$,
-[CH$_2$]$_{0-1}$-C(O)NH(1-4C)alkyl,
-[CH$_2$]$_{0-1}$-C(O)N[(1-4C)alkyl]$_2$,
-[CH$_2$]$_{0-1}$-NH(1-4C)alkyl,
-[CH$_2$]$_{0-1}$-N[(1-4C)alkyl]$_2$,
-[CH$_2$]$_{0-1}$-S(O)$_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),
-[CH$_2$]$_{0-1}$-C(O)(1-4C)alkyl,
-[CH$_2$]$_{0-1}$-C(O)O-(1-4C)alkyl,
a group of the formula:

-Y_1-[CH$_2$]$_{0-1}$-Z_1

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -S(O)$_2$-; and
Z_1 is (3-6C)cycloalkyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)NH$_2$ or (1-2C)alkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, (1-2C)alkoxy, (1-2C)alkyl or (1-2C)haloalkyl;

(34) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

-[CH$_2$]$_{0-1}$-(1-4C)alkoxy,
-[CH$_2$]$_{0-1}$-C(O)NH$_2$,
a group of the formula:

[CH$_2$]$_{0-1}$-Z_1

wherein Z_1 is (3-6C)cycloalkyl or a 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)NH$_2$ or (1-2C)alkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, (1-2C)alkoxy, (1-2C)alkyl or (1-2C)haloalkyl;

(35) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, -(1-4C)alkoxy, -$[CH_2]_{0\text{-}1}$-C(O)NH_2,

a group of the formula:

$[CH_2]_{0\text{-}1}$-Z_1

wherein Z_1 is (3-6C)cycloalkyl or a 5-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)NH_2 or (1-2C)alkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy or cyano;

(36) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)alkoxy, -$[CH_2]_{0\text{-}1}$-C(O)NH_2,

a group of the formula:

$[CH_2]_{0\text{-}1}$-Z_1

wherein Z_1 is (3-6C)cycloalkyl or a 5-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)NH_2 or (1-2C)alkoxy; and

Z_1 is optionally substituted by one or more cyano;

(37) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, halo(1-4C)alkyl, hydroxy(1-4C)alkyl, cyano(1-4C)alkyl, amino(1-4C)alkyl, (1-2C)alkoxy(1-4C)alkyl, (1-4C)alkoxy, halo(1-4C)alkoxy, hydroxy(1-4C)alkoxy, -$[CH_2]_{0\text{-}3}$-C(O)NH_2,

a group of the formula:

$[CH_2]_{0\text{-}1}$-Z_1

wherein Z_1 is (3-6C)cycloalkyl or a 5-membered heteroaryl;

and wherein Z_1 is optionally substituted by one or more cyano;

(38) R_b and R_d are each independently selected from hydrogen, halo, (1-2C)alkyl, (1-2C)alkoxy,

a group of the formula:

$[CH_2]_{0\text{-}1}$-Z_1

wherein Z_1 is (3-4C)cycloalkyl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo;

(39) R_b and R_d are each independently selected from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, methoxy, ethoxy, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, $-CH_2CN$, $-CH_2CH_2OH$, $-CF_3$, $-OCF_3$, $-O-CH_2CH_2OH$, $-O-CH_2CF_3$, $-C(O)NH_2$, $-CH_2-C(O)NH_2$, $-CH(CH_3)CN$, $-C(CH_3)_2CN$, cyclopropyl, 1-cyanocyclopropyl, cyclopropylmethyl, furanylmethyl (e.g. furan-3-ylmethyl), imidazolylmethyl (e.g. imidazo-1-ylmethyl), pyrazolylmethyl (e.g. pyrazol-4-ylmethyl), oxazolylmethyl (e.g. oxazo-4-ylmethyl);

(40) R_b and R_d are each independently selected from hydrogen, fluoro, chloro, bromo, methyl, $-OCF_3$, or cyclopropyl;

(41) One of R_b and R_d is hydrogen, halogen, (1-2C)alkyl, halo(1-2C)alkyl, (1-2C)alkoxy, halo(1-2C)alkoxy, (1-2C)alkoxy(1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkyl(1-2C)alkyl and the other is selected from any one of the options defined in paragraphs (27) to (40) above;

(42) One of R_b and R_d is hydrogen or halogen or $-OCF_3$ and the other is selected from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, methoxy, ethoxy, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, $-CH_2CN$, $-CH_2CH_2OH$, $-CF_3$, $-OCF_3$, $-O-CH_2CH_2OH$, $-O-CH_2CF_3$, $-C(O)NH_2$, $-CH_2-C(O)NH_2$, $-CH(CH_3)CN$, $-C(CH_3)_2CN$, cyclopropyl, 1-cyanocyclopropyl, cyclopropylmethyl, furanylmethyl (e.g. furan-3-ylmethyl), imidazolylmethyl (e.g. imidazo-1-ylmethyl), pyrazolylmethyl (e.g. pyrazol-4-ylmethyl), oxazolylmethyl (e.g. oxazo-4-ylmethyl);

(43) One of R_b and R_d is hydrogen or halogen or $-OCF_3$ and the other is selected from hydrogen, fluoro, chloro, bromo, methyl, $-OCF_3$ or cyclopropyl;

(44) R_c is selected from hydrogen, halo, cyano, $-C(O)NH_2$, (1-4C)alkyl,

$-[CH_2]_{0-2}$-(1-4C)alkoxy,

$-[CH_2]_{0-2}$-(3-6C)cycloalkoxy,

$-[CH_2]_{0-2}-C(O)NH_2$,

$-[CH_2]_{0-2}$-C(O)NH(1-4C)alkyl,

$-[CH_2]_{0-2}$-C(O)N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-2}$-NH(1-4C)alkyl,

$-[CH_2]_{0-2}$-N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-2}-S(O)_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

$-[CH_2]_{0-2}$-C(O)(1-4C)alkyl,

$-[CH_2]_{0-2}$-C(O)O-(1-4C)alkyl,

$-[CH_2]_{0-2}$-N(H)C(O)-(1-4C)alkyl,

$-[CH_2]_{0-2}-S(O)_2$NH(1-4C)alkyl,

$-[CH_2]_{0-2}-S(O)_2N[(1-4C)alkyl]_2$,

$-[CH_2]_{0-2}-N(H)SO_2$-(1-4C)alkyl,

a group of the formula:

$$-Y_2-[CH_2]_{0-2}-Z_2$$

wherein Y_2 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or $-S(O)_2$-; and

Z_2 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_c substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, $-C(O)NH_2$, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, $-C(O)NH_2$, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, $-C(O)N[(1-2C)alkyl]_2$, -NH(1-2C)alkyl, $-N[(1-2C)alkyl]_2$, $-S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, $-N(R_f)$C(O)-(1-2C)alkyl, $-S(O)_2$NH(1-2C)alkyl, $-S(O)_2N[(1-2C)alkyl]_2$, or $-NHSO_2$-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl or (1-2C)alkoxy;

(45) R_c is selected from hydrogen, halo, cyano, $-C(O)NH_2$, (1-4C)alkyl,

$-[CH_2]_{0-1}$-(1-4C)alkoxy,

$-[CH_2]_{0-1}$-(3-6C)cycloalkoxy,

$-[CH_2]_{0-1}-C(O)NH_2$,

$-[CH_2]_{0-1}$-C(O)NH(1-4C)alkyl,

$-[CH_2]_{0-1}-C(O)N[(1-4C)alkyl]_2$,

$-[CH_2]_{0-1}$-NH(1-4C)alkyl,

$-[CH_2]_{0-1}-N[(1-4C)alkyl]_2$,

$-[CH_2]_{0-1}-S(O)_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

-$[CH_2]_{0\text{-}1}$-C(O)(1-4C)alkyl,

-$[CH_2]_{0\text{-}1}$-C(O)O-(1-4C)alkyl,

-$[CH_2]_{0\text{-}1}$-N(H)C(O)-(1-4C)alkyl,

-$[CH_2]_{0\text{-}1}$-$S(O)_2$NH(1-4C)alkyl,

-$[CH_2]_{0\text{-}1}$-$S(O)_2$N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0\text{-}1}$-N(H)SO_2-(1-4C)alkyl,

a group of the formula:

-Y_2-$[CH_2]_{0\text{-}1}$-Z_2

wherein Y_2 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -$S(O)_2$-; and

Z_2 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_c substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -$S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -$S(O)_2$NH(1-2C)alkyl, -$S(O)_2$N[(1-2C)alkyl]$_2$, or -NHSO_2-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl or (1-2C)alkoxy;

(46) R_c is selected from hydrogen, halo, cyano, -C(O)NH_2, (1-4C)alkyl,

-$[CH_2]_{0\text{-}2}$-(1-2C)alkoxy,

-$[CH_2]_{0\text{-}2}$-(3-6C)cycloalkoxy,

-$[CH_2]_{0\text{-}2}$-C(O)NH_2,

-$[CH_2]_{0\text{-}2}$-C(O)NH(1-2C)alkyl,

-$[CH_2]_{0\text{-}2}$-C(O)N[(1-2C)alkyl]$_2$,

-$[CH_2]_{0\text{-}2}$-NH(1-2C)alkyl,

-$[CH_2]_{0-2}$-N[(1-2C)alkyl]$_2$,

-$[CH_2]_{0-2}$-$S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2),

-$[CH_2]_{0-2}$-C(O)(1-2C)alkyl,

-$[CH_2]_{0-2}$-C(O)O-(1-2C)alkyl,

-$[CH_2]_{0-2}$-N(H)C(O)-(1-2C)alkyl,

-$[CH_2]_{0-2}$-$S(O)_2$NH(1-2C)alkyl,

-$[CH_2]_{0-2}$-$S(O)_2$N[(1-2C)alkyl]$_2$,

-$[CH_2]_{0-2}$-N(H)SO_2-(1-2C)alkyl,

a group of the formula:

-Y_2-$[CH_2]_{0-2}$-Z_2

wherein Y_2 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -$S(O)_2$-; and

Z_2 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_c substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -$S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -$S(O)_2$NH(1-2C)alkyl, -$S(O)_2$N[(1-2C)alkyl]$_2$, or -NHSO_2-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl or (1-2C)alkoxy;

(47) R_c is selected from hydrogen, halo, cyano, -C(O)NH_2, (1-4C)alkyl,

-$[CH_2]_{0-1}$-(1-2C)alkoxy,

-$[CH_2]_{0-1}$-(3-6C)cycloalkoxy,

-$[CH_2]_{0-1}$-C(O)NH_2,

-$[CH_2]_{0-1}$-C(O)NH(1-2C)alkyl,

-$[CH_2]_{0-1}$-C(O)N[(1-2C)alkyl]$_2$,

-$[CH_2]_{0-1}$-NH(1-2C)alkyl,

-$[CH_2]_{0-1}$-N[(1-2C)alkyl]$_2$,

-$[CH_2]_{0-1}$-$S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2),

-$[CH_2]_{0-1}$-C(O)(1-2C)alkyl,

-$[CH_2]_{0-1}$-C(O)O-(1-2C)alkyl,

-$[CH_2]_{0-1}$-N(H)C(O)-(1-2C)alkyl,

-$[CH_2]_{0-1}$-$S(O)_2$NH(1-2C)alkyl,

-$[CH_2]_{0-1}$-$S(O)_2$N[(1-2C)alkyl]$_2$,

-$[CH_2]_{0-1}$-N(H)SO_2-(1-2C)alkyl,

a group of the formula:

-Y_2-$[CH_2]_{0-1}$-Z_2

wherein Y_2 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -$S(O)_2$-; and

Z_2 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_c substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -$S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -$S(O)_2$NH(1-2C)alkyl, -$S(O)_2$N[(1-2C)alkyl]$_2$, or -NHSO_2-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl or (1-2C)alkoxy;

(48) R_c is selected from hydrogen, halo, cyano, -C(O)NH_2, (1-4C)alkyl,

-$[CH_2]_{0-2}$-(1-4C)alkoxy,

-$[CH_2]_{0-2}$-(3-6C)cycloalkoxy,

$-[CH_2]_{0-2}-C(O)NH_2$,

$-[CH_2]_{0-2}$-C(O)NH(1-4C)alkyl,

$-[CH_2]_{0-2}$-C(O)N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-2}$-NH(1-4C)alkyl,

$-[CH_2]_{0-2}$-N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-2}-S(O)_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

$-[CH_2]_{0-2}$-C(O)(1-4C)alkyl,

$-[CH_2]_{0-2}$-C(O)O-(1-4C)alkyl,

$-[CH_2]_{0-2}$-N(H)C(O)-(1-4C)alkyl,

$-[CH_2]_{0-2}-S(O)_2$NH(1-4C)alkyl,

$-[CH_2]_{0-2}-S(O)_2$N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-2}-N(H)SO_2$-(1-4C)alkyl,

a group of the formula:

$$-Y_2-[CH_2]_{0-2}-Z_2$$

wherein Y_2 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or $-S(O)_2-$; and

Z_2 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_c substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, $-C(O)NH_2$, or (1-2C)alkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, (1-2C)alkoxy, (1-2C)alkyl, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, $-S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, or -C(O)O-(1-2C)alkyl, and wherein any (1-2C)alkoxy or (1-2C)alkyl group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy or (1-2C)alkoxy;

(49) R_c is selected from hydrogen, halo, cyano, $-C(O)NH_2$, (1-4C)alkyl,

$-[CH_2]_{0-1}$-(1-4C)alkoxy,

$-[CH_2]_{0-1}$-(3-6C)cycloalkoxy,

$-[CH_2]_{0-1}-C(O)NH_2$,

$-[CH_2]_{0-1}-C(O)NH$(1-4C)alkyl,

$-[CH_2]_{0-1}-C(O)N$[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-1}-NH$(1-4C)alkyl,

$-[CH_2]_{0-1}-N$[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-1}-S(O)_q-$(1-4C)alkyl (wherein q is 0, 1 or 2),

$-[CH_2]_{0-1}-C(O)$(1-4C)alkyl,

$-[CH_2]_{0-1}-C(O)O-$(1-4C)alkyl,

$-[CH_2]_{0-1}-N(H)C(O)-$(1-4C)alkyl,

$-[CH_2]_{0-1}-S(O)_2NH$(1-4C)alkyl,

$-[CH_2]_{0-1}-S(O)_2N$[(1-4C)alkyl]$_2$,

$-[CH_2]_{0-1}-N(H)SO_2-$(1-4C)alkyl,

a group of the formula:

$$-Y_2-[CH_2]_{0-1}-Z_2$$

wherein Y_2 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or $-S(O)_2-$; and

Z_2 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_c substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, $-C(O)NH_2$, or (1-2C)alkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, (1-2C)alkoxy, (1-2C)alkyl, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, $-S(O)_q-$(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, or -C(O)O-(1-2C)alkyl, and wherein any (1-2C)alkoxy or (1-2C)alkyl group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy or (1-2C)alkoxy;

(50) R_c is selected from hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)alkoxy,

a group of the formula:

$$-Y_2-[CH_2]_{0-1}-Z_2$$

wherein Y_2 is absent or -O-; and

Z_2 is (3-6C)cycloalkyl or phenyl;

and wherein:

any alkyl or alkoxy substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, or (1-2C)alkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, (1-2C)alkoxy, (1-2C)alkyl, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -S(O)$_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, or -C(O)O-(1-2C)alkyl, and wherein any (1-2C)alkoxy or (1-2C)alkyl group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy or (1-2C)alkoxy;

(51) R_c is selected from hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)alkoxy, a group of the formula:

$$-Y_2-[CH_2]_{0-1}-Z_2$$

wherein Y_2 is absent or -O-; and

Z_2 is (3-6C)cycloalkyl or phenyl;

and wherein:

any alkyl or alkoxy substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, or (1-2C)alkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, (1-2C)alkoxy, or (1-2C)alkyl, and wherein any (1-2C)alkoxy or (1-2C)alkyl group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy or (1-2C)alkoxy;

(52) R_c is selected from hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)alkoxy, a group of the formula:

$$-Y_2-[CH_2]_{0-1}-Z_2$$

wherein Y_2 is absent or -O-; and

Z_2 is (3-6C)cycloalkyl or phenyl;

and wherein:

any alkyl or alkoxy substituent group is optionally substituted by one or more substituents selected from halo or cyano; and

Z_2 is optionally substituted by one or more (1-2C)alkyl substituents, and wherein a (1-2C)alkyl group is optionally substituted by one or more hydroxy substituents;

(53) R_c is selected from hydrogen, halo, cyano, (1-2C)alkyl or (1-2C)alkoxy, wherein any alkyl or alkoxy substituent group is optionally substituted by one or more halo substituents;

(54) R_c is selected from hydrogen, halo or (1-2C)alkoxy, wherein an alkoxy substituent group is optionally substituted by one or more halo substituents;

(55) R_c is selected from hydrogen, halo or halo(1-2C)alkoxy,

(56) R_c is selected from hydrogen, halo or (1-2C)alkoxy, wherein an alkoxy substituent group is optionally substituted by one or more fluoro substituents;

(57) R_c is selected from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, methoxy, ethoxy, $-O-CH(CH_3)_2$, $-CH_2CN$, $-CF_3$, $-OCF_3$, $-O-CH_2CF_3$, cyclopropyl, cyclopropoxy, cyclobutoxy, cyclopentoxy, phenyl or 2-hydroxymethylphenyl;

(58) R_c is selected from hydrogen, fluoro, chloro, bromo, cyano, methoxy, ethoxy, $-O-CH(CH_3)_2$, $-CH_2CN$, $-CF_3$, $-OCF_3$, $-O-CH_2CF_3$, cyclopropyl, cyclopropoxy, cyclobutoxy, cyclopentoxy, phenyl or 2-hydroxymethylphenyl;

(59) R_c is selected from hydrogen, fluoro, chloro or $-OCF_3$;

(60) R_c is selected from hydrogen, chloro or $-OCF_3$.

[0068] Suitably, in any of the definitions of formula I set out herein, at least one of R_a, R_b, R_c, R_d or R_e is a non-hydrogen substituent. By "non-hydrogen substituent" we mean a substituent selected from any one of the options defined herein for R_a, R_b, R_c, R_d or R_e other than hydrogen. More suitably, one to four of R_a, R_b, R_c, R_d or R_e is/are a non-hydrogen substituent(s). Most suitably, one to three of R_a, R_b, R_c, R_d or R_e is/are a non-hydrogen substituent(s).

[0069] Suitably, in any of the definitions of formula I set out herein, up to four of R_a, R_b, R_c, R_d or R_e are hydrogen and the remainder are non-hydrogen substituents (i.e. selected from any one of the options set out herein for R_a, R_b, R_c, R_d or R_e other than hydrogen). More suitably, two to four of R_a, R_b, R_c, R_d or R_e are hydrogen and the remainder are non-hydrogen substituents.

[0070] In a particular group of compounds of formula I, if R_c is a group of the formula $-Y_2-[CH_2]_{0-3}-Z_2$, then R_b and R_d cannot be a group of the formula $-Y_1-[CH_2]_{0-3}-Z_1$.

[0071] In a further group of compounds of formula I, if one or both of R_b and R_d is a group of the formula $-Y_1-[CH_2]_{0-3}-Z_1$ as defined herein, then R_c cannot be a group of the formula $-Y_2-[CH_2]_{0-3}-Z_2$.

[0072] In a particular group of compounds of formula I:

(i) if R_c is a group of the formula $-Y_2-[CH_2]_{0-3}-Z_2$ then R_b and R_d cannot be a group of the formula $-Y_1-[CH_2]_{0-3}-Z_1$; and/or

(ii) if one or both of R_b and R_d is a group of the formula $-Y_1-[CH_2]_{0-3}-Z_1$ as defined herein, then R_c cannot be a group of the formula $-Y_2-[CH_2]_{0-3}-Z_2$.

[0073] In another particular group of compounds of formula I:

(i) if R_c is a group of the formula $-Y_2-[CH_2]_{0-3}-Z_2$ then R_b and R_d cannot be a group of the formula $-Y_1-[CH_2]_{0-3}-Z_1$; and

(ii) if one of R_b and R_d is a group of the formula $-Y_1-[CH_2]_{0-3}-Z_1$ as defined herein, then the other cannot be a group of the formula $-Y_1-[CH_2]_{0-3}-Z_1$ and R_c cannot be a group of the formula $-Y_2-[CH_2]_{0-3}-Z_2$.

[0074] Suitably, in any of the definitions of formula I set out herein, a heteroaryl is a 5- or 6-membered heteroaryl ring comprising one, two or three heteroatoms selected from N, O or S.

[0075] Suitably, in any of the definitions of formula I set out herein, a heterocyclyl group is a 4-, 5- or 6-membered heterocyclyl ring comprising one, two or three heteroatoms selected from N, O or S. Most suitably, a heterocyclyl group is a 4-, 5- or 6-membered ring comprising one or two heteroatoms selected from N, O or S [e.g. morpholinyl (e.g. 4-morpholinyl), piperidinyl, piperazinyl or pyrrolidinyl].

[0076] Suitably, in any of the definitions of formula I set out herein, R_1 is as defined in formula I above or as defined in either paragraph (1) and/or (2) above. In a particular group of compounds of the invention, R_1 is as defined in paragraph (1) above. In another particular group of compounds of the invention, R_1 is as defined in paragraph (2) above.

[0077] Suitably, in any of the definitions of formula I set out herein, Q is as defined in formula I above or is as defined in any one of paragraphs (3) to (14) above.

[0078] Suitably, in any of the definitions of formula I set out herein, R_a and R_e are as defined in any one of paragraphs (15) to (26) above. More suitably, R_a and R_e are as defined in any one of paragraphs (16), (21), (22), (23) or (26) above. Even more suitably, R_a and R_e are as defined in any one of paragraphs (21), (22), (23) or (26) above. Most suitably, R_a and R_e are as defined in paragraphs (23) or (26) above.

[0079] In a particular group of compounds of formula I, R_a and R_e are as defined in paragraph (16) above, and R_1, Q, R_b, R_c, and R_d are each as defined in formula I above.

[0080] In a particular group of compounds of formula I, R_a and R_e are as defined in paragraph (21) above, and R_1, Q, R_b, R_c and R_d are each as defined in formula I above.

[0081] In a particular group of compounds of formula I, R_a and R_e are as defined in paragraph (22) above, and R_1, Q, R_b, R_c and R_d are each as defined in formula I above.

[0082] In a particular group of compounds of formula I, R_a and R_e are as defined in paragraph (23) above, and R_1, Q, R_b, R_c and R_d are each as defined in formula I above.

[0083] In a particular group of compounds of formula I, R_a and R_e are as defined in paragraph (26) above, and R_1, Q, R_b, R_c and R_d are each as defined in formula I above.

[0084] Suitably, in any of the definitions of formula I set out herein, R_b and R_d are as defined in any one of paragraphs (27) to (43) above. More suitably, R_b and R_d are as defined in any one of paragraphs (36), (37), (38), (39), (40), (41), (42) or (43) above. Even more suitably, R_a and R_e are as defined in any one of paragraphs (39), (40), (41), (42) or (43) above. Most suitably, R_a and R_e are as defined in paragraphs (38) or (43) above.

[0085] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (28) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0086] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (30) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0087] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (32) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0088] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (34) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0089] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (36) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0090] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (37) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0091] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (38) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0092] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (39) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0093] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (40) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0094] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (41) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0095] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (42) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0096] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (43) above, and R_1, Q, R_a, R_c and R_e are each as defined in formula I above.

[0097] Suitably, in any of the definitions of formula I set out herein, R_c is as defined in any one of paragraphs (44) to (60) above. More suitably, R_c is as defined in any one of paragraphs (51), (52), (53), (54), (55), (56), (57), (58), (59) or (60) above. Even more suitably, R_c is as defined in any one of paragraphs (56), (56), (57), (58), (59) or (60) above. Most suitably, R_c is as defined in paragraphs (58), (59) or (60) above.

[0098] In a particular group of compounds of formula I, R_c is as defined in paragraph (45) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[0099] In a particular group of compounds of formula I, R_c is as defined in paragraph (47) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[00100] In a particular group of compounds of formula I, R_c is as defined in paragraph (49) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[00101] In a particular group of compounds of formula I, R_c is as defined in paragraph (51) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[00102] In a particular group of compounds of formula I, R_c is as defined in paragraph (53) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[00103] In a particular group of compounds of formula I, R_c is as defined in paragraph (55) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[00104] In a particular group of compounds of formula I, R_c is as defined in paragraph (56) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[00105] In a particular group of compounds of formula I, R_c is as defined in paragraph (57) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[00106] In a particular group of compounds of formula I, R_c is as defined in paragraph (58) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[00107] In a particular group of compounds of formula I, R_c is as defined in paragraph (59) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[00108] In a particular group of compounds of formula I, R_c is as defined in paragraph (60) above, and R_1, Q, R_a, R_b, R_d and R_e are each as defined in formula I above.

[00109] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I above;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (27) above; and

R_e is as defined in paragraph (44) above.

[00110] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I above;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (28) above; and

R_e is as defined in paragraph (45) above.

[00111] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (29) above; and

R_e is as defined in paragraph (46) above.

[00112] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (30) above; and

R_e is as defined in paragraph (47) above.

[00113] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (31) above; and

R_e is as defined in paragraph (48) above.

[00114] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (32) above; and

R_e is as defined in paragraph (49) above.

[00115] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (33) above; and

R_e is as defined in paragraph (50) above.

[00116] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (34) above; and

R_e is as defined in paragraph (51) above.

[00117] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (35) above; and

R_e is as defined in paragraph (52) above.

[00118] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (36) above; and

R_e is as defined in paragraph (53) above.

[00119] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (26) above;

R_b and R_d are both as defined in paragraph (37) above; and

R_e is as defined in paragraph (54) above.

[00120] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (26) above;

R_b and R_d are both as defined in paragraph (38) above; and

R_e is as defined in paragraph (54) above.

[00121] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (26) above;

R_b and R_d are both as defined in paragraph (39) above; and

R_e is as defined in paragraph (58) above.

[00122] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (26) above;

R_b and R_d are both as defined in paragraph (41) above; and

R_e is as defined in paragraph (58) above.

[00123] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (26) above;

R_b and R_d are both as defined in paragraph (40) above; and

R_e is as defined in paragraph (59) above.

[00124] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (26) above;

R_b and R_d are both as defined in paragraph (43) above; and

R_e is as defined in paragraph (59) above.

[00125] In a particular group of compounds of formula I defined herein:

R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (26) above;

R_b and R_d are both as defined in paragraph (40) above; and

R_e is as defined in paragraph (60) above.

[00126] In a particular group of compounds of formula I defined herein:

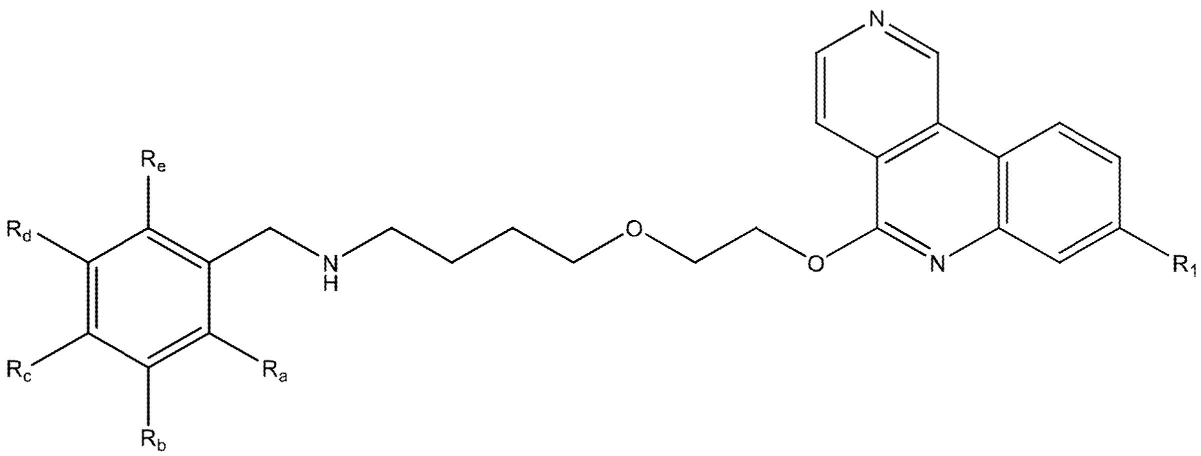
R_1 and Q are both as defined in formula I;

R_a and R_e are both as defined in paragraph (26) above;

R_b and R_d are both as defined in paragraph (43) above; and

R_e is as defined in paragraph (60) above.

[00127] In a particular group of compounds of the invention, the compound is a compound of formula I defined herein in which Q is as defined in paragraph (11) above, i.e. the compounds have the formula Ic shown below, or a pharmaceutically acceptable salt thereof:



(Ic)

wherein R_1, R_a, R_b, R_c, R_d and R_e each have any one of the definitions set out herein.

[00128] In a particular group of compounds of formula Ic:

R_1 is selected from -C(O)OH or -C(O)NH_2;

R_a and R_e are both as defined in paragraph (23) above;

R_b and R_d are both as defined in paragraph (36) above; and

R_c is as defined in paragraph (50) above.

[00129] In a particular group of compounds of formula Ic:

R_1 is selected from -C(O)OH or -C(O)NH$_2$;

R_a and R_e are both as defined in paragraph (26) above;

R_b and R_d are both as defined in paragraph (38) above; and

R_c is as defined in paragraph (54) above.

[00130] In a particular group of compounds of formula Ic:

R_1 is selected from -C(O)OH or -C(O)NH$_2$;

R_a and R_e are both as defined in paragraph (20) above;

R_b and R_d are both as defined in paragraph (40) above; and

R_c is as defined in paragraph (58) above.

[00131] In a particular group of compounds of formula Ic:

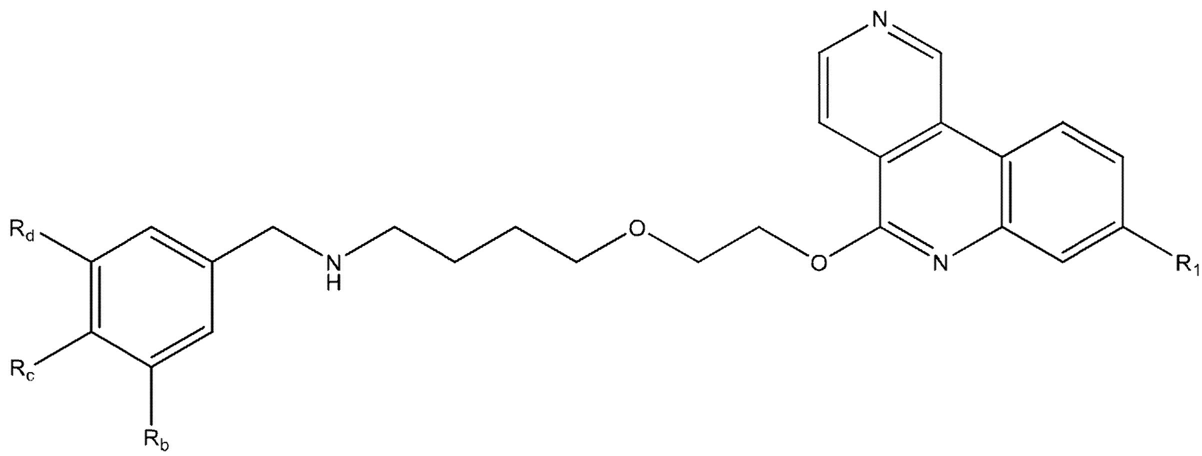
R_1 is -C(O)OH;

R_a and R_e are both as defined in paragraph (20) above;

R_b and R_d are both as defined in paragraph (43) above; and

R_c is as defined in paragraph (60) above.

[00132] In a particular group of compounds of the invention, the compound is a compound of formula I defined herein in which Q is as defined in paragraph (11) above and R_a and R_e are as defined in paragraph (20) above, i.e. the compounds have the formula Id shown below, or a pharmaceutically acceptable salt thereof:



(Id)

wherein R_1, R_b, R_c and R_d each have any one of the definitions set out hereinbefore.

[00133] In a particular group of compounds of formula Id:

R_1 is selected from -C(O)OH or -C(O)NH_2;

R_b and R_d are both as defined in paragraph (36) above; and

R_c is as defined in paragraph (50) above.

[00134] In a particular group of compounds of formula Id:

R_1 is selected from -C(O)OH or -C(O)NH_2;

R_b and R_d are both as defined in paragraph (38) above; and

R_c is as defined in paragraph (54) above.

[00135] In a particular group of compounds of formula Id:

R_1 is selected from -C(O)OH or -C(O)NH_2;

R_b and R_d are both as defined in paragraph (40) above; and

R_c is as defined in paragraph (58) above.

[00136] In a particular group of compounds of formula Id:

R_1 is -C(O)OH;

R_b and R_d are both as defined in paragraph (43) above; and

R_c is as defined in paragraph (60) above.

[00137] In a particular group of compounds of formula I, Ic or Id defined herein R_b and R_d are selected from hydrogen or fluoro.

[00138] In a particular group of compounds of formula I, Ic or Id defined herein R_b and R_d are hydrogen.

[00139] In a particular group of compounds of formula I, Ic or Id defined herein R_b and R_d are fluoro.

[00140] In a particular group of compounds of formula I, Ic or Id defined herein R_c is -OCF_3.

[00141] In a particular group of compounds of formula I, Ic or Id defined herein R_b and R_d are selected from hydrogen or fluoro and R_c is -OCF_3.

[00142] In a particular group of compounds of formula I, Ic or Id defined herein R_b and R_d are hydrogen and R_c is -OCF_3.

[00143] In a particular group of compounds of formula I, Ic or Id defined herein R_b and R_d are fluoro and R_c is -OCF_3.

[00144] Particular compounds of the present invention include any of the compounds described in the example section of the present application, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and, in particular, any of the following:

5-((2-(4-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chlorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-(((2-chloro-2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)methyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-(cyclopentyloxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-cyclopropoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(2-hydroxyethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chlorobenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-cyclobutoxy-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-chloro-3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((4-cyclopropyl-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chlorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(2-hydroxyethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-chloro-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-chloro-4-cyclopropoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(2-hydroxyethoxy)-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-cyclobutoxy-3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide

5-((2-(4-((3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(2-hydroxyethoxy)-4-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(aminomethyl)-5-chlorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chloro-4-cyclobutoxybenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(hydroxymethyl)-5-methylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((2-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-chloro-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-cyano-4-cyclopropylbenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((4-cyclobutoxy-3-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((2-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-cyano-3-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-4-(2,2,2-trifluoroethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-4-isopropoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-(cyclopentyloxy)-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-chloro-3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((2-chloro-3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((2-chloro-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-ethoxy-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-4-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(S)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-methoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-5-(2-cyanopropan-2-yl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-5-(1-cyanocyclopropyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-bromo-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((4-chloro-3-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-chloro-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-bromo-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-cyclopropyl-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-fluoro-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-chloro-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-bromo-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-cyclopropyl-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-chloro-5-(1-cyanocyclopropyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-chloro-5-(2-cyanopropan-2-yl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-cyclopropyl-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-methyl-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-methoxy-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3,4-dichloro-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-ethoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyclopropyl-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(R)-5-((2-(4-((3-chloro-5-(1-cyanoethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(S)-5-((2-(4-((3-chloro-5-(1-cyanoethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-(2,2,2-trifluoroethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-cyclopropyl-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-bromo-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((4-chloro-3-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-methyl-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-methoxy-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3,4-dichloro-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(S)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)-2-methylpropan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-ethylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-(cyclopropylmethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)-2-methylpropan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-(methoxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(oxazol-4-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-cyano-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(oxazol-4-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(2-hydroxyethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(2-hydroxyethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(S)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(S)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-carbamoyl-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-carbamoyl-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(2-amino-2-oxoethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(2-amino-2-oxoethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-((1H-imidazol-1-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(furan-3-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-((1H-imidazol-1-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-((1H-pyrazol-4-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(furan-3-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-((1H-pyrazol-4-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(R)-5-((1-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(R)-5-((1-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(R)-5-((1-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(R)-5-((1-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid; or

5-(2-(4-((3,5-Difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide.

[00145] Though the present invention may relate to any compound or particular group of compounds defined herein by way of optional, preferred or suitable features or otherwise in terms of particular embodiments, the present invention may also relate to any compound or particular group of compounds that specifically excludes said optional, preferred or suitable features or particular embodiments.

[00146] Suitably, the present invention excludes any individual compounds not possessing the biological activity defined herein.

Salts and Solvates

[00147] The compounds (including final products and intermediates) described herein may be isolated and used *per se* or may be isolated in the form of a salt, suitably pharmaceutically acceptable salts. It should be understood that the terms “salt(s)” and “salt form(s)” used by themselves or in conjunction with another term or terms encompasses all inorganic and organic salts, including industrially acceptable salts, as defined herein, and pharmaceutically acceptable salts, as defined herein, unless otherwise specified. As used herein, industrially acceptable salts are salts that are generally suitable for manufacturing and/or processing (including purification) as well as for shipping and storage, but may not be salts that are typically administered for clinical or therapeutic use. Industrially acceptable salts may be prepared on a laboratory scale, i.e. multi-gram or smaller, or on a larger scale, i.e. up to and including a kilogram or more.

[00148] Pharmaceutically acceptable salts, as used herein, are salts that are generally chemically and/or physically compatible with the other ingredients comprising a formulation, and/or are generally physiologically compatible with the recipient thereof. Pharmaceutically acceptable salts may be prepared on a laboratory scale, i.e. multi-gram or smaller, or on a larger scale, i.e. up to and including a kilogram or more. It should be understood that pharmaceutically acceptable salts are not limited to salts that are typically administered or approved by the FDA or equivalent foreign regulatory body for clinical or therapeutic use in humans. A practitioner of ordinary skill will readily appreciate that some salts are both industrially acceptable as well as pharmaceutically acceptable salts. It should be understood that all such salts, including mixed salt forms, are within the scope of the application.

[00149] In one embodiment, the compounds of Formula I and sub-formulae thereof are isolated as pharmaceutically acceptable salts.

[00150] A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, trifluoroacetic, formic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

[00151] In general, salts of the present application can be prepared *in situ* during the isolation and/or purification of a compound (including intermediates), or by separately reacting the compound (or intermediate) with a suitable organic or inorganic acid or base (as appropriate) and isolating the salt thus formed. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised. In practice, the various salts may be precipitated (with or without the addition of one or more co-solvents and/or anti-solvents) and collected by filtration or the salts may be recovered by evaporation of solvent(s). Salts of the present application may also be formed via a "salt switch" or ion exchange/double displacement reaction, i.e. reaction in which one ion is replaced (wholly or in part) with another ion having the same charge. One skilled in the art will appreciate that the salts may be prepared and/or isolated using a single method or a combination of methods.

[00152] Representative salts include, but are not limited to, acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate, trifluoroacetate and the like. Other examples of representative salts include alkali or alkaline earth metal cations such as, but not limited to, sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, lysine, arginine, benzathine, choline, tromethamine, diolamine, glycine, meglumine, olamine and the like.

[00153] Certain compounds of the Formula I and sub-formulae thereof may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms that possess the biological activity described herein.

Polymorphs

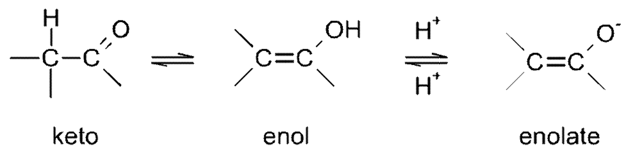
[00154] It is also to be understood that certain compounds of the Formula I and sub-formulae thereof may exhibit polymorphism, and that the invention encompasses all such forms that possess the biological activity described herein.

N-oxides

[00155] Compounds of the Formula I and sub-formulae thereof containing an amine function may also form N-oxides. A reference herein to a compound of the Formula I and sub-formulae thereof that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as, but not limited to, hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm*. 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (*m*CPBA), for example, in an inert solvent such as, but not limited to, dichloromethane.

Tautomers

[00156] Compounds of the Formula I and sub-formulae thereof may exist in a number of different tautomeric forms and references to compounds of the Formula I and sub-formulae thereof include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by Formula I and sub-formulae thereof. Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), pyrimidone/hydroxypyrimidine, imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



Isomers

[00157] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[00158] Certain compounds of Formula I and sub-formulae thereof may have one or more asymmetric centres and therefore can exist in a number of stereoisomeric configurations. Consequently, such compounds can be synthesized and/or isolated as mixtures of enantiomers and/or as individual (pure) enantiomers, and, in the case of two or more asymmetric centres, single diastereomers and/or mixtures of diastereomers. It should be understood that the present application includes all such enantiomers and diastereomers and mixtures thereof in all ratios.

Isotopes

[00159] The compounds of the present invention are described herein using structural formulas that do not specifically recite the mass numbers or the isotope ratios of the constituent atoms. As such it is intended that the present application includes compounds in which the constituent atoms are present in any ratio of isotope forms. For example, carbon atoms may be present in any ratio of ^{12}C, ^{13}C, and ^{14}C; hydrogen atoms may be present in any ratio of ^{1}H, ^{2}H, and ^{3}H; etc. Preferably, the constituent atoms in the compounds of the present invention are present in their naturally occurring ratios of isotope forms.

Prodrugs and Metabolites

[00160] The compounds of Formula I and sub-formulae thereof may be administered in the form of a pro-drug which is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a carboxy group or a hydroxy group in a compound of the Formula I and *in-vivo* cleavable amide derivatives that may be formed at a carboxy group or an amino group in a compound of the Formula I and sub-formulae thereof.

[00161] Accordingly, the present invention includes those compounds of the Formula I and sub-formulae thereof as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of the Formula I that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the Formula I and sub-formulae thereof may be a synthetically-produced compound or a metabolically-produced compound.

[00162] A suitable pharmaceutically acceptable pro-drug of a compound of the Formula I and sub-formulae thereof is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

[00163] Various forms of pro-drug have been described, for example in the following documents :-

a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);

c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988);

f) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984);

g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and

h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

[00164] A suitable pharmaceutically acceptable pro-drug of a compound of the Formula I and sub-formulae thereof that possesses a carboxy group is, for example, an *in vivo* cleavable ester thereof. An *in vivo* cleavable ester of a compound of the Formula I containing a carboxy group is, for example, a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkyl esters such as, but not limited to, methyl, ethyl and *tert*-butyl, C_{1-6}alkoxymethyl esters such as, but not limited to, methoxymethyl esters, C_{1-6}alkanoyloxymethyl esters such as, but not limited to, pivaloyloxymethyl esters, 3-phthalidyl esters, C_{3-8}cycloalkylcarbonyloxy- C_{1-6}alkyl esters such as, but not limited to, cyclopentylcarbonyloxymethyl and 1-cyclohexylcarbonyloxyethyl esters, 2-oxo-1,3-dioxolenylmethyl esters such as, but not limited to, 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl esters and C_{1-6}alkoxycarbonyloxy- C_{1-6}alkyl esters such as, but not limited to, methoxycarbonyloxymethyl and 1-methoxycarbonyloxyethyl esters.

[00165] A suitable pharmaceutically acceptable pro-drug of a compound of the Formula I and sub-formulae thereof that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of the Formula I and sub-formulae thereof containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as, but not limited to, phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include C_{1-10}alkanoyl groups such as, but not limited to, acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C_{1-10}alkoxycarbonyl groups such as, but not limited to, ethoxycarbonyl, *N,N*–$(C_{1-6})_2$carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N,N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C_{1-4}alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α-acyloxyalkyl groups such as, but not limited to, acetoxymethyl and pivaloyloxymethyl groups.

[00166] A suitable pharmaceutically acceptable pro-drug of a compound of the Formula I and sub-formulae thereof that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as, but not limited to, ammonia, a C_{1-4}alkylamine such as, but not limited to, methylamine, a $(C_{1-4}alkyl)_2$amine such as, but not limited to, dimethylamine, *N*-ethyl-*N*-methylamine or diethylamine, a C_{1-4}alkoxy- C_{2-4}alkylamine such as, but not limited to, 2-methoxyethylamine, a phenyl-C_{1-4}alkylamine such as, but not limited to, benzylamine and amino acids such as, but not limited to, glycine or an ester thereof.

[00167] A suitable pharmaceutically acceptable pro-drug of a compound of the Formula I and sub-formulae thereof that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C_{1-10}alkanoyl groups such as, but not limited to, an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N,N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C_{1-4}alkyl)piperazin-1-ylmethyl.

[00168] The *in vivo* effects of a compound of the Formula I and sub-formulae thereof may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the Formula I and sub-formulae thereof. As stated hereinbefore, the *in vivo* effects of a compound of the Formula I and sub-formulae thereof may also be exerted by way of metabolism of a precursor compound (a pro-drug).

Pharmaceutical Compositions

[00169] According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with a pharmaceutically acceptable diluent or carrier.

[00170] The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

[00171] The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

[00172] An effective amount of a compound of the present invention for use in therapy is an amount sufficient to treat or prevent a proliferative condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

[00173] The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the individual treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 1.5 g of active agent (more suitably from 0.5 to 600 mg, for example from 1 to 200 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

[00174] The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

[00175] It is to be noted that dosages and dosing regimens may vary with the type and severity of the condition to be alleviated, and may include the administration of single or multiple doses, i.e. QD (once daily), BID (twice daily), etc., over a particular period of time (days or hours). It is to be further understood that for any particular subject or patient, specific dosage regimens may need to be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the pharmaceutical compositions. For example, doses may be adjusted based on pharmacokinetic or pharmacodynamic parameters, which may include clinical effects such as toxic effects and/or laboratory values. Thus, the present application encompasses intra-patient dose-escalation as determined by the person skilled in the art. Procedures and processes for determining the appropriate dosage(s) and dosing regimen(s) are well-known in the relevant art and would readily be ascertained by the skilled artisan. As such, one of ordinary skill would readily appreciate and recognize that the dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the pharmaceutical compositions described herein.

[00176] In using a compound of the invention for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous or intraperitoneal administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used.

[00177] For the compounds of the present invention, oral administration is particularly suitable. The compounds of the present invention may be formulated as a tablet, capsule or solution for oral administration. Suitably, the compound of the present invention is formulated in a unit dosage form (e.g. a tablet or capsule) for oral administration. Typically, unit dosage forms will contain about 0.5 mg to 1.5 g of a compound of this invention.

Synthesis

[00178] The compounds of the present invention can be prepared by any suitable technique known in the art. Particular methods for forming compounds of formula I defined herein are shown below and in the accompanying examples.

[00179] In the description of the synthetic methods described herein and in any referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

[00180] It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilised.

[00181] It will be appreciated that during the synthesis of the compounds of the invention in the processes defined herein, or during the synthesis of certain starting materials, it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

[00182] For Examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule.

[00183] Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[00184] By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as, but not limited to, acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or tbutoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as, but not limited to, an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

[00185] A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting

groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively, an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[00186] A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a t-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[00187] Resins may also be used as a protecting group.

[00188] The methodology employed to synthesise a compound of formula (I) will vary depending on the nature of R_1, Q, R_a, R_b, R_c, R_d and R_e and any substituent groups associated therewith. Suitable processes for their preparation are described further in the accompanying Examples.

[00189] Once a compound of formula (I) has been synthesised by any one of the processes defined herein, the processes may then further comprise one or more of the additional steps of:

(i) removing any residual protecting groups present; or optionally converting any COOMe groups present (e.g. in the R_1 position) to $CONH_2$;

(ii) converting the compound formula (I) into another compound of formula (I);

(iii) forming a pharmaceutically acceptable salt, hydrate or solvate of the compound of formula I; and/or

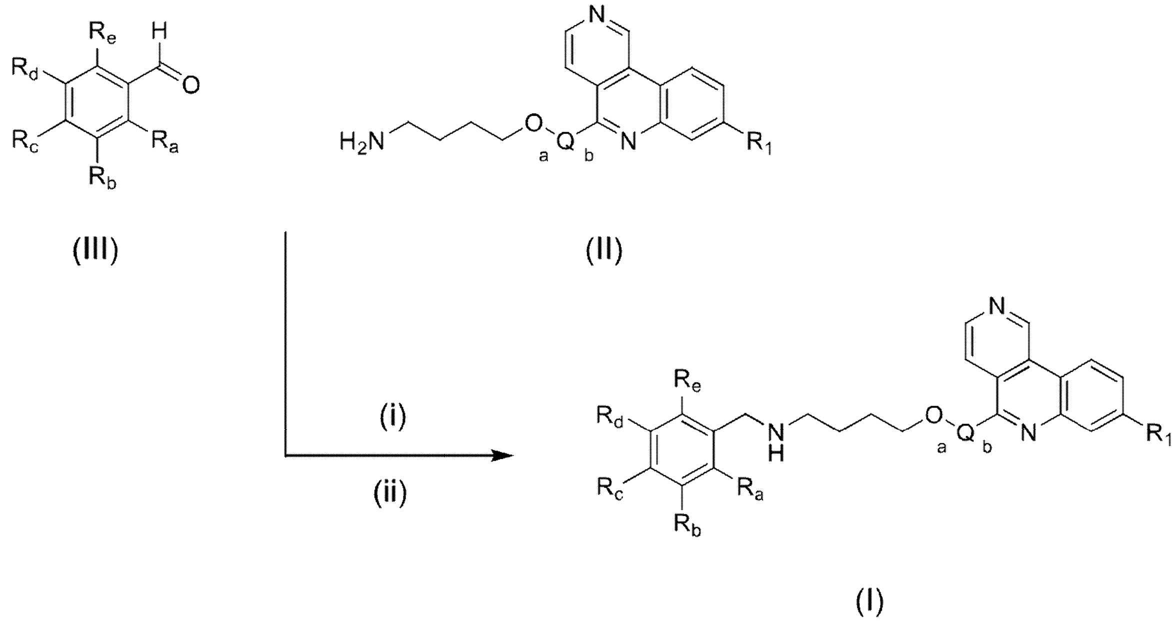
(iv) forming a prodrug of the compound of formula I.

[00190] An Example of (ii) above is when a compound of formula (I) is synthesised and then one or more of the groups of R_1, Q, R_a, R_b, R_c, R_d and R_e may be further reacted to change the nature of the group and provide an alternative compound of formula (I).

[00191] The resultant compounds of formula (I) can be isolated and purified using techniques well known in the art.

[00192] According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I) as hereinbefore described which comprises:

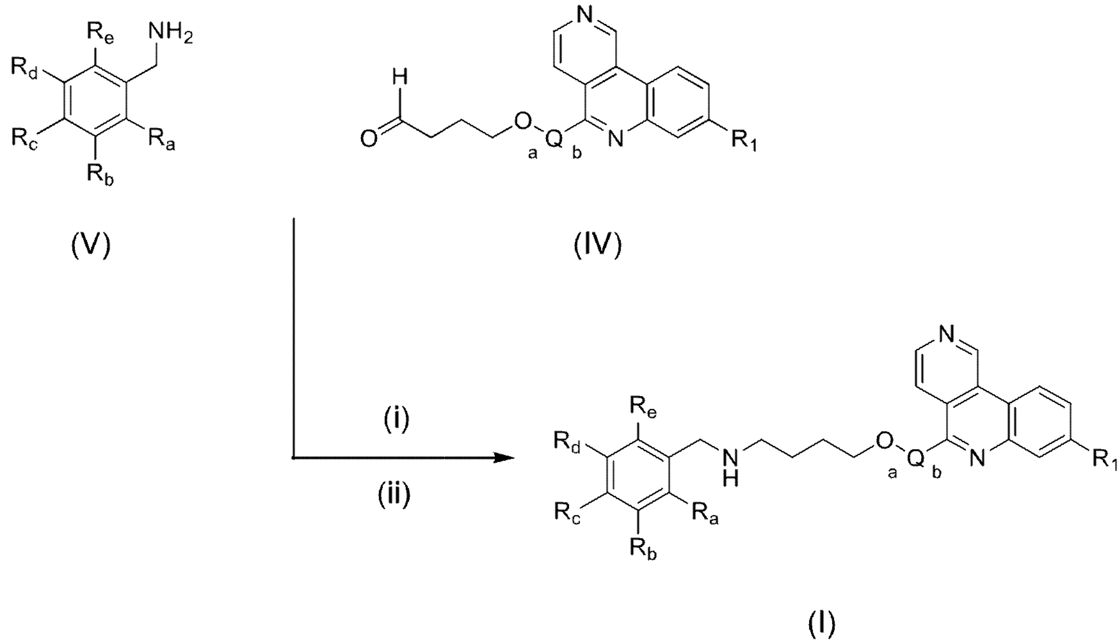
(a) preparing a compound of formula (I) by reacting a compound of formula (III) with a compound of formula (II), where, if necessary, followed by a suitable deprotection step:



Scheme 1

wherein $_{a}Q_{b}$ and $R_{a\text{-}e}$ are as hereinbefore described, and R_1 may be $-CONH_2$, $-CO_2H$ or CO_2PG, a protected form of $-CO_2H$, wherein PG is methyl; or

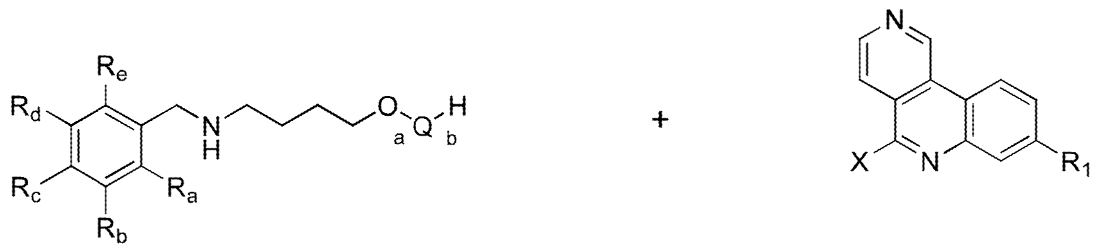
(b) preparing a compound of formula (I) by reacting a compound of formula (IV) with a compound of formula (V), where, if necessary, followed by a suitable deprotection step:



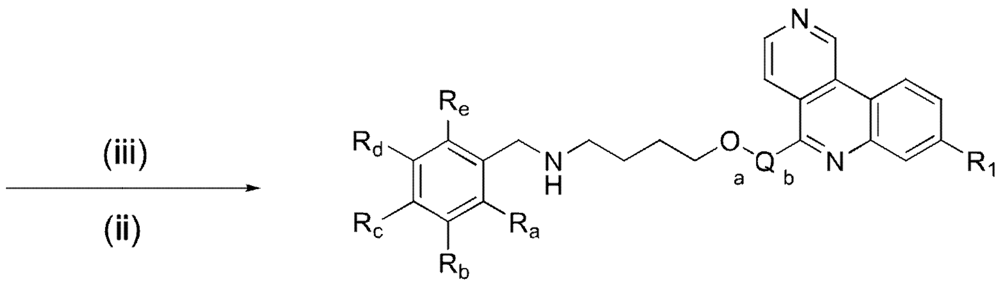
Scheme 2

wherein ${}_aQ_b$ and $R_{a\text{-}e}$ are as hereinbefore described, and R_1 may be -$CONH_2$, -CO_2H or CO_2PG, a protected form of -CO_2H, wherein PG is methyl; or

(c) preparing a compound of formula (I) by reacting a compound of formula (VII) with a compound of formula (VI), where, if necessary, followed by a suitable deprotection step:



(VII) (VI)



(I)

Scheme 3

wherein ${}_aQ_b$ and $R_{a\text{-}e}$ are as hereinbefore described, and R_1 may be -$CONH_2$, -CO_2H or CO_2PG (wherein PG is methyl), a protected form of -CO_2H,

[00193] In process (a) above:

Step (i) comprises a reductive amination step, which typically comprises formation of an imine in an alcoholic solvent, either with or without acid or base, followed by reduction with a hydride-based reagent. Preferred conditions comprise sodium triacetoxyborohydride or sodium cyanoborohydride in methanol either with or without sodium acetate or DIPEA at from 0 °C to 50 °C.

When R_1 is -CO_2PG, step (ii) comprises a hydrolysis reaction with a suitable inorganic hydroxide in a mixture of water and an alcoholic solvent. Preferred conditions comprise lithium hydroxide in methanol with water at room temperature.

[00194] In process (b) above:

Step (i) and step (ii) comprise a reductive amination step followed by a suitable deprotection step if necessary, as described in process (a).

[00195] In process (c) above:

Step (iii) comprises an aromatic substitution reaction which typically comprises a base in a suitable organic solvent. Preferred conditions comprise NaH in THF at from 0 °C to 60 °C.

Where a protecting group is employed, step (ii) comprises a deprotection reaction. Where PG is a Boc group, preferred conditions comprise HCl in 1,4-dioxane.

[00196] Compounds of formula (II), (III), (IV), (V), (VI) or (VII) are either commercially available, prepared according to the methods described herein, or prepared according to the literature.

Therapeutic Uses and Applications

[00197] The compounds of the present invention are potent inhibitors of Casein Kinase 2 alpha (CK2α). Data showing the CK2α inhibition for the exemplified compounds is presented in the accompanying example section.

[00198] The compounds of the present invention are designed to bind to the catalytic ATP site of CK2α (to drive potent enzyme inhibition) and the αD site (to drive high levels of selectivity over other kinases) [Brear *et al*, Chem Sci 2016].

[00199] Accordingly, the compounds of formula I are useful for the treatment and/or prevention of diseases and conditions in which CK2α activity is implicated, such as, for example, but not limited to, the treatment and/or prevention of proliferative disorders (e.g. cancer), viral infections, inflammation, diabetes, vascular and ischemic disorders, neurodegeneration and the regulation of circadian rhythm.

[00200] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in therapy.

[00201] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a disease or condition in which CK2α activity is implicated.

[00202] In another aspect, the present invention provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of a disease or condition in which CK2α activity is implicated.

[00203] In another aspect, the present invention provides a method of treating a disease or condition in which CK2α activity is implicated, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[00204] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a disease or condition associated with aberrant activity of CK2α.

[00205] In another aspect, the present invention provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of a disease or condition associated with aberrant activity of CK2α.

[00206] In another aspect, the present invention provides a method of treating a disease or condition associated with aberrant activity of CK2α, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[00207] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of proliferative disorders (e.g. cancer or benign neoplasms), viral infections, an inflammatory disease or condition, diabetes, vascular and ischemic disorders, neurodegenerative disorders and/or the regulation of circadian rhythm.

[00208] In another aspect, the present invention provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of proliferative disorders (e.g. cancer or benign neoplasms), viral infections, an inflammatory disease or condition, diabetes, vascular and ischemic disorders, neurodegenerative disorders and/or the regulation of circadian rhythm.

[00209] In another aspect, the present invention provides a method of treating a proliferative disorder (e.g. cancer or benign neoplasms), a viral infection, an inflammatory disease or condition, diabetes, vascular and ischemic disorders, neurodegenerative disorders and/or regulating cardiac rhythm, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[00210] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a proliferative disorder.

[00211] In another aspect, the present invention provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of a proliferative disorder (e.g. cancer or a benign neoplasms).

[00212] In another aspect, the present invention provides a method of treating a proliferative disorder (e.g. cancer or benign neoplasms), said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[00213] The terms "proliferative disorder" and “proliferative condition” are used interchangeably herein and pertain to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether *in vitro* or *in vivo*.

[00214] Examples of proliferative conditions include, but are not limited to, pre-malignant and malignant cellular proliferation, including but not limited to, cancers, psoriasis, bone diseases, fibroproliferative disorders (e.g. of connective tissues), and atherosclerosis. Any type of cell may be treated, including but not limited to, lung, colon, breast, ovarian, prostate, liver, pancreas, brain, blood and skin.

[00215] In certain aspects of the present invention, the proliferative disorder is cancer, suitably a cancer selected from lung, colon/colorectal, breast, ovarian, prostate, liver, pancreas, brain, blood, cholangiocarcinoma and skin cancer.

[00216] In a particular aspect of the invention, the proliferative disorder is colon/colorectal, cholangiocarcinoma, ovarian or prostate cancer.

[00217] In a particular aspect of the invention, the proliferative disorder is colorectal cancer.

[00218] In certain aspects of the present invention, the proliferative disorder is hematopoietic tumour, including: myelogenous and granulocytic leukemia (malignancy of the myeloid and granulocytic white blood cell series); lymphatic, lymphocytic, and lymphoblastic leukemia (malignancy of the lymphoid and lymphocytic blood cell series); polycythemia vera and erythremia (malignancy of various blood cell products, but with red cells predominating); and myelofibrosis.

[00219] A benign neoplasm may be, for example, hemangiomas, hepatocellular adenoma, cavernous haemangioma, focal nodular hyperplasia, acoustic neuromas, neurofibroma, bile duct adenoma, bile duct cystanoma, fibroma, lipomas, leiomyomas, mesotheliomas, teratomas, myxomas, nodular regenerative hyperplasia, trachomas, pyogenic granulomas, moles, uterine fibroids, thyroid adenomas, adrenocortical adenomas or pituitary adenomas. The benign neoplasm may be endometrial implants or a keratocystic odontogenic tumor.

[00220] In another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a cancer.

[00221] In another aspect, the present invention the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of a cancer.

[00222] In another aspect, the present invention provides a method of treating cancer, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[00223] The cancer may be non-metastatic or metastatic and which may be a solid tumour or a haematological ("liquid") cancer. The cancer may, for example, be selected from:

(1) Carcinoma, including for example tumours derived from stratified squamous epithelia (squamous cell carcinomas) and tumours arising within organs or glands (adenocarcinomas). Examples include breast, colon, lung, prostate, ovary, esophageal carcinoma (including, but not limited to, esophageal adenocarcinoma and squamous cell carcinoma), basal-like breast carcinoma, basal cell carcinoma (a form of skin cancer), squamous cell carcinoma (various tissues), head and neck carcinoma (including, but not limited to, squamous cell carcinomas), stomach carcinoma (including, but not limited to, stomach adenocarcinoma, gastrointestinal stromal tumor), signet ring cell carcinoma, bladder carcinoma (including transitional cell carcinoma (a malignant neoplasm of the bladder)), bronchogenic carcinoma, colorectal carcinoma (including, but not limited to, colon carcinoma and rectal carcinoma), anal

carcinoma, gastric carcinoma, lung carcinoma (including but not limited to small cell carcinoma (SCLC) and non-small cell carcinoma of the lung (NSCLC), lung adenocarcinoma, squamous cell carcinoma, large cell carcinoma, bronchioloalveolar carcinoma, and mesothelioma), neuroendocrine tumors (including but not limited to carcinoids of the gastrointestinal tract, breast, and other organs), adrenocortical carcinoma, thyroid carcinoma, pancreatic carcinoma (including, but not limited to, pancreatic ductal adenocarcinoma, pancreatic adenocarcinoma, acinar cell carcinoma, intraductal papillary mucinous neoplasm with invasive carcinoma, mucinous cystic neoplasm with invasive carcinoma, islet cell carcinoma and neuroendocrine tumors), breast carcinoma (including, but not limited to, ductal carcinoma, lobular carcinoma, inflammatory breast cancer, clear cell carcinoma, mucinous carcinoma), ovarian carcinoma (including, but not limited to, ovarian epithelial carcinoma or surface epithelial-stromal tumor including serous tumor, endometrioid tumor and mucinous cystadenocarcinoma, sex-cord-stromal tumor), liver and bile duct carcinoma (including, but not limited to, hepatocellular carcinoma, cholangiocarcinoma and hemangioma), prostate carcinoma, adenocarcinoma, brain tumours (including, but not limited to glioma, glioblastoma and medulloblastoma), germ cell tumors, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, kidney carcinoma (including, but not limited to, renal cell carcinoma, clear cell carcinoma and Wilm's tumor), medullary carcinoma, ductal carcinoma in situ or bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, cervical carcinoma, uterine carcinoma (including, but not limited to, endometrial adenocarcinoma, uterine papillary serous carcinoma, uterine clear-cell carcinoma, uterine sarcomas and leiomyosarcomas, mixed mullerian tumors), testicular carcinoma, osteogenic carcinoma, epithelial carcinoma, sarcomatoid carcinoma, nasopharyngeal carcinoma, laryngeal carcinoma; oral and oropharyngeal squamous carcinoma;

(2) Sarcomas, including: osteosarcoma and osteogenic sarcoma (bone); chondrosarcoma (cartilage); leiomyosarcoma (smooth muscle); rhabdomyosarcoma (skeletal muscle); mesothelial sarcoma and mesothelioma (membranous lining of body cavities); fibrosarcoma (fibrous tissue); angiosarcoma and hemangioendothelioma (blood vessels); liposarcoma (adipose tissue); glioma and astrocytoma (neurogenic connective tissue found in the brain); myxosarcoma (primitive embryonic connective tissue); chordoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, Ewing's sarcoma, mesenchymous and mixed mesodermal tumor (mixed connective tissue types) and other soft tissue sarcomas;

(3) Myeloma and multiple myeloma;

(4) Hematopoietic tumours, including: myelogenous and granulocytic leukemia (malignancy of the myeloid and granulocytic white blood cell series); lymphatic, lymphocytic, and

lymphoblastic leukemia (malignancy of the lymphoid and lymphocytic blood cell series); polycythemia vera and erythremia (malignancy of various blood cell products, but with red cells predominating); myelofibrosis.

(5) Lymphomas, including: Hodgkin and Non-Hodgkin lymphomas;

(6) Solid tumors of the nervous system including medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma and schwannoma;

(7) Melanoma, uveal melanoma and retinoblastoma; and

(8) Mixed Types, including, e.g., adenosquamous carcinoma, mixed mesodermal tumor, carcinosarcoma or teratocarcinoma.

[00224] Suitably, a compound of the invention, or a pharmaceutically acceptable salt thereof may be for use in the treatment of a cancer selected from cancer selected from lung, colon/colorectal, breast, ovarian, prostate, liver, pancreas, brain, blood, cholangiocarcinoma and skin cancer.

[00225] More suitably, the cancer is selected from colon/colorectal cancer, prostate cancer, ovarian cancer or cholangiocarcinoma.

[00226] In a particular aspect of the present invention, the cancer is colorectal cancer.

[00227] In a particular aspect of the present invention, the cancer is cholangiocarcinoma.

[00228] In another aspect of the present invention, the cancer is a hematopoietic tumour.

[00229] It is hypothesised that the compounds of the present invention will be particularly suited to the treatment of wnt pathway mutated cancers, e.g. wnt pathway mutated colorectal cancer or cholangiocarcinoma (Di Maira *et al*, 2019).

[00230] In addition to CK2α having a very well characterized function in wnt pathway activity, it also plays a role in other key cellular pathways known to be upregulated in cancer, such as, but not limited to, the DNA damage response (Ruzzene & Pinna, 2010; Montenarh, Transl. Cancer Res 2016). Thus, the compounds of the present invention may have a further use in the treatment of PARP insensitive tumors in prostate/ovarian cancer.

[00231] CK2a has also recently been identified as a key host protein required for viral replication (e.g. in SARS-CoV2) and as such could represent an antiviral treatment (Gordon *et al*. Nature 2020).

[00232] Thus, in another aspect, the present invention provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a viral infection.

[00233] In another aspect, the present invention provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for use in the treatment of a viral infection.

[00234] In another aspect, the present invention provides a method of treating a viral infection, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[00235] Suitably, the virus is a coronavirus, e.g. SARS-CoV2.

Routes of Administration

[00236] The compounds of the invention or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

[00237] Routes of administration include, but are not limited to, oral (e.g. by ingestion); buccal; sublingual; transdermal (e.g. by a patch, plaster, etc.); transmucosal (e.g. by a patch, plaster, etc.); intranasal (e.g. by nasal spray); ocular (e.g. by eye drops, eye ointment etc.); pulmonary (e.g. by inhalation or insufflation therapy, for example via an aerosol, for example by the nose or mouth); rectal (e.g. by suppository or enema); vaginal (e.g. by pessary); parental, for example by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir dosage form, for example subcutaneously or intramuscularly.

[00238] The compounds of the present invention are particularly suitable for oral administration.

Combination Therapies

[00239] The compounds of the invention and salts, solvates thereof defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, one or more additional therapeutic agents, e.g. an anti-tumour agent.

[00240] In the context of cancer treatment, in addition to the compound of the invention therapy may involve conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

- other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as, but not limited to, alkylating agents (for example cisplatin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as, but not limited to, fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

- cytostatic agents such as, but not limited to, antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as, but not limited to, finasteride;

- anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase];

- inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* (Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as, but not limited to, *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as, but not limited to, lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as, but not limited to, imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as, but not limited to, farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336)), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as, but not limited to, CDK2 and/or CDK4 inhibitors;

- antiangiogenic agents such as, but not limited to, those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such as, but not limited to, vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as, but not limited to, those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin)];

- vascular damaging agents such as, but not limited to, Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669,
WO 01/92224, WO 02/04434 and WO 02/08213;

- an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

- antisense therapies, for example those which are directed to the targets listed above, such as, but not limited to, ISIS 2503, an anti-ras antisense;

- gene therapy approaches, including for example approaches to replace aberrant genes such as, but not limited to, aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as, but not limited to, those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

- immunotherapy approaches, including for example *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumour cells, such as, but not limited to, transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as, but not limited to, cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

[00241] In a particular embodiment, the antiproliferative treatment defined hereinbefore may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy.

[00242] In a further particular embodiment, the antiproliferative treatment defined hereinbefore may involve, in addition to the compound of the invention, standard chemotherapy for the cancer concerned.

[00243] In a particular embodiment, the antiproliferative treatment defined hereinbefore may involve, in addition to the compound of the invention, therapy with K-ras inhibitors and/or DNA damage repair inhibitors (e.g. PARP inhibitors).

[00244] Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

[00245] According to this aspect of the invention there is provided a combination for use in the treatment of a cancer (for example a cancer involving a solid tumour) comprising a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and another anti-tumour agent.

[00246] According to this aspect of the invention there is provided a combination for use in the treatment of a proliferative condition, such as, but not limited to, cancer (for example a cancer involving a solid tumour), comprising a compound of the invention as defined hereinbefore, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and any one of the anti-tumour agents listed herein above.

[00247] In a further aspect of the invention there is provided a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate thereof, for use in the treatment of cancer in combination with another anti-tumour agent, optionally selected from one listed herein above.

[00248] Herein, where the term “combination” is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention “combination” refers to simultaneous administration. In another aspect of the invention “combination” refers to separate administration. In a further aspect of the invention “combination” refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination. In one embodiment, a combination refers to a combination product.

[00249] According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the invention, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in combination with an anti-tumour agent (optionally selected from one listed herein above), in association with a pharmaceutically acceptable diluent or carrier.

Biological Activity

[00250] The biological assay described in the example section (Biological Assay 1) may be used to measure the pharmacological effects of the compounds of the present invention.

[00251] Although the pharmacological properties of the compounds of formula I vary with structural change, as expected, the compounds of the invention were found to be active in the assays described in Biological Assay 1. In general, the compounds of the invention demonstrate an IC_{50} of 500 nM or less in the assay described in Biological Assay 1, with preferred compounds of the invention demonstrating an IC_{50} of 100 nM or less and the most preferred compounds of the invention demonstrating an IC_{50} of 30 nM or less.

[00252] Compounds of the invention may also show activity in Assay 3 described in the accompanying Biological Assay section.

EXAMPLES

[00253] The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples. Compounds are named using conventional IUPAC nomenclature, or as named by the chemical supplier.

[00254] The following synthetic procedures are provided for illustration of the methods used; for a given preparation or step the precursor used may not necessarily derive from the individual batch synthesized according to the step in the description given.

Analytical Methods (AM)

[00255] Where examples and preparations cite analytical data, the following analytical methods were used unless otherwise specified.

[00256] All **LCMS** spectra were obtained by using one of the below methods.

Method 1 (AM1): (5-95 A-B_1.5 min_220 & 254 nm): Instrument: Agilent 1100\G1956A; Column: Kinetex@ 5um EVO C18 30 × 2.1 mm× 5 μm; Run Time: 1.5 min; Solvents: A) 0.0375% TFA in water (v/v), B) 0.01875% TFA in acetonitrile (v/v). The gradient runs with 5% B; Gradient: 5-95% B with A, 0.8 min; hold at 95% B to 1.2 min; 5% B at 1.21 min and hold at 5% B to1.5 min @ 1.5 mL/min, 50°C.

Method 2 (AM2): (5-95 A-B_1.5 min_220 & 254 nm): Instrument: Agilent 1200\G6110A; Column: Kinetex@ 5um EVO C18 30 × 2.1 mm× 5 μm; Run Time: 1.5 min; Solvents: A) 0.0375% TFA in water (v/v), B) 0.01875% TFA in acetonitrile (v/v). The gradient runs with 5% B; Gradient: 5-95% B with A, 0.8 min; hold at 95% B to 1.2 min; 5% B at 1.21 min and hold at 5% B to1.5 min @ 1.5 mL/min, 50°C.

Method 3 (AM3): (5–95 A–B_1.55 min_220 & 254 nm): Instrument: SHIMADZU **LCMS**-2020; Column: Kinetex EVO C18 30 × 2.1 mm× 5 μm; Run Time: 1.55 min; Solvents: A) 0.0375% TFA in water (v/v), B) 0.01875% TFA in acetonitrile (v/v). The gradient runs with 5% B; Gradient: 5–95% B with A, 0.8 min; hold at 95% B to 1.2 min; 5% B at 1.21 min and hold at 5% B to 1.55 min @ 1.5 mL/min, 50°C.

Method 4 (AM4): (5–95 A–B_1.5 min_220 & 254 nm): Instrument: Agilent 1200 LC/G1956A MSD; Column: Kinetex EVO C18 30 × 2.1 mm× 5 μm; Run Time: 1.5 min; Solvents: A) 0.0375% TFA in water (v/v), B) 0.01875% TFA in acetonitrile (v/v). The gradient runs with 5% B; Gradient: 5–95% B with A, 0.8 min; hold at 95% B to 1.2 min; 5% B at 1.21 min and hold at 5% B to 1.5 min @ 1.5 mL/min, 50°C.

Method 5 (AM5): (0-60 A–B_1.55 min_220 & 254 nm): Instrument: SHIMADZU **LCMS**-2020; Column: Kinetex EVO C18 30 × 2.1 mm× 5 μm; Run Time: 1.55 min; Solvents: A) 0.0375% TFA in water (v/v), B) 0.01875% TFA in ACN (v/v). The gradient runs with 0% B; Gradient: 0–60% B with A, 0.8 min; hold at 60% B to 1.20 min; 0% B at 1.21 min and hold at 0% B to 1.55 min @ 1.5 mL/min, 50°C.

Method 6 (AM6): (0–60 C–D_2.20 min_220 & 254 nm): Instrument: SHIMADZU **LCMS**-2020; Column: Kinetex EVO C18 30 × 2.1 mm× 5 μm; Run Time: 2.20 min; Solvents: A) 0.025% NH3·H2O in water (v/v), B) acetonitrile. The gradient runs with 0% B; Gradient: 0–60% B with A, 1.2 min; hold at 60% B to 1.6 min; 0% B at 1.61 min and hold at 0% B to 2.2 min @ 1.5 mL/min, 40°C.

Method 7 (AM7): (5-95 C–D_1.5 min_R_220&254_POS): Instrument: SHIMADZU **LCMS**-2020; Column: Kinetex EVO C18 30 × 2.1 mm× 5 μm; Run Time: 1.5 min; Solvents A) 0.025% NH3·H2O in water（v/v） B) Acetonitrile. The gradient runs with 5% B. Gradient: 5-95% B with A 0.8 min, hold at 95% B to 1.2 min; 5% B at 1.21 min and hold at 5% B to 1.5 min @ 1.5 ml/min, 40°C.

Method 8 (AM8): (10–80 C–D_2.00 min_220 & 254 nm): Instrument: Agilent 1200\G6110A; Column: ACE Excel 5 C18 30 × 2.1 mm× 5 μm; Run Time: 2.00 min; Solvents: A) 0.025% NH_3•H_2O in water (v/v), B) Acetonitrile (v/v). The gradient runs with 10% B; Gradient: 10–80% B with A, 1.2 min; hold at 80% B to 1.6 min; 10% B at 1.61 min and hold at 10% B to 2.00 min @ 1.0 mL/min, 40°C.

Method 9 (AM9): (10–80 A–B_7 min_220 & 254 nm): Instrument: SHIMADZU **LCMS**-2020; Column: AB:Xtimate C18 30 × 2.1 mm× 3 μm; Run Time: 7.0 min; Solvents: A) 0.0375% TFA in water (v/v), B) 0.01875% TFA in acetonitrile (v/v). The gradient runs with 10% B; Gradient: 10–80% B with A, 6.5 min; hold at 80% B to 7 min; 10% B at 6.5 min and hold at 10% B to 7 min @ 1.5 mL/min, 50°C.

^{1}H NMR spectra were acquired on a Bruker Avance Ⅲ spectrometer at 400 MHz using residual undeuterated solvent as reference, and annotated using ACD Labs.

Purification Methods (PM)

Chromatography

Purification method	Column	Eluent	Eluent Ratio
PM1	SiO_2	PE	1
PM2	SiO_2	PE:EA	1:1
PM3	SiO_2	PE:EA	2:1
PM4	SiO_2	PE:EA	3:1
PM5	SiO_2	PE:EA	4:1
PM6	SiO_2	PE:EA	5:1
PM7	SiO_2	PE:EA	10:1
PM8	SiO_2	PE:EA	13:1

PM9	SiO_2	PE:EA	15:1
PM10	SiO_2	PE:EA	16:1
PM11	SiO_2	PE:EA	20:1
PM12	SiO_2	PE:EA	30:1
PM13	SiO_2	PE:EA	40:1
PM14	SiO_2	PE:EA	50:1
PM15	SiO_2	PE:EA	60:1
PM16	SiO_2	PE:EA	80:1
PM17	SiO_2	PE:EA	100:1
PM18	SiO_2	PE:EA	200:1

Reverse-phase HPLC conditions

Purification Method (PM)	Column	Mobile phase	Gradient
PM19	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.05% HCl)-ACN	55%–75%, 12 min
PM20	Phenomenex luna C18 250 × 50 mm × 10 μm	water (0.1% TFA)–ACN	50%–70%, 10 min
PM21	Phenomenex luna C18 250 × 50 mm × 10 μm	water (0.1% TFA)–ACN	20%–40%, 10 min
PM22	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)–ACN]	10%–90%, 20 min
PM23	Waters Xbridge 150 × 25 mm × 5 μm	water (10 mM NH_4HCO_3)–ACN	11%–44%, 11 min
PM24	Phenomenex luna C18 250 × 50 mm × 10 μm	water (0.1% TFA)–ACN	15%–45%, 10 min
PM25	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.075% TFA)–ACN	12%–42%, 9 min
PM26	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.075% TFA)–ACN	5%–35%, 9 min
PM27	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	20%–40%, 10 min
PM28	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.075% TFA)–ACN	10%–40%, 9 min
PM29	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	22%–42%, 10 min
PM30	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	25%–45%, 10 min
PM31	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	15%–35%, 10 min
PM32	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	12%–32%, 10 min
PM33	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.1% TFA)–ACN	15%–45%, 7 min
PM34	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.1% TFA)–ACN	12%–42%, 7 min

PM35	Phenomenex luna C18 250 × 50 mm × 10 μm	water (0.1% TFA)–ACN	15%–45%, 9 min)
PM36	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.1% TFA)–ACN	1%–30%, 7 min
PM37	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	18%–38%, 10 min
PM38	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	18%–38%, 20 min
PM39	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.1% TFA)–ACN	2%–32%, 7 min
PM40	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	1%–22%, 10 min
PM41	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.1% TFA)–ACN	8%–38%, 7 min
PM42	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.1% TFA)–ACN	15%–25%, 7min
PM43	Welch Xtimate C18 150 × 40 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	13%-43%, 10 min
PM44	Welch Xtimate C18 150 × 40 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	5%–25%, 10 min
PM45	Welch Xtimate C18 150 × 40 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	2%–32%, 10 min
PM46	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.1% TFA)–ACN	20%–30%, 7 min
PM47	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	10%–90%, 20 min
PM48	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	12%–32%, 10 min
PM49	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.1% TFA)–ACN	22%–32%, 7 min
PM50	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.1% TFA)–ACN	18%–28%, 7min
PM51	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.1% TFA)–ACN	12%–22%, 7 min
PM52	Waters Xbridge 150 × 50 mm × 10 μm	water (10 mM NH_4HCO_3)–ACN	10%–40%, 10 min
PM53	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)-ACN	6%–36%, 10 min
PM54	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)-ACN	23%–50%, 7 min
PM55	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)-ACN	5%–33%, 7 min
PM56	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	18%–38%, 20 min
PM57	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonia hydroxide v/v)-ACN	25%–55%, 10 min
PM58	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	8%–28%, 10 min
PM59	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	15%–45%, 8.5 min

PM60	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	25%–55%, 8.5 min
PM61	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	28%–58%, 8.5 min
PM62	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	0%–30%, 8.5 min
PM63	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	5%–35%, 8.5 min
PM64	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	20%–50%, 8.5 min
PM65	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	10%–40%, 10 min
PM66	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	18%–48%, 8.5 min
PM67	Phenomenex luna C18 150 × 40 mm × 15 μm	water (0.225% FA)–ACN	14%–44%, 11 min
PM68	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 μm	water (0.225% FA)–ACN	1%–30%, 10 min
PM69	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	3%–33%, 8.5 min
PM70	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	2%–32%, 10 min
PM71	Shim-pack C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	8%–38%, 10 min
PM72	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	1%–30%, 10 min
PM73	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 μm	water (0.225% FA)–ACN	1%–25%, 10 min
PM74	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	3%–33%, 10 min
PM75	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	7%–35%, 10 min
PM76	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	7%–37%, 10 min
PM77	Welch Xtimate C18 150 × 30 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	5%–35%, 11.5 min
PM78	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	7%–37%, 10 min
PM79	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	8%–38%, 11 min
PM80	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	10%–40%, 11 min
PM81	Welch Xtimate C18 150 × 30 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	6%–36%, 11.5 min
PM82	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% ammonium hydroxide v/v)–ACN	10%–90%, 20 min
PM83	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	6%–36%, 11 min
PM84	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	38%–68%, 11 min

PM85	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	26%–55%, 9 min
PM86	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	27%–57%, 9 min
PM87	Waters Xbridge 150 × 25 mm × 5 μm	water (10 mM NH_4HCO_3)–CAN	11%–41%, 10 min
PM88	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	19%–49%, 10 min
PM89	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	13%–43%, 10 min
PM90	Welch Ultimate XB-SiOH 250 × 50 mm × 10 μm	Heptane–EtOH (0.1% ammonium hydroxide)	35%–75%, 10 min
PM91	Phenomenex luna C18 150 ´ 25 mm ´ 10 mm	water (0.1% TFA)-ACN	23%-53%, 11 min
PM92	Welch Xtimate C18 150 × 30 mm × 5 μm	water (10 mM NH_4HCO_3)–ACN	20%–50%, 11.5 min
PM93	Welch Ultimate XB-CN 250 × 70 mm × 10 μm	Heptane–EtOH (0.1% ammonium hydroxide)	40%–80%, 10 min
PM94	Welch Xtimate C18 150 × 30 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	14%–44%, 11.5 min
PM95	Welch Ultimate XB-SiOH 250 × 50 mm × 10 μm	0.1% ammonium hydroxide in EtOH, Hexane–EtOH	25%–65%, 15 min
PM96	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	7%–37%, 10 min
PM97	Welch Ultimate XB-SiOH 250 × 50 mm × 10 μm	0.1% ammonium hydroxide in EtOH, Hexane–EtOH	20%–60%, 15 min
PM98	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	32%–62%, 11 min
PM99	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	30%–60%, 11 min
PM100	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	34%–64%, 11.5 min
PM101	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	10%–40%, 11 min
PM102	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	13%–43%, 11 min
PM103	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	8%–38%, 11 min
PM104	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	17%–47%, 11 min
PM105	Welch Ultimate XB-CN 250 × 70 mm × 10 μm	Hexane–EtOH	40%–80%, 15 min
PM106	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	5%–35%, 10 min
PM107	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	3%–33%, 10 min
PM108	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	30%–60%, 7 min

PM109	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	8%–38%, 7 min
PM110	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	27%–57%, 7 min
PM111	Waters Xbridge 150 × 50 mm × 10 μm	water (10 mM NH_4HCO_3)–ACN	16%–46%, 11 min
PM112	Waters Xbridge 150 × 50 mm × 10 μm	water (10 mM NH_4HCO_3)–ACN	20%–50%, 11 min
PM113	Waters Xbridge 150 × 50 mm × 10 μm	water (10 mM NH_4HCO_3)–ACN	22%–52%, 11 min
PM114	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	12%–42%, 7 min
PM115	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	14%–44%, 7 min
PM116	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	15%–45%, 7 min
PM117	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	13%–43%, 7 min
PM118	Waters Xbridge 150 × 25 mm × 5 μm	water (10 mM NH_4HCO_3)–ACN	17%–47%, 9 min
PM119	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN	25%–55%, 10 min
PM120	Phenomenex luna C18 150 × 40 mm × 15 μm	water (0.05% HCl)–ACN	10%–40%, 10 min
PM121	Shim-pack C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	17%–47%, 10 min
PM122	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)–ACN]	10%–90%, 20 min
PM123	Phenomenex luna C18 150 × 40 mm × 15 μm	water (0.05% HCl)–ACN	10%–40%, 10min
PM124	Welch Ultimate XB-SiOH 250 × 50 mm × 10 μm	Hexane–EtOH	30%–70%, 15 min
PM125	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammonium hydroxide v/v)–ACN	18%–48%, 11 min
PM126	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammoniam hydroxide v/v)-ACN	25%–55%, 11 min
PM127	Welch Ultimate XB-SiOH 250 × 50 mm × 10 μm	Hexane–EtOH	35%–75%, 15 min
PM128	Waters Xbridge 150 × 50 mm × 10 μm	water (0.05% ammoniam hydroxide v/v)-ACN	23%–53%, 11 min
PM129	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	6%–36%, 11.5 min
PM130	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	17%–47%, 10 min
PM131	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	21%–51%, 9 min
PM132	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	18%–48%, 9 min
PM133	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	10%–40%, 7 min

PM134	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	20%–50%, 7 min
PM135	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	1%-33%, 11 min
PM136	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.225% FA)–ACN	1%–30%, 7 min
PM137	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	24%–54%, 11.5 min
PM138	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	8%–38%, 10 min
PM139	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	11%-41%, 11.5 min
PM140	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	8%–38%, 11.5 min
PM141	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 μm	water (0.225% FA)–ACN	20%–40%, 10 min
PM142	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	6%–36%, 10 min
PM143	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	28%–58%, 10 min
PM144	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 μm	water (0.225% FA)–ACN	25%–45%, 10 min
PM145	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	11%–41%, 10 min
PM146	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	1%-31%, 10 min
PM147	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 μm	water (0.225% FA)–ACN	13%–33%, 10 min
PM148	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	13%–43%, 10 min
PM149	Waters Xbridge 150 × 25 mm × 5 μm	water (10 mM NH_4HCO_3)–ACN	15%–45%, 10 min
PM150	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% FA)–ACN]	10%–90%, 20 min
PM151	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% ammonium hydroxide)–ACN]	10%–90%, 20 min
PM152	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.05% ammonium hydroxide v/v)–ACN	45%–70%, 8 min
PM153	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	28%–58%, 10 min
PM154	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.225% FA)–ACN	8%–28%, 7 min
PM155	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.225% FA)–ACN	12%–32%, 7 min
PM156	Waters Xbridge 150 × 25 mm × 5 μm	water (10 mM NH_4HCO_3)–ACN	39%–69%, 10 min
PM157	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.225% FA)–ACN	9%–39%, 10 min
PM158	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.225% FA)–ACN	15%–45%, 7 min
PM159	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)–ACN	12%-42%, 10 min

PM160	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.225% FA)–ACN	12%–42%, 7 min
PM161	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.05% ammonium hydroxide v/v)–ACN	9%–39%, 10 min
PM162	Shim-pack C18 150 × 25 mm × 10 µm	water (0.225% FA)–ACN	22%–42%, 10 min
PM163	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.05% ammonium hydroxide v/v)–ACN	17%–47%, 7 min
PM164	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.225% FA)–ACN	1%–30%, 7 min
PM165	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.05% ammonium hydroxide v/v)–ACN	18%–48%, 10 min
PM166	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.225% FA)–ACN	12%–42%, 7 min
PM167	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.225% FA)–ACN	0%–25%, 7 min
PM168	Waters Xbridge 150 × 25 mm × 5 µm	water (0.05% ammonium hydroxide v/v)–ACN	43%-73%, 10 mins
PM169	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.225% FA)–ACN	8%–38%, 2 min
PM170	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.225% FA)–ACN	18%–48%, 7 min
PM171	Waters Xbridge 150 × 25 mm × 5 µm	water (10 mM NH_4HCO_3)–ACN	40%–70%, 9 min
PM172	Waters Xbridge 150 × 25 mm × 5 µm	water (0.05% ammonium hydroxide v/v)–ACN	12%-42%, 10 min
PM173	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.225% FA)–ACN	22%–52%, 7 min
PM174	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.225% FA)–ACN	20%–50%, 7 min
PM175	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.225% FA)–ACN	12%–42%, 2 min
PM176	Phenomenex luna C18 75 x 30 mm x 3 µm	water (0.1% TFA)–ACN]	46%-76%, 7 min
PM177	Waters Xbridge 150 × 25 mm × 5 µm	water (10 mM NH_4HCO_3)–ACN	22%–52%, 8 min
PM178	Phenomenex Synergi C18 150 × 25 mm × 10 µm	water (0.225% FA)–ACN	11%–41%, 10 min
PM179	Waters Xbridge 150 × 25 mm × 5 µm	water (10 mM NH_4HCO_3)–ACN	23%–53%, 10 min
PM180	Phenomenex Gemini-NX C18 75 × 30 mm × 3 µm	water (0.225% FA)–ACN	28%–38%, 7 min
PM181	Waters Xbridge 150 × 25 mm × 5 µm	water (10 mM NH_4HCO_3)–ACN	60%–90%, 8 min
PM182	Waters Xbridge 150 × 25 mm × 5 µm	water (10 mM NH_4HCO_3)–ACN	25%-55%, 7 min
PM183	Waters Xbridge 150 × 25 mm × 5 µm	water (10 mM NH_4HCO_3)–ACN	45%-75%, 7 min
PM184	Waters Xbridge 150 × 25 mm × 5 µm	water (0.05% ammonium hydroxide v/v)–ACN	13%-43%, 9 min

PM185	Waters Xbridge 150 × 25 mm × 5 μm	water (10 mM NH_4HCO_3)–ACN	24%-57%, 8 min
PM186	Waters Xbridge 150 × 25 mm × 5 μm	water (10 mM NH_4HCO_3)–ACN	32%-62%, 10 min
PM187	Waters Xbridge 150 × 25 mm × 5 μm	water (10 mM NH_4HCO_3)–ACN	29%-59%, 10 min
PM188	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	21%–51%, 10 min
PM189	Phenomenex luna C18 75 x 30 mm x 3 μm	water (0.1% TFA)–ACN]	25%-55%, 7 min
PM190	Phenomenex luna C18 150 x 40 mm x 15 μm	water (0.1% TFA)–ACN]	25%-55%, 11 min
PM191	Phenomenex luna C18 75 x 30 mm x 3 μm	water (0.1% TFA)–ACN]	30%–60%, 7 min
PM192	Waters Xbridge 150 × 25 mm × 5 μm	water (0.05% ammonium hydroxide v/v)–ACN	10%-40%, 9min
PM193	Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm	water (0.225% FA)–ACN	25%–55%, 7 min
PM194	Phenomenex luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)–ACN]	16%–46%, 11 min

Abbreviations

[00257] Wherein the following abbreviations have been used, the following meanings apply:

ACN is acetonitrile,

AcOH is acetic acid,

$AlCl_3$ is aluminum chloride,

AM is analytical method,

aq. is aqueous,

9-BBN is 9-borabicyclo(3.3.1)nonane,

Boc_2O is di-tert-butyl dicarbonate,

Br_2 is bromine solution,

CBr_4 is carbon tetrabromide,

CDI is 1,1'-carbonyldiimidazole,

$CHCl_3$-*d* is deuterated chloroform,

$CsCO_3$ is cesium carbonate,

CsF is cesium fluoride,

CuI is copper iodide,

DCE is dichloroethane,

DCM is dichloromethane,

DIPEA is N,N-diisopropylethylamine,

DMAP is dimethylaminopyridine,

DME is 1,2-dimethoxyethane,

DMF is N,N-dimethylformamide,

DMP is Dess-Martin periodinane,

DMS is dimethylsulfide,

DMSO is dimethyl sulfoxide,

DMSO-d_6 is deuterated dimethyl sulfoxide,

dppf is 1,1'-ferrocenediyl-bis(diphenylphosphine),

EA is ethyl acetate,

EDCI is N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride,

EtOH is ethanol,

FA is formic acid,

Fmoc is 9-fluorenylmethoxycarbonyl,

h is hours,

NMR is Nuclear Magnetic Resonance

HATU is (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

HCl is hydrochloric acid,

HOBt is 1-hydroxybenzotriazole,

H_2O is water,

H_2O_2 is hydrogen peroxide,

HPLC is High Performance Liquid Chromatography,

KF is potassium fluoride,

K_2CO_3 is potassium carbonate,

K_2SO_4 is potassium sulphate,

LAH is lithium aluminum hydride,

LCMS is Liquid Chromatography Mass Spectrometry,

$LiOH.H_2O$ is lithium hydroxide monohydrate,

mCPBA is meta-chloroperoxybenzoic acid,

MeI is methyl iodide,

MeOH is methanol,

MeOH-d_4 is deuterated methanol,

min is minutes

MnO_2 is manganese dioxide,

MS is molecular sieves,

MTBE is methyltertbutylether,

N_2 is nitrogen gas,

NaH is sodium hydride,

NH_4Cl is ammonium chloride,

$NaHCO_3$ is sodium bicarbonate,

NaHMDS is sodium bis(trimethylsilyl)amide,

NaOH is sodium hydroxide,

NaOMe is sodium methoxide,

Na_2SO_4 is anhydrous sodium sulfate,

n-BuLi is n-butyllithium,

NCS is N-chlorosuccinimide,

$Pd(PPh_3)_4$ is tetrakis(triphenylphosphine)palladium(0),

$Pd(dppf)Cl_2$ is [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)

$Pd(dppf)Cl_2.CHCl_2$ is [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane

PE is petroleum ether,

PM is purification method,

$POCl_3$ is phosphorous oxychloride

rt is retention time,

SEM is silylethoxymethyl,

$SOCl_2$ is thionyl chloride,

TBAC is tetrabutylammonium chloride,

TBAF is tetrabutylammonium fluoride,

TBAI is tetramethylammonium iodide,

TEA is triethylamine,

TFA is trifluoroacetic acid,

TFAA is trifluoroacetic anhydride,

THF is tetrahydrofuran,

TLC is thin layer chromatography,

TMEDA is N'-tetramethylethylenediamine

TMSCN is trimethylsilyl cyanide,

T3P is propylphosphonic anhydride, and

$TsOH.H_2O$ is p-toluenesulfonic acid monohydrate.

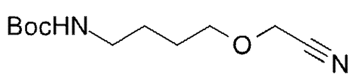
Preparation of Intermediates

[00258] The following Preparations describe the methods used for common intermediates required for synthesis of the Examples.

[00259] Compound 1.1 may be prepared according to the method described in J. Med. Chem. 2011, 54 (2), 635-654.

Synthesis of Intermediate E

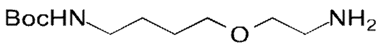
tert-butyl (4-(cyanomethoxy)butyl)carbamate 1.19



To a mixture of tert-butyl (4-hydroxybutyl)carbamate (7 g, 36.99 mmol) and 2-bromoacetonitrile (8.87 g, 73.98 mmol) in DCM (100 mL) was added silver(I) oxide (18.55 g, 80.05 mmol) and TBAI (2.94 g, 7.96 mmol) at 25 °C. The mixture was stirred at 25 °C for 16 h. The mixture was filtered, the filtrate washed with aq. $NaHCO_3$ (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified (PM7) to afford **compound 1.19** (1.0 g, 4.38 mmol, 11.8% yield) as a yellow oil.

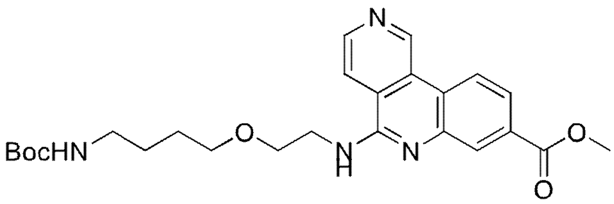
^1H NMR (CDCl3, 400 MHz) δ: 4.56 (br s, 1H), 4.24 (s, 2H), 3.62–3.59 (t, 2H), 3.18–3.13 (m, 2H), 1.71–1.63 (m, 2H), 1.58–1.53 (m, 2H), 1.45 (s, 9H) ppm.

tert-butyl (4-(2-aminoethoxy)butyl)carbamate 1.20



To a solution of **compound 1.19** (1.0 g, 4.38 mmol) in MeOH (10 mL) was added ammonium hydroxide (2 mL, 25% wt.) and Raney nickel (100 mg, 1.17 mmol) under nitrogen protection at 25 °C. The suspension was degassed under vacuum and purged with hydrogen three times. The mixture was stirred under hydrogen (45 psi) at 25 °C for 16 h. The mixture was filtered and the filtrate concentrated *in vacuo* to afford **compound 1.20** (1 g) as a green oil, which was used directly in the next step.

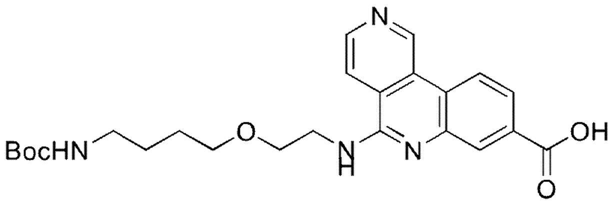
Methyl 5-((2-(4-((tert-butoxycarbonyl)amino)butoxy)ethyl)amino)benzo[c][2,6] naphthyridine-8-carboxylate, 1.58



To a solution of **compound 1.1** (3.20 g, 11.74 mmol) in DMSO (50 mL) was added DIPEA (3.03 g, 23.48 mmol) and **compound 1.20** (3 g, 12.91 mmol), sequentially at 25 °C. The reaction mixture was then heated to 75 °C and stirred for 12 h. The mixture was diluted with water (100 mL) and extracted with EA (100 mL × 2). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford **compound 1.58** (5 g) as a brown solid.

LCMS (AM3): rt = 0.841 min, (469.3 $[M+H]^+$), 63.4% purity.

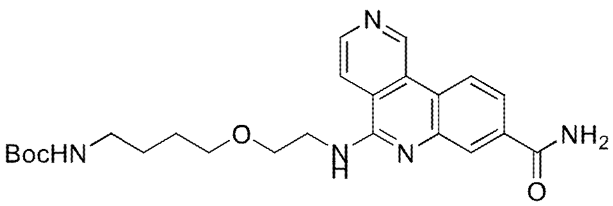
5-((2-(4-((tert-butoxycarbonyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid, 1.59



[00260] To a solution of **compound 1.58** (5 g, 10.67 mmol) in THF (15 mL), MeOH (15 mL) and water (15 mL) was added NaOH (853.65 mg, 21.34 mmol) at 20 °C. The reaction mixture was then stirred at 20 °C for 4 h. The organic solvents were concentrated *in vacuo* and the remaining aqueous solution was acidified with aq. HCl (1 N) to pH5. The resulting precipitate was collected by filtration and dried under vacuum to afford **compound 1.59** (4.5 g) as a brown solid.

LCMS (AM3): rt = 0.808 min, (455.3 $[M+H]^+$), 88.98% purity.

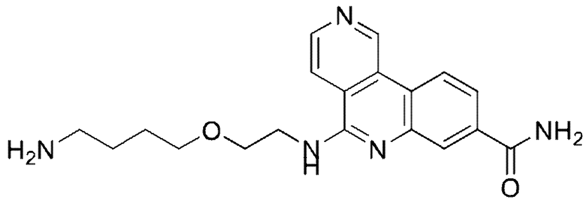
tert-butyl (4-(2-((8-carbamoylbenzo[c][2,6]naphthyridin-5-yl)amino)ethoxy)butyl) carbamate, 1.60



[00261] To a stirred solution of **compound 1.59** (4.5 g, 9.90 mmol) in DMF (25 mL) was added EDCI (2.85 g, 14.85 mmol), HOBt (2.01 g, 14.85 mmol), DIPEA (1.92 g, 14.85 mmol) and NH_4Cl (2.12 g, 39.60 mmol), sequentially at 20 °C. The reaction mixture was then stirred for 3 h at 20 °C. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL × 2). The combined organic layer was washed with brine (80 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM19) to afford **compound 1.60** (3.8 g, 6.70 mmol, 67.6% yield, TFA salt) as a yellow oil.

LCMS (AM3): rt = 0.758 min, (454.4 $[M+H]^+$), 59.9% purity.

5-((2-(4-aminobutoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide, Intermediate E

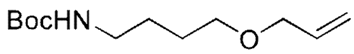


[00262] To a solution of **compound 1.60** (3.8 g, 8.38 mmol) in MeOH (5 mL) was added a solution of HCl in MeOH (4 M, 2.09 mL) dropwise at 0 °C. The reaction mixture was then warmed to 20 °C and stirred for 2 h. The reaction mixture was concentrated *in vacuo* to afford **Intermediate E** (2.8 g, 7.18 mmol, 85.7% yield, HCl salt) as a yellow solid.

LCMS (AM3): rt = 0.229 min, (354.1 $[M+H]^+$), 89.5% purity.

<u>**Synthesis of Intermediate 1.57**</u>

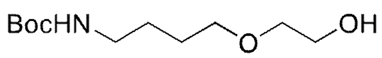
tert-butyl (4-(allyloxy)butyl)carbamate, 1.53



[00263] To a solution of NaOH (2.11 g, 52.84 mmol) in 1,4-dioxane (176.1 mL) was added tert-butyl N-(4-hydroxybutyl)carbamate (10 g, 52.84 mmol) and 3-bromoprop-1-ene (12.78 g, 105.68 mmol), sequentially at 20 °C. The reaction mixture was heated to 70 °C and stirred for 12 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (80 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM6) to afford **compound 1.53** (5.5 g, 23.98 mmol, 45.4% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 5.93–5.82 (m, 1H), 5.27–5.20 (m, 1H), 5.16–5.11 (m, 1H), 4.70 (br, s, 1H), 3.93–3.91 (m, 2H), 3.43–3.39 (t, 2H), 3.12–3.08 (m, 2H), 1.62–1.49 (m, 4H), 1.40 (s, 9H) ppm.

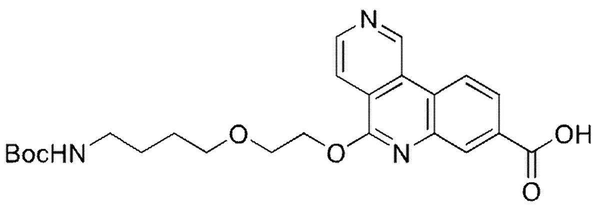
tert-butyl (4-(2-hydroxyethoxy)butyl)carbamate, 1.54



[00264] O_3 was bubbled into a solution of **compound 1.53** (5.5 g, 23.98 mmol) in DCM (50 mL) at -78 °C until the mixture turned blue, then the reaction mixture was warmed to 0 °C and $NaBH_4$ (1.77 g, 46.79 mmol) was added slowly at 0 °C. The reaction mixture was warmed to 20 °C and stirred for 12 h. The reaction was quenched with water (50 mL) and extracted with DCM (80 mL × 2). The combined organic layer was washed with brine (80 mL × 2), dried over anhydrous Na_2SO_4, then filtered and concentrated *in vacuo*. The residue was purified (PM3) to afford **compound 1.54** (2.65 g, 11.36 mmol, 47.4% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 4.78 (br s, 1H), 3.72−3.71 (m, 2H), 3.53−3.51 (t, 2H), 3.51−3.46 (t, 2H), 3.13−3.12 (m, 2H), 2.41 (br s, 1H), 1.66−1.50 (m, 4H), 1.42 (s, 9H) ppm.

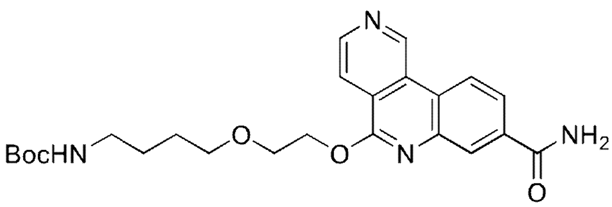
5-(2-(4-((tert-butoxycarbonyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid, 1.55



[00265] To a mixture of **compound 1.54** (427.79 mg, 1.83 mmol) in DMF (10 mL) was added NaH (110.02 mg, 2.75 mmol) in one portion followed by **compound 1.1** (500 mg, 1.83 mmol), under nitrogen protection at 0 °C. The mixture was then heated to 80 °C and stirred for 12 h. The mixture was diluted with water (50 mL) and extracted with EA (50 mL × 2). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified (PM20) to afford **compound 1.55** (300 mg, 645.44 μmol, 35.2% yield, 98.2% purity) as a light yellow solid.

LCMS (AM3): rt = 0.903 min, (456.3 $[M+H]^+$), 98.2% purity.

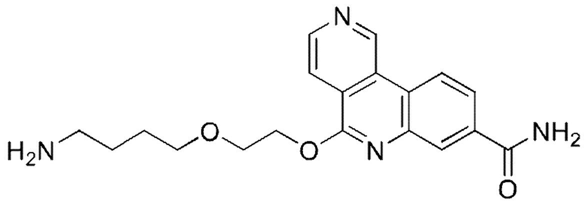
tert-butyl (4-(2-((8-carbamoylbenzo[c][2,6]naphthyridin-5-yl)oxy)ethoxy)butyl) carbamate, 1.56



[00266] To a mixture of **compound 1.55** (300 mg, 645.44 μmol), ammonium chloride (51.79 mg, 968.16 μmol) and DIPEA (208.54 mg, 1.61 mmol) in DMF (10 mL) was added HATU (294.50 mg, 774.53 μmol) at 25 °C. The resulting mixture was stirred at 25 °C for 11 h under nitrogen protection. The reaction mixture was filtered and concentrated *in vacuo* to give a residue which was purified (PM21) to afford **compound 1.56** (250 mg, 473.03 μmol, 73.3% yield, 86.2% purity) as a light yellow solid.

LCMS (AM3): rt = 0.757 min, (455.3 $[M+H]^+$), 86.2% purity.

5-(2-(4-aminobutoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide, 1.57

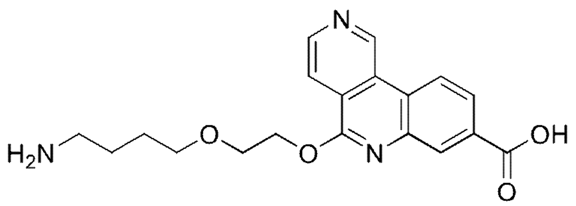


[00267] To a mixture of **compound 1.56** (250 mg, 473.03 μmol, 1 eq) in DCM (20 mL) was added TFA (6.16 g, 54.03 mmol, 4 mL) at 25 °C and the mixture was stirred for 0.5 h. The reaction mixture was concentrated *in vacuo* and purified (PM21) to afford **compound 1.57** (220 mg, 432.09 μmol, 91.3% yield, 92.1% purity, TFA salt) as a light yellow solid.

LCMS (AM3): rt = 0.675 min, (355.2 $[M+H]^+$), 92.1% purity.

__Synthesis of Intermediate Q__

5-(2-(4-Aminobutoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid; Intermediate Q

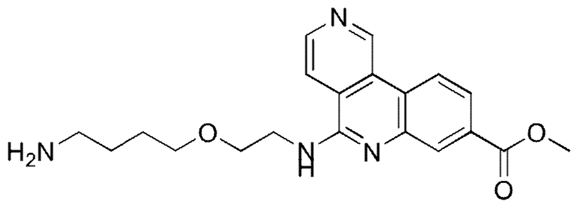


[00268] To a solution of **compound 1.55** (100 mg, 219.54 μmol) in DCM (5 mL) was added TFA (1 mL, 13.51 mmol). The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated *in vacuo* to afford **Intermediate Q** (100 mg, 213.03 μmol, 97% yield, TFA salt) as a brown solid, which was used without purification.

LCMS (AM3): rt = 0.745 min, (356.3 $[M+H]^+$), 79.9% purity.

Synthesis of Intermediate 1.154

Methyl 5-((2-(4-aminobutoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.154

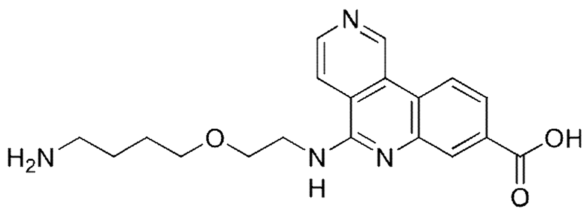


[00269] To solution of **compound 1.58** (200 mg, 426.85 μmol) in 1,4-dioxane (5 mL) was added a solution of HCl in 1,4-dioxane (4 M, 5 mL) at 20 °C. The mixture was stirred at 20 °C for 1 h. The mixture was concentrated *in vacuo* to afford **compound 1.154** (201 mg, HCl salt) as a yellow oil, which was used directly without purification.

LCMS (AM3): rt = 0.673 min, (369.2 $[M+H]^+$), 99% purity.

Synthesis of Intermediate R

5-((2-(4-Aminobutoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid; Intermediate R

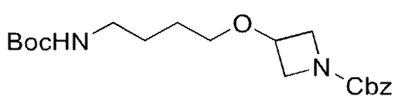


[00270] **Compound 1.59** (4 g, 8.80 mmol) in a solution of HCl in 1,4-dioxane (40.00 mL, 4 M) was stirred at 25 °C for 16 h. The precipitate was collected by filtration and dried under vacuum to afford **Intermediate R** (2.5 g, HCl salt) as a yellow solid.

LCMS (AM3): rt = 0.501 min, (354.9 $[M+H]^+$), 96.1% purity.

Synthesis of Intermediate O

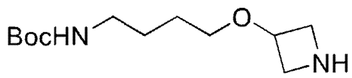
Benzyl 3-(4-((tert-butoxycarbonyl)amino)butoxy)azetidine-1-carboxylate 1.493



[00271] To a mixture of 4-((tert-butoxycarbonyl)amino)butyl 4-methylbenzenesulfonate (77.3 g, 225.08 mmol) (*Journal of Medicinal Chemistry*, 2006, 49 (14), 4183–4195), benzyl 3-hydroxyazetidine-1-carboxylate (31.09 g, 150.05 mmol), TBAI (13.86 g, 37.51 mmol) in toluene (500 mL) and water (100 mL) was added NaOH (60.02 g, 1.50 mol). The mixture was heated to 60 °C and stirred for 12 h. The mixture was diluted with water (1 L) and extracted with MTBE (200 mL × 3). The combined organic layer was washed with brine (200 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified (PM2) to afford **compound 1.493** (43.5 g, 76.6% yield).

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.35–7.26 (m, 5H), 5.07 (s, 2H), 4.74 (br s, 1H), 4.23–4.17 (m, 1H), 4.14–4.07 (m, 2H), 3.88–3.85 (m, 2H), 3.34 (t, *J* = 5.6 Hz , 2H), 3.12–3.08 (m, 2H), 1.61–1.48 (m, 4H), 1.41 (s, 9H) ppm.

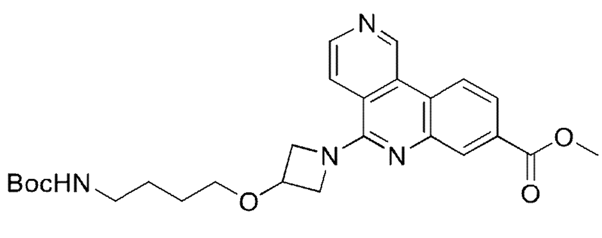
tert-Butyl (4-(azetidin-3-yloxy)butyl)carbamate 1.494



[00272] To a solution of **compound 1.493** (43.5 g, 114.94 mmol) in MeOH (500 mL) was added 10% palladium on carbon (5 g) under nitrogen protection at 20 °C. The reaction mixture was degassed three times and purged with hydrogen. The mixture was hydrogenated under one atmosphere H_2 at 20 °C for 12 h. The mixture was filtered and concentrated *in vacuo* to obtain **compound 1.494** (26.37 g, 93.9% yield) as a light yellow oil, which was used without further purification.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 4.89 (br s, 1H), 4.26–4.19 (m, 1H), 3.67–3.65 (m, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 3.28 (t, *J* = 6.0 Hz, 2H), 3.10–3.00 (m, 2H), 1.55–1.45 (m, 4H), 1.37 (s, 9H) ppm.

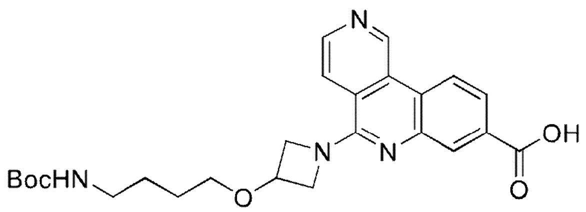
Methyl 5-(3-(4-((tert-butoxycarbonyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6] naphthyridine-8-carboxylate 1.495



[00273] To a solution of **compound 1.1** (9.5 g, 34.84 mmol) and **compound 1.494** (11.07 g, 45.29 mmol) in DMSO (200 mL) was added DIPEA (22.51 g, 174.19 mmol). The mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was poured into water (600 mL) and stirred for 10 min. The precipitate was collected by filtration and dried under vacuum to afford **compound 1.495** (14.1 g, 27.29 mmol, 78.3% yield) as a yellow solid.

LCMS (AM3): rt = 0.839 min, (481.3 $[M+H]^+$), 93.3% purity.

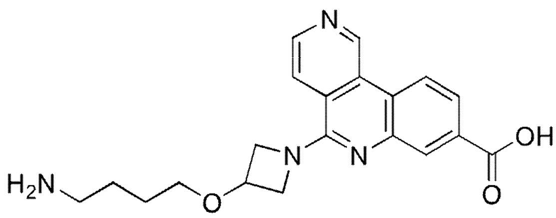
5-(3-(4-((tert-Butoxycarbonyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid 1.496



[00274] To a mixture of **compound 1.495** (14.1 g, 29.34 mmol) in THF (100 mL), water (100 mL) and MeOH (50 mL) was added lithium hydroxide monohydrate (6.16 g, 146.71mmol), and the reaction mixture was heated to 50 °C and stirred for 3 h. The solvent was removed under reduced pressure and acidified to pH 5 with aq. 1 M HCl. The precipitate was collected by filtration and the filter cake was washed with water and dried under vacuum to afford **compound 1.496** (15.6 g) as a yellow solid.

LCMS (AM3): rt = 0.813 min, (467.3 $[M+H]^+$) ,98.7% purity.

5-(3-(4-Aminobutoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid; Intermediate O

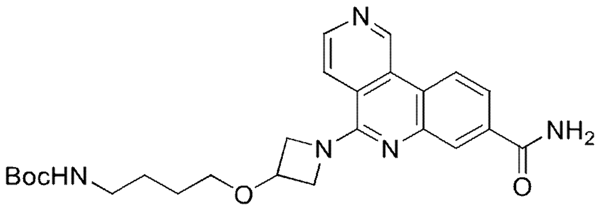


[00275] **Compound 1.496** (7.6 g, 16.29 mmol) in a solution of HCl in dioxane (80.07 mL, 4 M) was stirred at 20 °C for 1 h. The mixture was concentrated *in vacuo* to afford **Intermediate O** (6.9 g, HCl salt) as a yellow solid.

LCMS (AM5): rt = 0.737 min, (367.2 $[M+H]^+$) ,99.3% purity.

Synthesis of Intermediate P

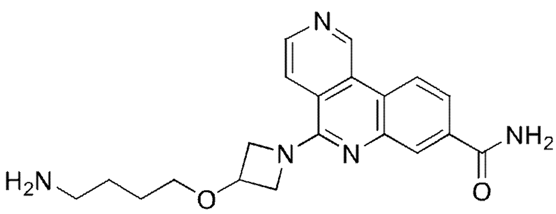
tert-Butyl (4-((1-(8-carbamoylbenzo[c][2,6]naphthyridin-5-yl)azetidin-3-yl)oxy)butyl)carbamate 1.497



[00276] To a solution of **compound 1.496** (8 g, 17.15 mmol), HATU (15.65 g, 20.58 mmol) and DIPEA (6.65 g, 51.44 mmol) in DMF (100 mL) was added NH_4Cl (917.27 mg, 17.15 mmol). The resulting mixture was stirred at 20 °C for 12 h. The mixture was poured into water (200 mL) and extracted with EA (100 mL × 2). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified (PM22) to afford **compound 1.497** (6.6 g, 14.05 mmol, 81.9% yield) as a yellow solid.

LCMS (AM3): rt = 0.793 min, (466.3 $[M+H]^+$), 99.2% purity.

5-(3-(4-Aminobutoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide; Intermediate P

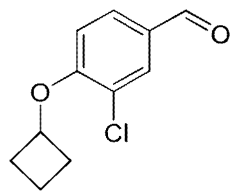


[00277] **Compound 1.497** (6.6 g, 14.18 mmol) in a solution of HCl in 1,4-dioxane (35 mL, 4 M) was stirred at 20 °C for 1 h. The mixture was concentrated *in vacuo* to give **Intermediate P** (5.5 g, HCl salt) as a yellow solid.

LCMS (AM5): rt = 0.690 min, (366.2 $[M+H]^+$), 92.4% purity

Synthesis of Intermediate 1.32

3-chloro-4-cyclobutoxybenzaldehyde 1.32

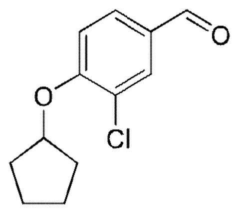


[00278] A mixture of bromocyclobutane (0.25 mL, 2.65 mmol), 3-chloro-4-hydroxybenzaldehyde (200 mg, 1.28 mmol) and potassium carbonate (440 mg, 3.18 mmol) in DMF (10 mL) was stirred at 80 °C for 15 h. The reaction mixture was poured into water (60 mL) and the resulting mixture was extracted with EA (20 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified (PM11) to afford **compound 1.32** (134 mg, 49.8% yield) as a colorless oil.

LCMS (AM1): rt = 0.969 min, (211.0 $[M+H]^+$), 66.6% purity.

Synthesis of Intermediate 1.33

3-chloro-4-(cyclopentyloxy)benzaldehyde 1.33

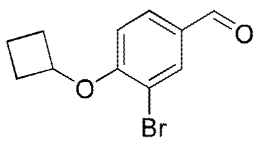


[00279] A mixture of bromocyclopentane (0.274 mL, 2.56 mmol,), 3-chloro-4-hydroxy-benzaldehyde (200 mg, 1.28 mmol) and potassium carbonate (441 mg, 3.19 mmol) in DMF (10 mL) was stirred at 80 °C for 15 h. The reaction mixture was poured into water (60 mL) and the resulting mixture was extracted with EA (20 mL x 3). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified (PM11) to afford **compound 1.33** (270 mg, 93.9% yield) as a colourless oil.

LCMS (AM3): rt = 1.017 min, (266.0 $[M+H_2O+Na]^+$), 96.9% purity.

Synthesis of Intermediate 1.47

3-bromo-4-cyclobutoxybenzaldehyde 1.46

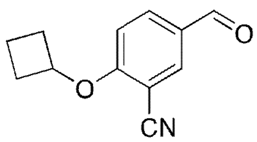


[00280] To a mixture of 3-bromo-4-hydroxybenzaldehyde (1.0 g, 4.97 mmol) and bromocyclobutane (1.01 g, 7.46 mmol) in DMF (10 mL) was added potassium carbonate (2.06 g, 14.92 mmol) at room temperature. The resulting mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was concentrated *in vacuo* to give a residue that was poured into water (10 mL) and extracted with EA (50 mL × 3). The combined organic phases were washed with brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo.* The crude product was purified (PM4) to afford **compound 1.46** (1.0 g, 3.80 mmol, 76.4% yield, 97% purity) as a yellow solid.

LCMS (AM3): rt = 0.983 min, (257.0 $[M+H]^+$), 86.62% purity.

^{1}H NMR (400 MHz, MeOD-*d4*) δ: 9.79 (s, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 7.84 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 4.93–4.85 (m, 1H), 2.61–2.48 (m, 2H), 2.29–2.14 (m, 2H), 1.99–1.65 (m, 2H) ppm.

2-cyclobutoxy-5-formylbenzonitrile 1.47



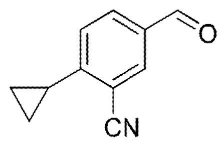
[00281] To a mixture of **compound 1.46** (200 mg, 783.98 μmol) in DMF (1 mL) was added zinc cyanide (460.32 mg, 3.92 mmol) and tetrakis(triphenylphosphine)palladium (90.59 mg, 78.40 μmol), sequentially at 25 °C under nitrogen protection. The reaction mixture was then heated to 100 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified (PM38) to afford **compound 1.47** (80 mg, 397.57 μmol, 50.7% yield, 100% purity) as a white solid.

LCMS (AM3): rt = 0.885 min, (202.0 $[M+H]^+$), 100.0% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.88 (s, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 8.03 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 4.88–4.81 (m, 1H), 2.59–2.49 (m, 2H), 2.38–2.28 (m, 2H), 2.03–1.91 (m, 1H), 1.85–1.73 (m, 1H) ppm.

Synthesis of Intermediate 1.52

2-cyclopropyl-5-formylbenzonitrile 1.52



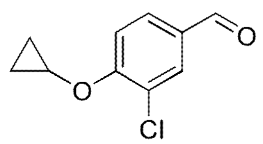
[00282] To a mixture of cyclopropylboronic acid (122.69 mg, 1.43 mmol) and 2-bromo-5-formylbenzonitrile (200 mg, 952.26 μmol) in 1,4-dioxane (1 mL) and water (0.1 mL) was added Pd(dppf)Cl_2.CH_2Cl_2 (77.77 mg, 95.23 μmol) and potassium carbonate (263.22 mg, 1.90 mmol), sequentially at 25 °C under nitrogen protection. The mixture was heated to 90 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified by prep-TLC (SiO_2, PE: EA = 3:1) to afford **compound 1.52** (100 mg, 566.61 μmol, 59.5% yield, 97% purity) as a white solid.

LCMS (AM3): rt = 0.808 min, (172.2 $[M+H]^+$), 97.81% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.96 (s, 1H), 8.09 (d, *J* = 1.6 Hz, 1H), 7.97 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 2.40 (m, 1H), 1.31–1.30 (m, 2H), 0.95–0.93 (m, 2H) ppm.

Synthesis of Intermediate 1.90

3-Chloro-4-cyclopropoxybenzaldehyde 1.90

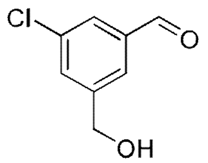


[00283] To a solution of 3-chloro-4-fluoro-benzaldehyde (1.8 g, 11.35 mmol) in acetonitrile (20 mL) was added potassium carbonate (2.35 g, 17.03 mmol) and cyclopropanol (725.27 mg, 12.49 mmol) at 25 °C. The reaction mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified (PM11) to afford **compound 1.90** (120 mg, 610.28 μmol, 5% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.87 (s, 1H), 7.90 (d, *J* = 2.1 Hz, 1H), 7.79 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 3.94–3.87 (m, 1H), 0.92 (d, *J* = 4.5 Hz, 4H) ppm.

Synthesis of Intermediate 1.102

3-Chloro-5-(hydroxymethyl)benzaldehyde, 1.102

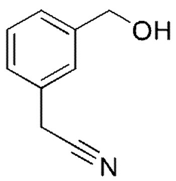


[00284] To a mixture of (3-bromo-5-chloro-phenyl)methanol (2 g, 9.03 mmol) and TMEDA (2.10 g, 18.05 mmol, 2.72 mL) in THF (20 mL) was added n-BuLi (2.4 M, 7.53 mL) at -78 °C dropwise, then the resulting mixture was allowed to warm to -20 °C and stirred for 1 h. The reaction mixture was cooled again to -78 °C and DMF (10 mL) was added. The resulting mixture was warmed to 20 °C and stirred for another 1 h. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (100 mL) and extracted with EA (20 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM2) to afford **compound 1.102** (400 mg, 2.34 mmol, 26% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.99 (s, 1H), 7.78 (m, 2H), 7.65 (s, 1H), 4.80 (d, *J* = 4.6 Hz, 2H) pm.

Synthesis of Intermediate 1.134

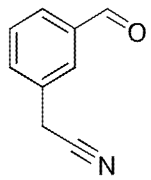
2-(3-(Hydroxymethyl)phenyl)acetonitrile 1.133



[00285] To a solution of methyl 3-(cyanomethyl)benzoate (1.5 g, 8.56 mmol) in THF (15 mL) was added $LiBH_4$ (2 M, 12.84 mL, 25.69 mmol) at ambient temperature. The reaction mixture was then heated to 70 °C and stirred for 4 h. The mixture was cooled to room temperature, quenched with aq. HCl (1 N, 50 mL) and extracted with EA (20 mL × 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified (PM6) to afford **compound 1.133** (1.0 g, 6.79 mmol, 79.3% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.35–7.18 (m, 4H), 4.65 (s, 2H), 3.68 (s, 2H) ppm.

2-(3-Formylphenyl)acetonitrile 1.134

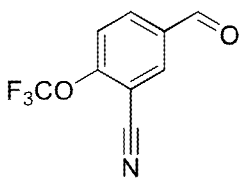


[00286] To a solution of compound **1.133** (500 mg, 3.40 mmol) in DCM (20 mL) was added manganese (IV) oxide (2.95 g, 33.97 mmol) at 30 °C. The reaction mixture was stirred at 30 °C for 12 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified (PM6) to afford **compound 1.134** (50 mg, 344.45 μmol, 10.1% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.05 (s, 1H), 7.89–7.87 (m, 2H), 7.67–7.57 (m, 2H), 3.86 (s, 2H) ppm.

<u>**Synthesis of Intermediate 1.136**</u>

5-Formyl-2-(trifluoromethoxy)benzonitrile 1.136

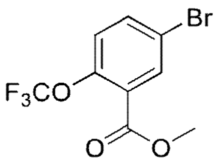


[00287] To a solution of 3-bromo-4-(trifluoromethoxy)benzaldehyde (500 mg, 1.86 mmol) in DMF (15 mL) was added zinc cyanide (0.82 g, 6.98 mmol) and tetrakis(triphenylphosphine) palladium (214.78 mg, 185.86 μmol) at ambient temperature. The reaction mixture was then heated to 100 °C and stirred for 12 h under nitrogen protection. The mixture was cooled to room temperature and poured into water (50 mL). The aqueous mixture was extracted with EA (20 mL × 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The obtained residue was purified (PM12) to afford **compound 1.136** (170 mg, 790.23 μmol, 42.5% yield) as a brown oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.03 (s, 1H), 8.25 (d, *J* = 1.4 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.58 (dd, *J* = 8.4, 1.8 Hz, 1H) ppm.

Synthesis of Intermediate 1.153

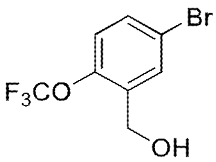
Methyl 5-bromo-2-(trifluoromethoxy)benzoate, 1.150



[00288] To an ice-cooled solution of 5-bromo-2-(trifluoromethoxy)benzoic acid (2 g, 7.02 mmol) in MeOH (20 mL) was added $SOCl_2$ (1.67 g, 14.03 mmol) slowly. The resulting mixture was heated to 70 °C and stirred for 1 h. The mixture was concentrated *in vacuo* and the obtained residue was diluted with EA (100 mL). The organic phase was washed with sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford **compound 1.150** (2.9 g) as a yellow oil, which was used directly without further purification.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 8.09 (d, *J* = 2.6 Hz, 1H), 7.68 (dd, *J* = 2.5, 8.7 Hz, 1H), 7.22 (dd, *J* = 1.0, 8.7 Hz, 1H), 3.95 (s, 3H) ppm.

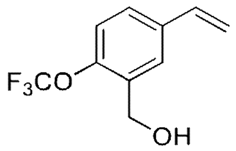
(5-Bromo-2-(trifluoromethoxy)phenyl)methanol, 1.151



[00289] To a solution of **compound 1.150** (2.9 g, 9.70 mmol) in THF (20 mL) was added $LiAlH_4$ (368.07 mg, 9.70 mmol) at 0 °C under nitrogen. The mixture was warmed to 20 °C and stirred for 1 h. The mixture was cooled to 0 °C and diluted with EA (10 mL). The resulting mixture was then quenched with water (0.2 mL) followed by addition of aq. 10% NaOH (0.2 mL) and water (0.6 mL). Anhydrous Na_2SO_4 (5 g) was added, the resulting suspension was stirred for another 0.5 h and then filtered. The filtrate was concentrated *in vacuo* to afford **compound 1.151** (2.23 g, 8.23 mmol, 84.8% yield) as a white solid, which was used directly without further purification.

LCMS (AM3): rt = 0.801 min, (290.3 $[M+NH_4]^+$), 85.1% purity.

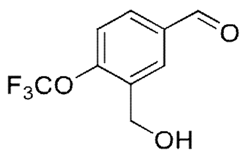
(2-(Trifluoromethoxy)-5-vinylphenyl)methanol, 1.152



[00290] To a solution of **compound 1.151** (2.23 g, 8.23 mmol) and tributyl(vinyl)stannane (2.61 g, 8.23 mmol) in toluene (50 mL) was added $Pd(PPh_3)_4$ (665.54 mg, 575.95 μmol) under nitrogen protection at ambient temperature. The mixture was heated to 95 °C and stirred for 12 h. The residue was poured into saturated aqueous KF solution (100 mL) and the resulting mixture was stirred for 15 min, then extracted with EA (50 mL × 3). The combined organic phase was washed with brine (100 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM7) to afford **compound 1.152** (1.43 g, 6.55 mmol, 79.7% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.49 (d, *J* = 2.2 Hz, 1H), 7.26 (dd, *J* = 2.2, 8.4 Hz, 1H), 7.10–7.08 (dd, 1H), 6.61 (dd, *J* = 10.9, 17.6 Hz, 1H), 5.67 (d, *J* = 17.6 Hz, 1H), 5.21 (d, *J* = 10.9 Hz, 1H), 4.67 (s, 2H), 2.12–2.04 (br s, 1H) ppm.

3-(Hydroxymethyl)-4-(trifluoromethoxy)benzaldehyde, 1.153

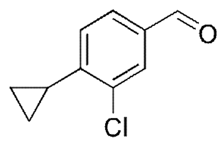


[00291] Ozone was bubbled into a solution of **compound 1.152** (500 mg, 2.29 mmol) in DCM (10 mL) at -70 °C until the mixture turned blue. Dimethyl sulfide (1.42 g, 22.92 mmol) was then added. The mixture was warmed up to 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified (PM7) to afford **compound 1.153** (326 mg, 1.48 mmol, 64.6% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.93 (s, 1H), 8.06 (d, 1H), 7.79 (dd, *J* = 2.1, 8.5 Hz, 1H), 7.31 (dd, *J* = 1.8, 8.4 Hz, 1H), 4.77 (s, 2H), 2.40 (br s, 1H) ppm.

Synthesis of Intermediate 1.202

3-Chloro-4-cyclopropylbenzaldehyde 1.202

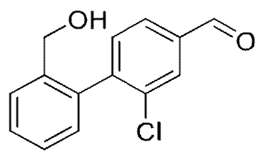


To a mixture of cyclopropylboronic acid (156 mg, 1.82 mmol) in 1,4-dioxane (8 mL) and water (2 mL) was added 4-bromo-3-chloro-benzaldehyde (200 mg, 0.911 mmol) followed by addition of K_2CO_3 (315 mg, 2.28 mmol) and Pd(dppf)Cl_2 (66 mg, 0.090 mmol) at ambient temperature. The mixture was degassed and purged with nitrogen three times, then it was heated to 80 °C and stirred for 14 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified (PM11) to afford **compound 1.202** (130 mg, 79% yield) as a colorless oil.

^{1}H NMR (400 MHz, MeOH-*d4*) δ: 9.89 (s, 1H), 7.87 (d, *J* = 1.6 Hz, 1H), 7.73 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 2.35–2.29 (m, 1H), 1.18–1.12 (m, 2H), 0.84–0.80 (m, 2H) ppm.

Synthesis of Intermediate 1.345

2-Chloro-2'-(hydroxymethyl)-[1,1'-biphenyl]-4-carbaldehyde, 1.345

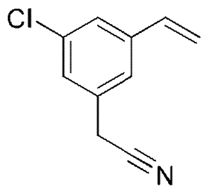


[00292] To a mixture of (2-(hydroxymethyl)phenyl)boronic acid (250 mg, 1.65 mmol), 4-bromo-3-chlorobenzaldehyde (361 mg, 1.64 mmol) and K_2CO_3 (569 mg, 4.12 mmol) in 1,4-dioxane (8 mL) and water (2 mL), was added Pd(dppf)Cl_2.CH_2Cl_2 (67 mg, 0.082 mmol). The reaction was degassed and purged with nitrogen three times, then the reaction mixture was heated to 80 °C and stirred for 17 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo.* The residue was purified (PM6) to afford **compound 1.345** (400 mg, 98.6% yield) as a colorless oil.

^{1}H NMR (400 MHz, DMSO-*d6*) δ: 10.05 (s, 1H), 8.07 (d, *J* = 1.6 Hz, 1H), 7.92 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.61 (dd, *J* = 0.8 Hz, 7.6 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.47–7.44 (t, 1H), 7.38–7.34 (t, 1H), 7.14 (dd, *J* = 1.2 Hz, 7.6 Hz, 1H), 5.12 (t, *J* = 5.6 Hz, 1H), 4.30–4.15 (qd, 2H) ppm.

Synthesis of intermediate 1.366

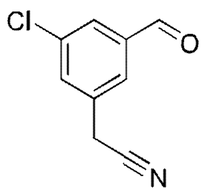
2-(3-Chloro-5-vinylphenyl)acetonitrile 1.365



[00293] A mixture of 2-(3-bromo-5-chlorophenyl)acetonitrile (500 mg, 1.08 mmol) (US2008221127A1), tributyl(vinyl)stannane (343.94 mg, 1.08 mmol) and $Pd(PPh_3)_4$ (125 mg, 1.08 μmol) in toluene (10 mL) was stirred at 90 °C for 15 h. The mixture was poured into saturated aqueous KF solution (100 mL) and then extracted with EA (100 mL × 2). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified (PM14) to afford **compound 1.365** (200 mg) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.37 (s, 1H), 7.23 (d, *J* = 6.0 Hz, 2H), 6.69–6.62 (dd, 1H), 5.82 (d, *J* = 12 Hz, 1H), 5.40 (d, *J* = 16.4 Hz, 1H), 3.74 (s, 2H) ppm.

2-(3-Chloro-5-formylphenyl)acetonitrile 1.366

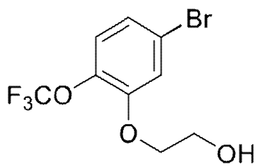


[00294] To a solution of **compound 1.365** (200 mg, 1.13 mmol) in DCM (20 mL) was bubbled ozone for 0.5 h at -78 °C; the reaction mixture turned blue, then DMS (3.66 g, 58.91 mmol) was added slowly to the above mixture at -78 °C. The reaction mixture was warmed up to 20 °C and stirred for another 12 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM7) to afford **compound 1.366** (150 mg, 835.18 μmol, 74.2% yield) as a white solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.99 (s, 1H), 7.84 (t, *J* = 1.6 Hz, 1H), 7.75 (d, *J* = 1.6 Hz, 1H), 7.62 (t, *J* = 1.2 Hz, 1H), 3.84 (s, 2H) ppm.

Synthesis of Intermediate 1.402

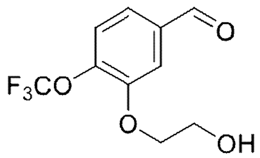
2-(5-Bromo-2-(trifluoromethoxy)phenoxy)ethanol 1.401



[00295] A mixture of 5-bromo-2-(trifluoromethoxy)phenol (900 mg, 3.5 mmol), 2-bromoethanol (0.63 mL, 8.87 mmol) and K_2CO_3 (1.21 g, 8.73 mmol) in acetonitrile (18 mL) was heated to 80 °C and stirred for 15 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM6) to afford **compound 1.401** (850 mg, 80.6% yield) as a colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.48 (d, *J* = 2.4 Hz, 1H), 7.32 (dd, *J* = 8.8 Hz, 1.2 Hz, 1H), 7.2 (dd, *J* = 8.8 Hz, 2.4Hz, 1H), 4.90 (t, *J* = 5.2 Hz, 1H), 4.12 (t, *J* = 4.8 Hz, 2H), 3.71 (q, *J* = 5.2 Hz, 2H) ppm.

3-(2-Hydroxyethoxy)-4-(trifluoromethoxy)benzaldehyde 1.402

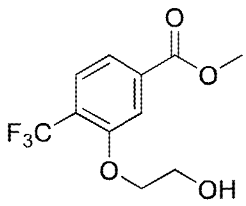


[00296] To a mixture of **compound 1.401** (650 mg, 2.16 mmol), DMF (315 mg, 4.32 mmol) and TMEDA (500 mg, 4.31 mmol) in THF (20 mL) was added *n*-BuLi (1.76 mL, 2.5 M in hexane) at -70 °C. The reaction mixture was stirred at -70 °C for 1 h, then it was warmed up to 25 °C and stirred for another 1 h. The reaction mixture was quenched by adding water (1 mL) and extracted with EA (50 mL × 2). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified (PM47) to afford **compound 1.402** (48 mg, 6% yield) as a yellow oil.

LCMS (AM2): rt = 0.739 min, (251.1 $[M+H]^+$), 66.6% purity.

Synthesis of intermediate 1.406

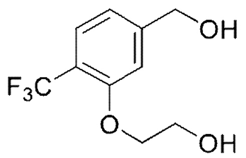
Methyl 3-(2-hydroxyethoxy)-4-(trifluoromethyl)benzoate 1.404



[00297] A mixture of methyl 3-hydroxy-4-(trifluoromethyl)benzoate (1.1 g, 5.00 mmol) (*Journal of Medicinal Chemistry*, **2005**, 48 (9), 3290–3312), 2-bromoethanol (0.71 mL, 10 mmol) and K_2CO_3 (1.39 g, 10.03 mmol) in DMF (15 mL) was stirred at 80 °C for 16 h. The reaction mixture was filtered and the filtrate was poured into water (100 mL) and extracted with EA (50 mL × 2). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified (PM47) to afford **compound 1.404** (850 mg, 64.4% yield) as a brown oil.

LCMS (AM2): rt = 0.779 min, (286.9 $[M+Na]^+$), 100 % purity.

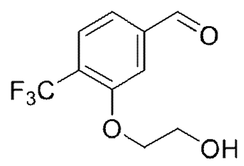
2-(5-(Hydroxymethyl)-2-(trifluoromethyl)phenoxy)ethanol 1.405



[00298] To a mixture of LAH (345 mg, 9.09 mmol) in THF (15 mL) at 0 °C was added **compound 1.404** (800 mg, 3.03 mmol) in THF (5 mL). The reaction mixture was then warmed to room temperature and stirred for 2 h. The reaction was quenched by addition of water (0.4 mL) followed by 0.4 mL of aq. NaOH solution (10%) and water (1.2 mL). After stirring for 0.5 h, Na_2SO_4 was added and the resulting suspension was stirred for another 30 min, filtered and the filtrate was concentrated *in vacuo* to afford **compound 1.405** (600 mg) as a brown oil, which was used directly without further purification.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.54 (d, J = 8.0 Hz. 1H), 7.19 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 5.41 (br, s, 1H), 4.86 (br, s, 1H), 4.55 (s, 2H), 4.10 (t, J = 5.2 Hz, 2H), 3.73 (t, J = 5.2 Hz, 2H) ppm.

3-(2-Hydroxyethoxy)-4-(trifluoromethyl)benzaldehyde 1.406

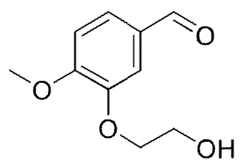


[00299] A mixture of **compound 1.405** (550 mg, 2.33 mmol) and manganese(IV) oxide (2.02 g, 23.28 mmol) in DCM (20 mL) was stirred at room temperature for 20 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified (PM5) to afford **compound 1.406** (380 mg, 59.2% yield) as a brown oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.08 (s, 1H), 7.86 (d, *J* = 8.0 Hz. 1H), 7.75 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 4.90 (t, *J* = 5.2 Hz, 1H), 4.24 (t, *J* = 5.2 Hz, 2H), 3.76 (q, *J* = 5.2 Hz, 2H) ppm.

Synthesis of Intermediate 1.410

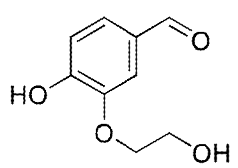
3-(2-Hydroxyethoxy)-4-methoxybenzaldehyde 1.408



A mixture of 3-hydroxy-4-methoxy-benzaldehyde (8.8 g, 57.84 mmol), 2-bromoethanol (8 mL, 113 mmol) and K_2CO_3 (16 g, 116 mmol) in acetonitrile (100 mL) was stirred at 80 °C for 14 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo.* The residue was purified (PM3) to afford **compound 1.408** (7.8 g, 66.7% yield) as a white solid.

LCMS (AM3): rt = 0.778 min, (197.2 $[M+H]^+$), 97.2 % purity.

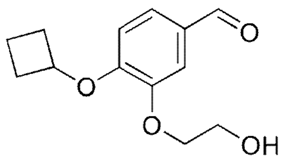
4-Hydroxy-3-(2-hydroxyethoxy)benzaldehyde 1.409



[00300] To a solution of **compound 1.408** (7.7 g, 39.25 mmol) in DCM (200 mL) was added $AlCl_3$ (26.18 g, 196.34 mmol) at room temperature. The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was poured into water (300 mL) at 0 °C and extracted with a solvent mixture of DCM and MeOH (v/v = 10:1, 50 mL × 10). The combined organic phase was washed with brine (400 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM2) to afford **compound 1.409** (5.3 g, 74.1% yield) as a yellow solid.

LCMS (AM3): rt = 0.699 min, (183.2 [M+H]$^+$), 97.9 % purity.

4-Cyclobutoxy-3-(2-hydroxyethoxy)benzaldehyde 1.410

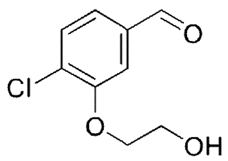


[00301] A mixture of **compound 1.409** (200 mg, 1.10 mmol), bromocyclobutane (296 mg, 2.19 mmol) and K_2CO_3 (378 mg, 2.73 mmol) in DMF (10 mL) was stirred at 100 °C for 24 h. The reaction mixture was poured into water (30 mL) and the resulting mixture was extracted with EA (10 mL × 5). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM4) to afford **compound 1.410** (250 mg, 96.4% yield) as a light yellow oil.

LCMS (AM3): rt = 0.805 min, (237.6 [M+H]$^+$), 98.5 % purity.

Synthesis of Intermediate 1.412

4-Chloro-3-(2-hydroxyethoxy)benzaldehyde, 1.412

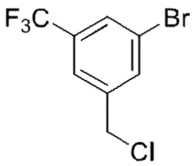


[00302] A mixture of 4-chloro-3-hydroxy-benzaldehyde (200 mg, 1.28 mmol), 2-bromoethanol (0.2 mL, 2.82 mmol) and K_2CO_3 (440 mg, 3.18 mmol) in acetonitrile (4 mL) was stirred at 80 °C for 12 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified (PM6) to afford **compound 1.412** (240 mg, 93.6% yield) as a colorless oil.

LCMS (AM3): rt = 0.723 min, (201.1 [M+H]$^+$), 93.4% purity.

Synthesis of Intermediate 1.469

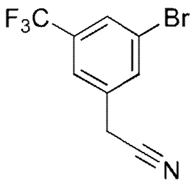
1-Bromo-3-(chloromethyl)-5-(trifluoromethyl)benzene 1.466



[00303] To a solution of (3-bromo-5-(trifluoromethyl)phenyl)methanol (2 g, 7.84 mmol) in 1,4-dioxane (10 mL) was added $SOCl_2$ (1.87 g, 15.68 mmol) at 0 °C. The mixture was then heated to 90 °C and stirred for 1 h. The mixture was concentrated *in vacuo* to give **compound 1.466** (2 g, crude) as a black oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.75 (d, *J* = 1.0 Hz, 2H), 7.59 (s, 1H), 4.59 (s, 2H) ppm.

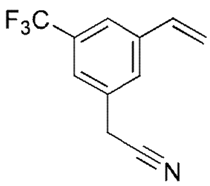
2-(3-Bromo-5-(trifluoromethyl)phenyl)acetonitrile 1.467



[00304] To a solution of trimethylsilanecarbonitrile (870.62 mg, 8.78 mmol) and **compound 1.466** (2 g, 7.31 mmol) in acetonitrile (4 mL) was added TBAF (8.78 mL, 8.78 mmol, 1 M in THF). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM14) to give **compound 1.467** (1.48 g, 5.61 mmol, 76.6% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.77 (s, 1H), 7.72 (s, 1H), 7.55 (s, 1H), 3.83 (s, 2H) ppm.

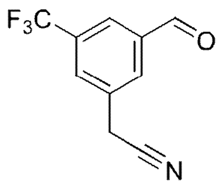
2-(3-(Trifluoromethyl)-5-vinylphenyl)acetonitrile 1.468



[00305] To a solution of **compound 1.467** (1.38 g, 5.23 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.21 g, 7.84 mmol, 1.33 mL) in DME (20 mL) was added $Pd(dppf)Cl_2$ (382.42 mg, 522.64 μmol) and CsF (1.59 g, 10.45 mmol). The mixture was heated to 80 °C and stirred for 12 h under nitrogen protection. The reaction mixture was poured into water (50 mL) and stirred for 1 min. The aqueous phase was extracted with EA (30 mL × 3). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM13) to afford **compound 1.468** (500 mg, 2.37 mmol, 45.3% yield) as a red oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.63 (s, 1H), 7.56 (s, 1H), 7.47 (s, 1H), 6.75 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.88 (d, *J* = 17.6 Hz, 1H), 5.45 (d, *J* = 11.2 Hz, 1H), 3.83 (s, 2H) ppm.

2-(3-Formyl-5-(trifluoromethyl)phenyl)acetonitrile 1.469

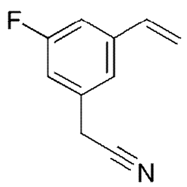


[00306] Ozone was bubbled into a solution of **compound 1.468** (500 mg, 2.37 mmol) in DCM (10mL) at -70 °C until the mixture turned blue. After excess ozone was purged, DMS (1.47 g, 23.68 mmol) was added at -70 °C. The mixture was then warmed to 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and (PM7) to afford **compound 1.469** (262 mg, 1.23 mmol, 51.9% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.10 (s, 1H), 8.14 (s, 1H), 8.08 (s, 1H), 7.88 (s, 1H), 3.95 (s, 2H) ppm.

<u>Synthesis of Intermediate 1.472</u>

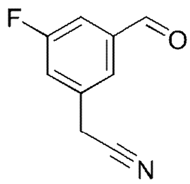
2-(3-Fluoro-5-vinylphenyl)acetonitrile 1.471



[00307] To a solution of 2-(3-bromo-5-fluorophenyl)acetonitrile (1.6 g, 7.48 mmol) and tributyl(vinyl)stannane (2.37 g, 7.48 mmol) in toluene (30 mL) was added $Pd(PPh_3)_4$ (604.68 mg, 523.28 μmol). The resulting mixture was heated to 95 °C and stirred for 12 h under nitrogen protection. The mixture was poured into saturated aqueous KF solution (100 mL) and stirred for 15 min. The aqueous phase was extracted with EA (50 mL × 3). The combined organic phase was washed with brine (100 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM14) to afford **compound 1.471** (900 mg, 5.58 mmol, 74.6% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.15 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.66 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.80 (d, *J* = 17.6 Hz, 1H), 5.38 (d, *J* = 10.8 Hz, 1H), 3.75 (s, 2H) ppm.

2-(3-Fluoro-5-formylphenyl)acetonitrile 1.472

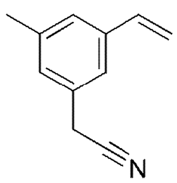


[00308] Ozone was bubbled into a solution of **compound 1.471** (500 mg, 3.10 mmol) in DCM (10 mL) at -70 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (1.93 g, 31.02 mmol) was added. The mixture was warm up to 20 °C and stirred for 12 h.. The mixture was concentrated *in vacuo* and the residue was purified (PM7) to afford **compound 1.472** (390 mg, 2.39 mmol, 77.1% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.09 (s, 1H), 7.68 (s, 1H), 7.56 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.36 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.87 (s, 2H) ppm.

__Synthesis of Intermediate 1.475__

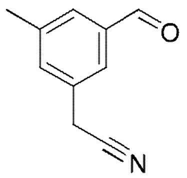
2-(3-Methyl-5-vinylphenyl)acetonitrile 1.474



[00309] To a solution of 2-(3-bromo-5-methylphenyl)acetonitrile (1.6 g, 7.62 mmol) and tributyl(vinyl)stannane (2.42 g, 7.62 mmol) in toluene (30 mL) was added $Pd(PPh_3)_4$ (616.09 mg, 533.16 μmol). The mixture was heated to 95 °C and stirred for 12 h under nitrogen protection. The mixture was poured into saturated aqueous KF solution (100 mL) and stirred for 15 min. The aqueous phase was extracted with EA (50 mL × 3). The combined organic phase was washed with brine (100 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM14) to give **compound 1.474** (820 mg, 5.22 mmol, 68.5% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.19 (s, 1H), 7.16 (s, 1H), 7.05 (s, 1H), 6.68 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.77 (d, *J* = 17.6 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 3.72 (s, 2H), 2.37 (s, 3H) ppm.

2-(3-Formyl-5-methylphenyl)acetonitrile 1.475

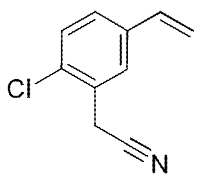


[00310] Ozone was bubbled into a solution of **compound 1.474** (500 mg, 3.18 mmol) in DCM (10 mL) at -70 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (1.98 g, 31.80 mmol) was added. The reaction mixture was warmed to 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified (PM7) to give **compound 1.475** (320 mg, 2.01 mmol, 63.2% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.00 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.45 (s, 1H), 3.81 (s, 2H), 2.47 (s, 3H) ppm.

<u>**Synthesis of Intermediate 1.478**</u>

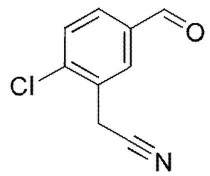
2-(2-Chloro-5-vinylphenyl)acetonitrile 1.477



[00311] To a solution of 2-(5-bromo-2-chlorophenyl)acetonitrile (1.4 g, 6.07 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.40 g, 9.11 mmol) in DME (20 mL) was added Pd(dppf)Cl_2 (444.44 mg, 607.40 μmol) and CsF (1.85 g, 12.15 mmol). The reaction mixture was heated to 80 °C and stirred for 12 h under nitrogen protection. The mixture was poured into water (50 mL) and the aqueous phase was extracted with EA (30 mL × 3). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM17) to give **compound 1.477** (600 mg, 3.38 mmol, 55.6% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.43 (s, 1H), 7.25 (m, 1H), 7.24–7.21 (m, 1H), 6.59 (dd, *J* = 17.6, 10.8, Hz, 1H), 5.70 (d, *J* = 17.6 Hz, 1H), 5.25 (d, *J* = 10.8 Hz, 1H), 3.74 (s, 2H) ppm.

2-(2-Chloro-5-formylphenyl)acetonitrile 1.478

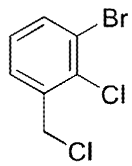


[00312] Ozone was bubbled into a solution of **compound 1.477** (400 mg, 2.25 mmol) in DCM (10 mL) at -70 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (1.40 g, 22.52 mmol) was added. The reaction mixture was warmed up to at 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified (PM11) to afford **compound 1.478** (200 mg, 1.11 mmol, 49.5% yield) as a light yellow solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.03 (s, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 7.86 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 2H) ppm.

<u>**Synthesis of intermediate 1.483**</u>

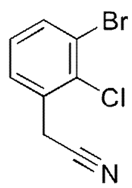
1-Bromo-2-chloro-3-(chloromethyl)benzene 1.480



[00313] To a solution of (3-bromo-2-chlorophenyl)methanol (1 g, 4.52 mmol) in 1,4-dioxane (10 mL) was added $SOCl_2$ (1.07 g, 9.03 mmol) at 0 °C. The reaction mixture was heated to 90 °C and stirred for 1 h. The mixture was concentrated *in vacuo* to give **compound 1.480** (1 g) as a black oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.63 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 4.74 (s, 2H) ppm.

2-(3-Bromo-2-chlorophenyl)acetonitrile 1.481

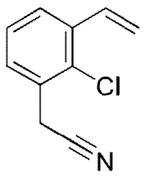


[00314] To a solution of trimethylsilylcyanide (516.86 mg, 5.21 mmol) and **compound 1.480** (1 g, 4.17 mmol) in acetonitrile (20 mL) was added TBAF (5.22 mL, 5.22 mmol, 1 M in

THF) at 25 °C. The mixture was stirred at 25 °C for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM14) to give **compound 1.481** (837 mg, 3.63 mmol, 87.1% yield) as a white solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.66 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 3.90 (s, 2H) ppm.

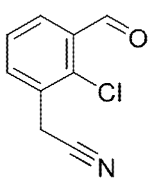
2-(2-Chloro-3-vinylphenyl)acetonitrile 1.482



To a solution of **compound 1.481** (837 mg, 3.63 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (838.93 mg, 5.45 mmol) in DME (10 mL) was added CsF (1.10 g, 7.26 mmol) and Pd(dppf)Cl_2 (265.71 mg, 363.14 μmol). The mixture was heated to 80 °C and stirred for 12 h under nitrogen protection. The mixture was poured into water (50 mL) and the aqueous phase was extracted with EA (30 mL × 3). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM12) to afford **compound 1.482** (300 mg, 1.69 mmol, 46.5% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.58 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 17.6, 12.0 Hz, 1H), 5.77 (d, *J* = 17.6 Hz, 1H), 5.45 (dd, *J* = 12.0 Hz, 1H), 3.87 (s, 2H) ppm.

2-(2-Chloro-3-formylphenyl)acetonitrile 1.483

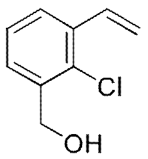


[00315] Ozone was bubbled into a solution of **compound 1.482** (300 mg, 1.69 mmol) in DCM (10 mL) at -70 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (1.05 g, 16.89 mmol) was added. The mixture was warmed up to 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified by (PM9) to afford **compound 1.483** (297 mg, 1.65 mmol, 97.9% yield) as a white solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.53 (s 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 3.94 (s, 2H) ppm.

Synthesis of Intermediate 1.485

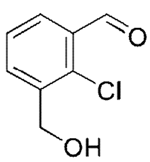
(2-Chloro-3-vinylphenyl)methanol 1.484



[00316] To a solution of tributyl(vinyl)stannane (1.43 g, 4.52 mmol) and (3-bromo-2-chlorophenyl)methanol (1.00 g, 4.52 mmol) in toluene (20 mL) was added $Pd(PPh_3)_4$ (365.62 mg, 316.40 μmol). The mixture was heated to 95 °C and stirred for 12 h under nitrogen protection. The reaction mixture was poured into saturated aqueous KF solution (100 mL) and stirred for 1 h. The aqueous phase was extracted with EA (50 mL × 3). The combined organic phase was washed with brine (100 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by (PM9) to give **compound 1.484** (650 mg, 3.85 mmol, 85.3% yield) as yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.50 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.40 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.25–7.23 (m, 1H), 7.15 (dd, *J* = 17.6, 10.0 Hz, 1H), 5.72 (d, *J* = 17.6 Hz, 1H), 5.39 (d, *J* = 10.0 Hz, 1H), 4.78 (s, 2H), 2.04 (br s, 1H) ppm.

2-Chloro-3-(hydroxymethyl)benzaldehyde 1.485

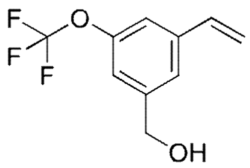


[00317] Ozone was bubbled into a solution of **compound 1.484** (379.71 mg, 2.25 mmol) in DCM (10 mL) at -70 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (1.40 g, 22.52 mmol) was added. The mixture was warmed up to 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified by (PM9) to give **compound 1.485** (230 mg, 1.35 mmol, 59.9% yield) as a light yellow solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.53 (s, 1H), 7.87 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 4.88 (s, 2H), 2.22 (s, 1H) ppm.

Synthesis of intermediate 1.488

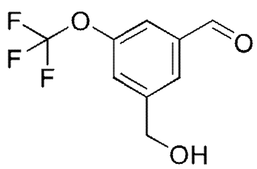
(3-(Trifluoromethoxy)-5-vinylphenyl)methanol



[00318] To a solution of [3-bromo-5-(trifluoromethoxy)phenyl]methanol (800 mg, 2.95 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (681.90 mg, 4.43 mmol) in DME (10 mL) was added Pd(dppf)Cl_2 (215.98 mg, 295.17 μmol) and CsF (896.72 mg, 5.90 mmol). The mixture was heated to 80 °C and stirred for 12 h under nitrogen protection. The mixture was poured into water (50 mL) and the aqueous phase was extracted with EA (30 mL × 3). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM12) to give **compound 1.487** (600 mg) as a colorless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.38 (t, *J* = 8.0 Hz, 1H), 7.33 (s, 1H), 7.25 (s, 1H), 6.69 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.80 (d, *J* = 17.2 Hz, 1H), 5.35 (d, *J* = 10.8 Hz, 1H), 4.73 (s, 2H) ppm.

3-(Hydroxymethyl)-5-(trifluoromethoxy)benzaldehyde 1.488

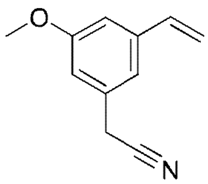


[00319] Ozone was bubbled into a solution of **compound 1.487** (200 mg, 916.71 μmol) in DCM (10 mL) at -70 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (569.55 mg, 9.17 mmol) was added. The mixture was warmed up to 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified (PM6) to give **compound 1.488** (110 mg, 499.67 μmol, 54.5% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.02 (s, 1H), 7.83 (s, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 4.84 (s, 2H) ppm.

Synthesis of Intermediate 1.491

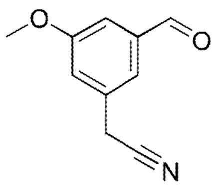
2-(3-Methoxy-5-vinylphenyl)acetonitrile 1.490



[00320] To a solution of 2-(3-bromo-5-methoxy-phenyl)acetonitrile (1.1 g, 4.87 mmol) (US2014/73629A1) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.12 g, 7.30 mmol) in DME (20 mL) was added Pd(dppf)Cl_2 (356.03 mg, 486.58 μmol) and CsF (1.48 g, 9.73 mmol). The mixture was heated to 80 °C and stirred for 12 h under nitrogen atmosphere protection. The mixture was poured into water (50 mL) and the aqueous phase was extracted with EA (30 mL × 3). The combined organic phase was washed with brine (80 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM11) to afford **compound 1.490** (550 mg, 3.18 mmol, 65.3% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 6.96 (s, 1H), 6.90 (s, 1H), 6.77 (s, 1H), 6.67 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.78 (d, *J* = 17.6 Hz, 1H), 5.32 (d, *J* = 10.8 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 2H) ppm.

2-(3-Formyl-5-methoxyphenyl)acetonitrile 1.491

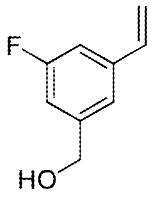


[00321] Ozone was bubbled into a solution of **compound 1.490** (550 mg, 3.18 mmol) in DCM (10 mL) at -70 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (1.97 g, 31.75 mmol) was added. The mixture was warmed up to 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and (PM7) to afford **compound 1.491** (240 mg, 1.37 mmol, 43.2% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.98 (s, 1H), 7.43 (s, 1H), 7.38 (s, 1H), 7.16 (s, 1H), 3.90 (s, 3H), 3.82 (s, 2H) ppm.

Synthesis of Intermediate 1.500

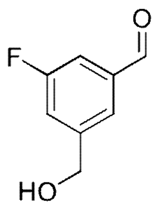
(3-Fluoro-5-vinylphenyl)methanol 1.499



[00322] To a solution of (3-bromo-5-fluoro-phenyl)methanol (3 g, 14.63 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane(3.38 g, 21.95 mmol) in 1. 4-dioxane (60 mL) and water (6 mL) was added K_2CO_3 (4.04 g, 29.26 mmol) and Pd(dppf)Cl_2.CH_2Cl_2 (1.19 g, 1.46 mmol) under nitrogen. The resulting mixture was stirred at 90 °C for 12 h. The mixture was concentrated *in vacuo* and the residue was (PM7) to afford **compound 1.499** (2.0 g, 13.15 mmol, 91% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.22 (s, 1H), 7.08 (dd, *J* = 10.0, 1.6 Hz, 1H), 6.99 (d, *J* = 9.6 1H), 6.72 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.82 (d, *J* = 17.6 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 4.60 (s, 2H) ppm.

3-Fluoro-5-(hydroxymethyl)benzaldehyde 1.500

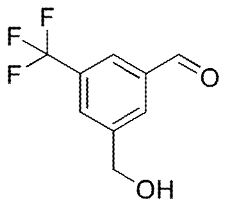


[00323] Ozone was bubbled into a solution of **compound 1.499** (3.15 g, 20.70 mmol) in DCM (50 mL) at -70 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (12.86 g, 207.01 mmol) was added. The mixture was warmed up to 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified (PM6) to give **compound 1.500** (2.9 g, 11.06 mmol, 53.4% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.98 (s, 1H), 7.67 (s, 1H), 7.48 (dd, *J* = 4.0, 2.4 Hz, 1H), 7.36 (d, *J* = 4.0 Hz, 1H), 4.80 (s, 2H) ppm.

Synthesis of Intermediate 1.501

3-(Hydroxymethyl)-5-(trifluoromethyl)benzaldehyde 1.501

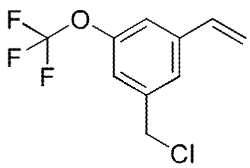


[00324] To a solution of (3-bromo-5-(trifluoromethyl)phenyl)methanol (10 g, 39.21 mmol) in THF (100 mL) was added *n*-BuLi (2.5 M, 32.94 mL) dropwise at -78 °C. After being stirred for 0.5 h, DMF (3.02 mL, 39.21 mmol) was added. The resulting mixture was stirred at -78 °C for another 0.5 h. The mixture was warmed to 20 °C and quenched with water (100 mL). The mixture was extracted with EA (150 mL × 3). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM7) to afford **compound 1.501** (3.8 g, 18.61 mmol, 47.47% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.08 (s, 1H), 8.06 (s, 1H), 7.92 (s, 1H), 7.65 (s, 1H), 4.89 (s, 2H), 2.49 (d, *J* = 8.0 Hz, 1H) ppm.

Synthesis of intermediate 1.504

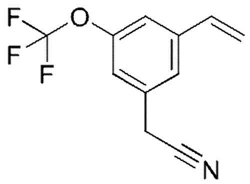
1-(Chloromethyl)-3-(trifluoromethoxy)-5-vinylbenzene 1.502



[00325] To a solution of **compound 1.487** (8.3 g, 38.04 mmol) in 1,4-dioxane (100 mL) was added $SOCl_2$ (9.05 g, 76.09 mmol) at 0 °C slowly. The mixture was then heated to 90 °C and stirred for 1 h. The mixture was concentrated and diluted with EA (20 mL). The mixture was poured into aq. $NaHCO_3$ solution (150 mL) and extracted with EA (80 mL × 3). The combined organic phase was washed with brine (150 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM14) to give **compound 1.502** (3.5 g, 14.79 mmol, 38.9% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.35 (s, 1H), 7.21 (s, 1H), 7.16 (s, 1H), 6.69 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.81 (d, *J* = 17.6 Hz, 1H), 5.39 (d, *J* = 11.2 Hz, 1H), 4.58 (s, 2H) ppm.

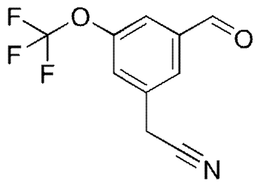
2-(3-(Trifluoromethoxy)-5-vinylphenyl)acetonitrile 1.503



[00326] To a solution of trimethylsilylcyanide (1.33 g, 13.41 mmol) and **compound 1.502** (3.5 g, 14.79 mmol) in acetonitrile (50 mL) was added TBAF (18.54 mL, 18.54 mmol, 1 M in THF). The mixture was stirred at 25 °C for 12 h. The mixture was concentrated *in vacuo* and purified (PM13) to give **compound 1.503** (2.6 g, 11.44 mmol, 77.4% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.31 (s, 1H), 7.23 (s, 1H), 7.08 (s, 1H), 6.69 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.83 (d, *J* = 17.6 Hz, 1H), 5.41 (d, *J* = 10.8 Hz, 1H), 3.78 (s, 2H) ppm.

2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile 1.504

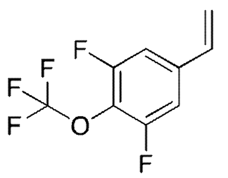


[00327] Ozone was bubbled into a solution of **compound 1.503** (2.6 g, 11.44 mmol) in DCM (30mL) at -70 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (7.11 g, 114.45 mmol) was added. The mixture was warmed up to 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and (PM7) to give **compound 1.504** (1.9 g, 8.29 mmol, 72.5% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.03 (s, 1H), 7.83 (s, 1H), 7.73 (s, 1H), 7.48 (s, 1H), 3.90 (s, 2H) ppm.

<u>**Synthesis of Intermediate 1.507**</u>

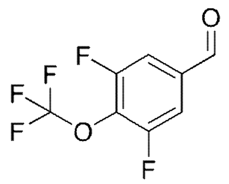
1,3-Difluoro-2-(trifluoromethoxy)-5-vinylbenzene 1.506



[00328] To a solution of 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (6.26 g, 40.62 mmol) and 5-bromo-1,3-difluoro-2-(trifluoromethoxy)benzene (7.5 g, 27.08 mmol) in DME (100 mL) was added Pd(dppf)Cl_2 (1.98 g, 2.71 mmol) and CsF (8.23 g, 54.15 mmol). The mixture was heated to 80 °C and stirred for 12 h under nitrogen. The mixture was poured into water (300 mL) and the aqueous phase was extracted with EA (150 mL × 3). The combined organic phase was washed with brine (300 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM14) to give **compound 1.506** (3.2 g, 14.28 mmol, 52.7% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.05 (s, 1H), 7.03 (s, 1H), 6.61 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.78 (d, *J* = 17.2 Hz, 1H), 5.43 (d, *J* = 10.8 Hz, 1H) ppm.

3,5-Difluoro-4-(trifluoromethoxy)benzaldehyde 1.507

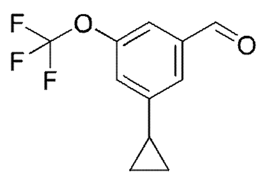


[00329] Ozone was bubbled into a solution of **compound 1.506** (3.2 g, 14.28 mmol) in DCM (40mL) at -70 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (8.87 g, 142.78 mmol) was added. The mixture was warmed up to 20 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified (PM6) to give **compound 1.507** (1.2 g, 5.31 mmol, 37.2% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.95 (s, 1H), 7.59 (s, 1H), 7.57 (s, 1H) ppm.

<u>**Synthesis of Intermediate 1.509**</u>

3-Cyclopropyl-5-(trifluoromethoxy)benzaldehyde 1.509

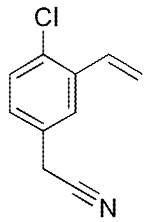


[00330] To a mixture of 3-bromo-5-(trifluoromethoxy)benzaldehyde (2 g, 7.43 mmol), cyclopropylboronic acid (702.47 mg, 8.18 mmol) and Pd(dppf)Cl_2 (271.99 mg, 371.73 μmol) in 1,4-dioxane (20 mL) and water (2 mL) was added K_2CO_3 (2.05 g, 14.87 mmol). The mixture was stirred at 80 °C for 12 h under nitrogen protection. The mixture was concentrated *in vacuo* and the residue was purified (PM14) to afford **compound 1.509** (1.1 g, 4.78 mmol, 64.3% yield) as a yellow oil.

LCMS (AM3): rt = 0.958 min, (231.1 $[M+H]^+$), 97.7% purity.

Synthesis of intermediate 1.521

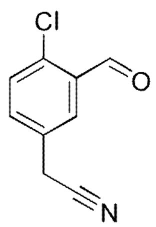
2-(4-Chloro-3-vinylphenyl)acetonitrile 1.520



[00331] To a mixture of 2-(3-bromo-4-chlorophenyl)acetonitrile (1.2 g, 5.21 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.20 g, 7.81 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (425.17 mg, 520.63 μmol) and K_2CO_3 (1.44 g, 10.41 mmol) under nitrogen protection. The mixture was heated to 90 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM6) to afford **compound 1.520** (840 mg, 4.73 mmol, 90.8% yield) as a yellow oil.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 7.61 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.4, 2.4 Hz, 1H), 7.07 (dd, J = 17.6, 11.2 Hz 1H), 5.82 (d, J = 17.6 Hz, 1H), 5.42 (d, J = 11.2 Hz, 1H), 3.89 (s, 2H) ppm.

2-(4-Chloro-3-formylphenyl)acetonitrile 1.521

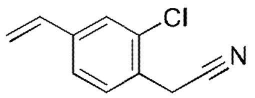


[00332] Ozone was bubbled into a solution of **compound 1.520** (840 mg, 4.73 mmol) in DCM (20 mL) at -78 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (2.94 g, 47.29 mmol) was added at -78 °C. The mixture was then warmed to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and the residue was dissolved in EA (60 mL) and washed with brine (50 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM11) to afford **compound 1.521** (600 mg, 3.34 mmol, 70.6% yield) as a yellow solid.

^1H NMR (400 MHz, MeOH-d_4) δ: 10.42 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.64–7.56 (m, 2H), 3.99 (s, 2H) ppm.

Synthesis of Intermediate 1.524

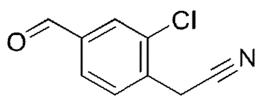
2-(2-Chloro-4-vinylphenyl)acetonitrile 1.523



[00333] To a mixture of 2-(4-bromo-2-chloro-phenyl)acetonitrile (1.6 g, 6.94 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.60 g, 10.41 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added Pd(dppf)Cl_2·CH_2Cl_2 (566.89 mg, 694.18 μmol) and K_2CO_3 (1.92 g, 13.88 mmol) under nitrogen protection. The mixture was heated to 90 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM6) to afford **compound 1.523** (1.1 g, 6.19 mmol, 89.2% yield) as a yellow oil.

^1H NMR (400 MHz, MeOH-d_4) δ: 7.50 (s, 1H), 7.46–7.43 (d, 1H), 7.40–7.38 (d, 1H), 6.69 (dd, *J* = 17.6, 11.8 Hz, 1H), 5.84 (d, *J* = 17.6 Hz, 1H), 5.33 (d, *J* = 11.8 Hz, 1H), 3.93 (s, 2H) ppm.

2-(2-Chloro-4-formylphenyl)acetonitrile 1.524

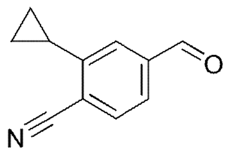


[00334] Ozone was bubbled into a solution of **compound 1.523** (1.1 g, 6.19 mmol) in DCM (20 mL) at -78 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (3.85 g, 61.93 mmol) was added. The mixture was warmed to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* to remove the solvent. The residue was dissolved in EA (60 mL) and washed with brine (50 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM11) to afford **compound 1.524** (0.6 g, 3.34 mmol, 53.9% yield) as a pink solid.

^1H NMR (400 MHz, MeOH-d_4) δ: 9.97 (s, 1H), 8.00 (s, 1H), 7.91 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 4.10 (s, 2H) ppm.

Synthesis of Intermediate 1.526

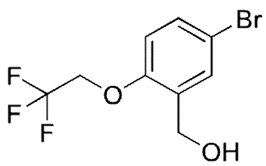
2-Cyclopropyl-4-formylbenzonitrile 1.526



[00335] To a mixture of cyclopropylboronic acid (122.69 mg, 1.43 mmol) and 2-bromo-4-formyl-benzonitrile (200, mg, 952.26 μmol) in 1,4-dioxane (10 mL) and water (1 mL) was added Pd(dppf)Cl_2·CH_2Cl_2 (77.77 mg, 95.23 μmol) and K_2CO_3 (263.22 mg, 1.90 mmol) under nitrogen protection. The mixture was heated to 90 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified (PM4) to afford **compound 1.526** (100 mg, 584.13 μmol, 61.3% yield) as a yellow oil, which was used without characterization.

Synthesis of Intermediate 1.530

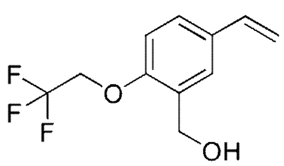
(5-Bromo-2-(2,2,2-trifluoroethoxy)phenyl)methanol 1.528



[00336] To a solution of 4-bromo-2-(hydroxymethyl)phenol (2 g, 9.85 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (2.29 g, 9.85 mmol) in DMF (10 mL) was added K_2CO_3 (2.04 g, 14.78 mmol). The mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue which was purified (PM10) to afford **compound 1.528** (1.83 g, 6.42 mmol, 65.2% yield) as a yellow solid.

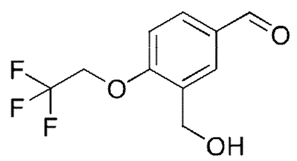
^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.48 (d, *J* = 2.4 Hz, 1H), 7.32 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 4.64 (s, 2H), 4.31 (q, *J* = 4.8 Hz, 2H), 1.87 (br s, 1H) ppm.

(2-(2,2,2-Trifluoroethoxy)-5-vinylphenyl)methanol 1.529



[00337] To a solution of **compound 1.528** (400 mg, 1.40 mmol) in toluene (5 mL) was added tributyl(vinyl)stannane (489.45 mg, 1.54 mmol) and $Pd(PPh_3)_4$ (81.08 mg, 70.16 μmol). The reaction mixture was heated to 100 °C and stirred for 12 h under nitrogen protection. The reaction mixture was diluted with saturated aqueous KF solution (80 mL) and extracted with EA (60 mL × 2). The organic layer was washed with brine (70 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM10) to afford **compound 1.529** (580 mg) as a yellow oil, which was used directly without characterization.

3-(Hydroxymethyl)-4-(2,2,2-trifluoroethoxy)benzaldehyde 1.530

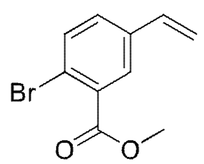


[00338] Ozone was bubbled into a solution of **compound 1.529** (200 mg, 861.33 μmol) in DCM (20 mL) at -78 °C until the reaction mixture turned blue. After excess ozone was purged, DMS (535.14 mg, 8.61 mmol) was added. The mixture was warmed to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo*, dissolved in EA (60 mL), washed with brine (50 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM6) to afford **compound 1.530** (60 mg, 256.22 μmol, 29.7% yield) as a yellow solid.

^1H NMR (400 MHz, MeOH-*d₄*) δ: 9.90 (s, 1H), 8.05 (s, 1H), 7.86 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 4.74–4.67 (m, 4H) ppm.

<u>**Synthesis of Intermediate 1.537**</u>

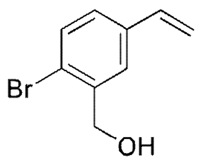
Methyl 2-bromo-5-vinylbenzoate 1.534



[00339] To a solution of methyl 2-bromo-5-iodobenzoate (5 g, 14.67 mmol) in toluene (80 mL) was added tributyl(vinyl)stannane (5.430 g, 17.12 mmol) and $Pd(PPh_3)_4$ (1.69 g, 1.47 mmol). The reaction mixture was heated to 90 °C and stirred for 12 h under nitrogen protection. The reaction mixture was poured into saturated aqueous KF solution (40 mL) and extracted with EA (50 mL × 3). The combined organic layer was washed with brine (80 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM1) to afford **compound 1.534** (3.2 g) as a white solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.79 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.65 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.79 (d, *J* = 17.2 Hz, 1H), 5.34 (d, *J* = 10.8 Hz, 1H), 3.93 (s, 3H) ppm.

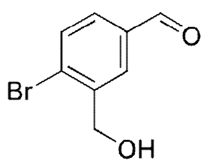
(2-Bromo-5-vinylphenyl)methanol 1.535



[00340] To a solution of **compound 1.534** (3.2 g, 13.27 mmol) in THF (50 mL) was added $LiAlH_4$ (503.79 mg, 13.27 mmol) slowly at 0 °C. The reaction mixture was warmed to 20 °C and stirred for 0.5 h. The reaction mixture was quenched with addition of EA (50 mL) under 0 °C followed by addition of water (0.5 mL), 10% NaOH aq. (0.5 mL) and water (1.0 mL). After being stirred for 0.5 h, anhydrous Na_2SO_4 was added. The resulting suspension was stirred for 0.5 h and filtered. The filtrate was concentrated *in vacuo* to afford **compound 1.535** (2.5 g, 11.73 mmol, 88.4% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.52 (d, *J* = 1.6 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.20 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.68 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.80 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.8 Hz, 1H), 4.74 (d, *J* = 6.4 Hz, 2H), 2.06 (t, *J* = 6.0 Hz, 1H) ppm.

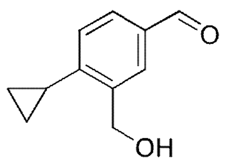
4-Bromo-3-(hydroxymethyl)benzaldehyde 1.536



[00341] Ozone was bubble into a solution of **compound 1.535** (2.5 g, 11.73 mmol) in DCM (20 mL) at -78 °C until the mixture turned blue. After excessive ozone was purged, DMS (15.6 g, 251.23 mmol) was added. The reaction mixture was warmed to 20 °C and stirred for 12.5 h. The residue was concentrated *in vacuo* and then diluted with water (40mL). The mixture was extracted with DCM (50 mL × 2) and the combined organic phase was washed with brine (50 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM12) to afford **compound 1.536** (1.5 g, 6.98 mmol, 59.45% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.99 (s, 1H), 8.03 (s, 1H), 7.70 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.65 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.81 (s, 2H), 2.47 (br s, 1H) ppm.

4-Cyclopropyl-3-(hydroxymethyl)benzaldehyde 1.537

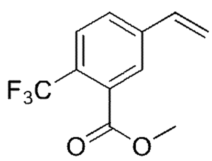


[00342] A mixture of **compound 1.536** (1.3 g, 6.05 mmol), cyclopropylboronic acid (571.20 mg, 6.65 mmol), Na_2CO_3 (1.28 g, 12.09 mmol) and Pd(dppf)Cl_2 (442.34 mg, 604.53 μmol) in 1,4-dioxane (20 mL) and water (2 mL) was stirred at 80 °C for 12 h under nitrogen protection. The reaction mixture was diluted with water (30 mL) and extracted with EA (50 mL × 2). The combined organic layer was washed with brine (80 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM47) to afford **compound 1.537** (120 mg, 681.00 μmol, 11.3% yield) as a yellow oil.

LCMS (AM3): rt = 0.763 min, (177.7 $[M+H]^+$), 94.3% purity. MeOH

<u>**Synthesis of intermediate 1.589**</u>

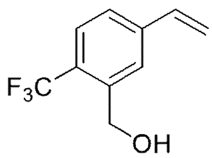
Methyl 2-(trifluoromethyl)-5-vinylbenzoate 1.587



[00343] To a solution of methyl 5-bromo-2-(trifluoromethyl)benzoate (730 mg, 2.58 mmol) in 1,4-dioxane (15 mL) and water (1.5 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (595.83 mg, 3.87 mmol), K_2CO_3 (712.92 mg, 5.16 mmol) and Pd(dppf)Cl_2·CH_2Cl_2 (210.62 mg, 257.91 μmol), then the reaction mixture was heated to 90 °C and stirred for 12 h under nitrogen protection. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified (PM7) to afford **compound 1.587** (600 mg) as a pink oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.79 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 6.75 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.90 (d, *J* = 17.6 Hz, 1H), 5.46 (d, *J* = 10.8 Hz, 1H), 3.94 (s, 3H) ppm.

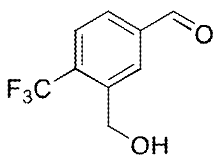
(2-(Trifluoromethyl)-5-vinylphenyl)methanol 1.588



[00344] To a solution of **compound 1.587** (600 mg, 2.61 mmol) in THF (10 mL) was added LAH (98.92 mg, 2.61 mmol) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with water (0.1 mL) slowly at 0 °C, followed by addition of 10% aq. NaOH solution (0.1 mL) and subsequently water (0.3 mL). After being stirred at 0 °C for 10 min, Na_2SO_4 (2 g) was added. The resulting suspension was stirred for 0.5 h and then was filtered. The filtrate was concentrated *in vacuo* to afford **compound 1.588** (450 mg, 2.23 mmol, 85.4% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.75 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 6.78 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.88 (d, *J* = 17.6 Hz, 1H), 5.40 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 5.4 Hz, 2H), 1.95 (br s, 1H) ppm.

3-(Hydroxymethyl)-4-(trifluoromethyl)benzaldehyde 1.589

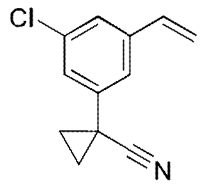


[00345] Ozone was bubbled into a solution of **compound 1.588** (450 mg, 2.23 mmol) in DCM (10 mL) at -78 °C until the reaction mixture turned blue. After excessive ozone was purged with nitrogen, DMS (1.46 g, 23.50 mmol) was added. The reaction mixture was warmed to 20 °C and stirred for 15.5 h. The reaction mixture was concentrated *in vacuo* and purified (PM6) to afford **compound 1.589** (380 mg, 1.86 mmol, 83.63% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.11 (s, 1H), 8.30 (s, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 4.98 (s, 2H) ppm.

Synthesis of Intermediate 1.630

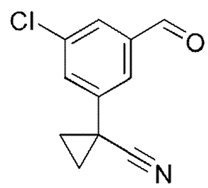
1-(3-Chloro-5-vinylphenyl)cyclopropanecarbonitrile 1.629



[00346] To a mixture of **compound 1.365** (2 g, 11.26 mmol) in DMF (30 mL) was added NaH (990.82 mg, 24.77 mmol, 60% dispersion in oil) at 0 °C. After being stirred at 0 °C for 0.5 h, 1,2-dibromoethane (2.12 g, 11.26 mmol) was added slowly. The mixture was then warmed to 25 °C and stirred for 11.5 h. The reaction mixture was quenched by addition of water (100 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM15) to afford **compound 1.629** (1.2 g, 5.89 mmol, 52.3% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.48–7.35 (m, 3H), 6.80 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.95 (d, *J* = 17.2 Hz, 1H), 5.52 (d, *J* = 10.8 Hz, 1H), 1.94–1.90 (m, 2H), 1.60–1.55 (m, 2H) ppm.

1-(3-Chloro-5-formylphenyl)cyclopropanecarbonitrile 1.630

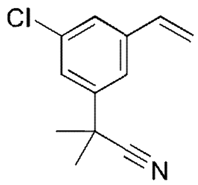


[00347] Ozone was bubbled to a solution of **compound 1.629** (1.34 g, 6.58 mmol) in DCM (15 mL) at -78 °C until the mixture turned blue. After excessive ozone was purged with nitrogen, DMS (5.31 g, 85.53 mmol) was added. The mixture was warmed up to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM14) to afford **compound 1.630** (800 mg, 3.89 mmol, 59.1% yield) as a white solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.99 (s, 1H), 7.80 (t, *J* = 1.6 Hz, 1H), 7.66 (t, *J* = 1.6 Hz, 1H), 7.60 (t, *J* = 2.0 Hz, 1H), 1.89–1.86 (t, 2H), 1.54–1.51 (t, 2H) ppm.

Synthesis of Intermediate 1.632

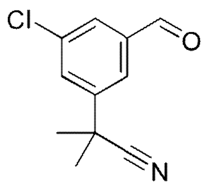
2-(3-Chloro-5-vinylphenyl)-2-methylpropanenitrile 1.631



[00348] To a solution of **compound 1.365** (3.85 g, 21.67 mmol) in DMF (50 mL) was added NaH (2.17 g, 54.19 mmol, 60% dispersion in oil) at 0 °C. After being stirred at 0 °C for 0.5 h, MeI (6.75 mL, 108.37 mmol) was added slowly. The resulting mixture was warmed to 25 °C and stirred for 11.5 h. The reaction mixture was quenched by addition of water (150 mL) and then extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM17) to afford **compound 1.631** (4 g, 19.45 mmol, 89.7% yield) as a red oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.38 (s, 1H), 7.32–7.20 (m, 2H), 6.60 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.73 (d, *J* = 17.6 Hz, 1H), 5.29 (d, *J* = 11.2 Hz, 1H), 1.19 (s, 6H) ppm.

2-(3-Chloro-5-formylphenyl)-2-methylpropanenitrile 1.632

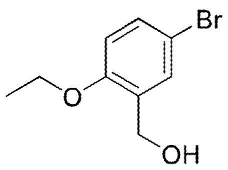


[00349] Ozone was bubbled to a solution of **compound 1.631** (4 g, 19.45 mmol) in DCM (40 mL) at -78 °C until the color turned blue. After excessive ozone was purged nitrogen, DMS (15.71 g, 252.82 mmol) was added. The mixture was warmed up to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified (PM16) to afford **compound 1.632** (750 mg, 3.61 mmol, 18.6% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.00 (s, 1H), 7.87 (s, 1H), 7.83 (s, 1H), 7.75 (s, 1H), 1.78 (s, 6H) ppm.

Synthesis of Intermediate 1.635

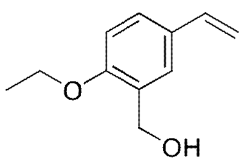
(5-Bromo-2-ethoxyphenyl)methanol 1.633



[00350] To a solution of 4-bromo-2-(hydroxymethyl)phenol (1 g, 4.93 mmol) and iodoethane (845.80 mg, 5.42 mmol) in ACN (5 mL) was added K_2CO_3 (1.02 g, 7.39 mmol) at 35 °C. The mixture was stirred at 35 °C for 12 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM11) to afford **compound 1.633** (860 mg, 3.72 mmol, 75.5% yield) as a white solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.43 (d, *J* = 2.4 Hz, 1H), 7.36 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 4.67 (s, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H) ppm.

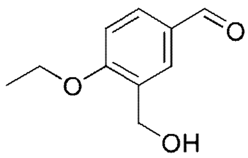
(2-Ethoxy-5-vinylphenyl)methanol 1.634



[00351] To a solution of **compound 1.633** (400 mg, 1.73 mmol) in toluene (5 mL) was added tributyl(vinyl)stannane (600 mg, 1.89 mmol) and $Pd(PPh_3)_4$ (100.01 mg, 86.55 µmol). The reaction mixture was heated to 100 °C and stirred for 12 h under nitrogen protection. The reaction mixture was poured into saturated aqueous KF solution (80 mL) and extracted with EA (60 mL × 2). The organic layer was washed with brine (70 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM10) to afford **compound 1.634** (280 mg, 1.41 mmol, 81.6% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.43 (d, *J* = 2.4 Hz, 1H), 7.29 (dd, *J* = 8.1, 2.4 Hz 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 6.67 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.63 (d, *J* = 17.6 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H), 4.66 (d, *J* = 6.4 Hz, 2H), 4.08–4.05 (m, 2H), 1.45–1.44 (m, 3H) ppm.

4-Ethoxy-3-(hydroxymethyl)benzaldehyde 1.635

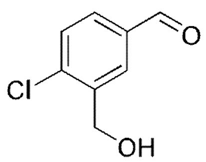


[00352] Ozone was bubbled into a solution of **compound 1.634** (280 mg, 1.57 mmol) in DCM (30 mL) at -78 °C until the mixture turned blue. After excessive ozone was purged with nitrogen, DMS (1.27 g, 20.42 mmol) was added. The mixture was warmed up to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM8) afford **compound 1.635** (170 mg, 943.40 µmol, 60.1% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.90 (s, 1H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.82 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 4.76 (s, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 1.49 (t, *J* = 6.8 Hz, 3H) ppm.

<u>**Synthesis of Intermediate 1.661**</u>

4-Chloro-3-(hydroxymethyl)benzaldehyde 1.661

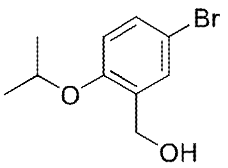


[00353] To a solution of (5-bromo-2-chloro-phenyl)methanol (1 g, 4.52 mmol) in THF (10 mL) was added n-BuLi (3.79 mL, 2.5 M) at -78 °C. After being stirred for 0.5 h, DMF (330.03 mg, 4.52 mmol) was added at -78 °C. The resulting mixture was stirred at -78 °C for an additional 0.5 h. The reaction mixture was quenched with water (50 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM7) to afford **compound 1.661** (450 mg, 2.64 mmol, 58.4% yield) as a white solid.

LCMS (AM3): rt = 0.474 min, (171.1 $[M+H]^+$), 75.7% purity.

Synthesis of Intermediate 1.668

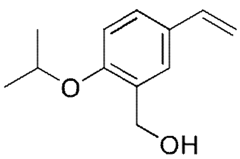
(5-Bromo-2-isopropoxyphenyl)methanol 1.666



[00354] To a solution of 4-bromo-2-(hydroxymethyl)phenol (1 g, 4.93 mmol) and 2-iodopropane (921.87 mg, 5.42 mmol) in ACN (10 mL) was added K_2CO_3 (1.02 g, 7.39 mmol) at 35 °C. The mixture was stirred at 35 °C for 12 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM10) to afford **compound 1.666** (900 mg, 3.67 mmol, 74.5% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.43 (d, *J* = 2.4 Hz, 1H), 7.35 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 4.64 (s, 2H), 4.58 (quint, *J* = 6.0 Hz, 1H), 1.95 (br s, 1H), 1.37 (d, *J* = 6.0 Hz, 6H) ppm.

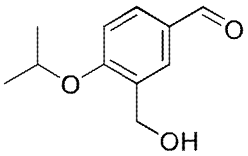
(2-Isopropoxy-5-vinylphenyl)methanol 1.667



[00355] To a solution of **compound 1.666** (400 mg, 1.73 mmol) in toluene (5 mL) was added tributyl(vinyl)stannane (569.22 mg, 1.80 mmol) and $Pd(PPh_3)_4$ (94.29 mg, 81.60 μmol). The reaction mixture was heated to 100 °C and stirred for 12 h under a nitrogen atmosphere. The reaction mixture was poured into saturated aqueous KF solution (80 mL) and then extracted with EA (60 mL × 2). The organic layer was washed with brine (70 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM11) to afford **compound 1.667** (200 mg, 1.04 mmol, 63.7% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.42 (d, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.66 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.63 (d, *J* = 17.6 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H), 4.67 (s, 2H), 4.59–4.55 (m, 1H), 1.36 (d, *J* = 6.0 Hz, 6H) ppm.

3-(Hydroxymethyl)-4-isopropoxybenzaldehyde 1.668

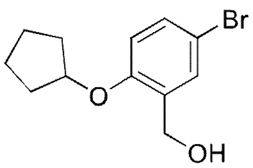


[00356] Ozone was bubbled to a solution of **compound 1.667** (190 mg, 988.28 μmol) in DCM (30 mL) at -78 °C until the mixture turned blue. After excessive ozone was purged with nitrogen, DMS (614.02 mg, 9.88 mmol) was added. The mixture was warmed up to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM6) to afford **compound 1.668** (20 mg, 102.97 μmol, 10.4% yield) as a yellow oil.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.83 (s, 1H), 7.98 (d, *J* = 2.0 Hz, 1H), 7.81 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 4.83–4.78 (m, 1H), 4.65 (s, 2H), 1.38 (d, *J* = 6.0 Hz, 6H) ppm.

Synthesis of Intermediate 1.671

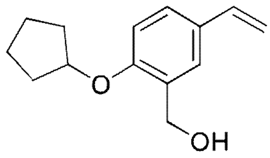
(5-Bromo-2-(cyclopentyloxy)phenyl)methanol 1.669



[00357] To a solution of 4-bromo-2-(hydroxymethyl)phenol (1 g, 4.93 mmol) and bromocyclopentane (808.18 mg, 5.42 mmol) in DMF (10 mL) was added K_2CO_3 (1.02 g, 7.39 mmol). The mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM10) to afford **compound 1.669** (700 mg, 2.58 mmol, 52.4% yield) as a yellow oil

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.40 (d, *J* = 2.4 Hz, 1H), 7.33 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 4.82–4.78 (m, 1H), 4.61 (s, 2H), 1.97–1.74 (m, 6H), 1.72–1.58 (m, 2H) ppm.

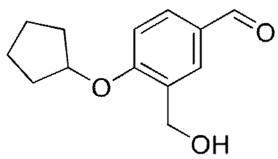
(2-(Cyclopentyloxy)-5-vinylphenyl)methanol 1.670



[00358] To a solution of **compound 1.669** (400 mg, 1.48 mmol) in toluene (5 mL) was added tributyl(vinyl)stannane (514.56 mg, 1.62 mmol) and $Pd(PPh_3)_4$ (85.23 mg, 73.76 μmol). The reaction mixture was heated to 100 °C and stirred for 12 h under a nitrogen atmosphere. The reaction mixture was poured into saturated aqueous KF solution (80 mL) and extracted with EA (60 mL × 2). The organic layer was washed with brine (70 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM10) to afford **compound 1.670** (300 mg, 1.37 mmol, 93.2% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.47 (d, *J* = 2.0 Hz, 1H), 7.32 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.68 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.69 (d, *J* = 17.6 Hz, 1H), 5.21 (d, *J* = 10.8 Hz, 1H), 4.75–4.72 (m, 2H), 4.45–4.43 (m, 1H), 1.68–1.52 (m, 4H), 1.42–1.25 (m, 4H) ppm.

4-(Cyclopentyloxy)-3-(hydroxymethyl)benzaldehyde 1.671

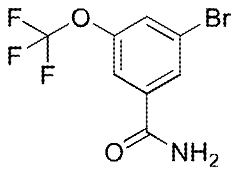


[00359] Ozone was bubbled into a solution of **compound 1.670** (300 mg, 1.37 mmol) in DCM (30 mL) at -78 °C until the mixture turned blue. After excessive ozone was purged with nitrogen, DMS (1.28 g, 20.61 mmol) was added. The mixture was warmed up to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and purified (PM6) to afford **compound 1.671** (50 mg, 227.00 μmol, 16.5% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.85 (s, 1H), 7.98 (d, *J* = 1.6 Hz, 1H), 7.82 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 5.01–4.98 (m, 1H), 4.64 (s, 2H), 1.90–1.81 (m, 4H), 1.75–1.65 (m, 4H) ppm.

Synthesis of Intermediate 1.675

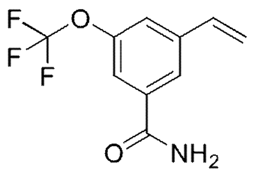
3-Bromo-5-(trifluoromethoxy)benzamide 1.673



To a solution of 3-bromo-5-(trifluoromethoxy)benzoic acid (2 g, 7.02 mmol) in DMF (20 mL) was added DIPEA (1.81 g, 14.03 mmol) and HATU (4.00 g, 10.53 mmol) at 20 °C. After being stirred at 20 °C for 0.1 h, NH_4Cl (1.50 g, 28.07 mmol) was added. The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into water (100 mL) and extracted with EA (50 mL × 2). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified (PM47) to afford **compound 1.673** (980 mg, 3.27 mmol, 46.6% yield) as a yellow solid.

LCMS (AM3): rt = 0.867 min, (284.0 $[M+H]^+$), 91.5% purity.

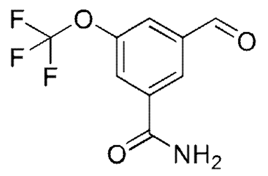
3-(Trifluoromethoxy)-5-vinylbenzamide 1.674



To a mixture of **compound 1.673** (980 mg, 3.45 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added K_2CO_3 (953.72 mg, 6.90 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (797.10 mg, 5.18 mmol) and Pd(dppf)Cl_2 (252.46 mg, 345.03 μmol) sequentially. The reaction mixture was then heated to 80 °C and stirred for 12 h under a nitrogen atmosphere. The reaction mixture was filtered and concentrated *in vacuo* and the crude product was purified (PM4) to afford **compound 1.674** (700 mg, 2.62 mmol, 75.8% yield) as a white solid.

LCMS (AM3): rt = 0.870 min, (232.1 $[M+H]^+$), 87.6% purity.

3-Formyl-5-(trifluoromethoxy)benzamide 1.675

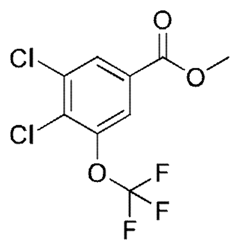


A solution of **compound 1.674** (0.7 g, 2.62 mmol) in DCM (10 mL) was cooled to -78 °C and bubbled with ozone until the colour of the mixture turned blue. The excess ozone was purged with nitrogen and then DMS (2.170 g, 34.92 mmol) was added slowly. The reaction mixture was warmed to 20 °C and stirred for another 12.5 h. The reaction mixture was concentrated *in vacuo* to give the crude product that was purified (PM150) to afford **compound 1.675** (260 mg, 1.12 mmol, 36.8% yield) as a white solid.

LCMS (AM3): rt = 0.731 min, (234.1 $[M+H]^+$), 97.5% purity.

<u>Synthesis of Intermediate 1.704</u>

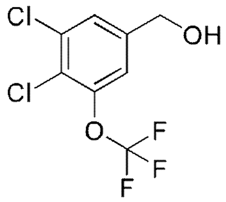
Methyl 3,4-dichloro-5-(trifluoromethoxy)benzoate 1.702



To a mixture of 3,4-dichloro-5-(trifluoromethoxy)benzoic acid (500 mg, 1.82 mmol) in MeOH (30 mL) was added $SOCl_2$ (1.08 g, 9.09 mmol) slowly at 0 °C. The mixture was then heated to 60 °C and stirred for 0.5 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with EA (50 mL × 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford **compound 1.702** (500 mg, 1.73 mmol, 95.2% yield) as a yellow oil.

^1H NMR (400 MHz, MeOH-d_4) δ: 8.15 (d, J = 2.0 Hz, 1H), 7.93 (d, J = 2.0 Hz, 1H), 3.95 (s, 3H) ppm.

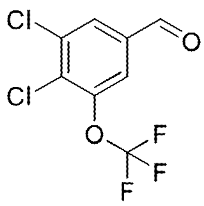
(3,4-Dichloro-5-(trifluoromethoxy)phenyl)methanol 1.703



To a solution of **compound 1.702** (500 mg, 1.73 mmol) in THF (20 mL) was added $LiAlH_4$ (78.78 mg, 2.08 mmol) slowly at 0 °C. The mixture was then warmed to 25 °C and stirred for 0.5 h. The mixture was cooled to 0 °C and diluted with EA (10 mL) and stirred for 2 min. The mixture was quenched by addition of water (0.2 mL), aq. 10% NaOH solution (0.2 mL) and water (0.6 mL). After stirring for 0.5 h, anhydrous Na_2SO_4 (3 g) was added and stirred for another 0.5 h. The resulting suspension was filtered and the filtrate was concentrated *in vacuo*. The residue was purified (PM2) to afford **compound 1.703** (400 mg, 1.48 mmol, 83% yield) as a yellow oil

^1H NMR (400 MHz, MeOH-d_4) δ: 7.55 (d, J = 1.6 Hz, 1H), 7.40 (d, J = 1.6 Hz, 1H), 4.61 (s, 2H) ppm.

3,4-Dichloro-5-(trifluoromethoxy)benzaldehyde 1.704

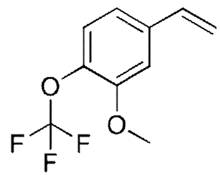


To a solution of **compound 1.703** (400 mg, 1.53 mmol) in DCM (100 mL) was added MnO_2 (1.33 g, 15.32 mmol) at 25 °C. The mixture was stirred at 25 °C for 2 h. The mixture was filtered and concentrated *in vacuo*. The residue was purified (PM7) to afford **compound 1.704** (140 mg, 540.52 µmol, 35.3% yield) as a yellow oil.

^1H NMR (400 MHz, MeOH-d_4) δ: 9.96 (s, 1H), 8.12 (d, J = 1.2 Hz, 1H), 7.92 (d, J = 1.2 Hz, 1H) ppm.

Synthesis of Intermediate 1.707

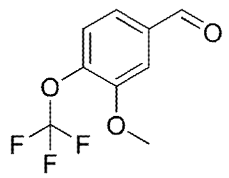
2-Methoxy-1-(trifluoromethoxy)-4-vinylbenzene 1.706



To a mixture of 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (596.66 mg, 3.87 mmol) and 4-bromo-2-methoxy-1-(trifluoromethoxy)benzene (0.7 g, 2.58 mmol) in 1,4-dioxane (10 mL) and H_2O (1 mL) was added K_2CO_3 (713.90 mg, 5.17 mmol) and Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (105.46 mg, 129.14 μmol). The mixture was heated to 90 °C and stirred for 12 h under a nitrogen atmosphere. The mixture was filtered and concentrated *in vacuo* and the residue was purified (PM14) to afford **compound 1.706** (0.28 g, 1.28 mmol, 49.7% yield) as a colorless oil.

^{1}H NMR (400 MHz, MeOH-*d4*) δ: 7.19-7.14 (m, 2H), 7.03 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.73 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.81 (d, *J* = 17.6 Hz, 1H), 5.29 (d, *J* = 0.8, 11.2 Hz, 1H), 3.89 (s, 3H) ppm.

3-Methoxy-4-(trifluoromethoxy)benzaldehyde 1.707

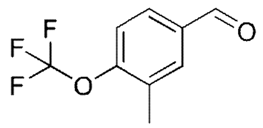


Ozone was bubbled into a solution of **compound 1.706** (0.28 g, 1.28 mmol) in DCM (20 mL) cooled to -78 °C until the colour of mixture turned blue. After excess ozone was purged by nitrogen, DMS (797.37 mg, 12.83 mmol) was added and the mixture was stirred at 25 °C for 12 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (PM14) to afford **compound 1.707** (0.22 g, 999.34 μmol, 77.9% yield) as a colourless oil.

^{1}H NMR (400 MHz, MeOH-*d4*) δ: 9.96 (s, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.57 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.47 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.96 (s, 3H) ppm.

Synthesis of Intermediate 1.709

3-Methyl-4-(trifluoromethoxy)benzaldehyde 1.709

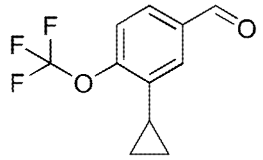


A mixture of 3-bromo-4-(trifluoromethoxy)benzaldehyde (750 mg, 2.79 mmol), $Pd(PPh_3)_4$ (322.16 mg, 278.79 μmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.40 g, 5.58 mmol) and K_2CO_3 (1.16 g, 8.36 mmol) in 1,4-dioxane (7 mL) was stirred at 100 °C for 12 h under nitrogen atmosphere. The residue was poured into water (20 mL) and extracted with EA (10 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PM1) to afford **compound 1.709** (400 mg, 1.96 mmol, 70.3% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.99 (s, 1H), 7.81 (d, *J* = 1.2 Hz, 1H), 7.76 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.37 (dd, *J* = 8.4, 1.2 Hz, 1H), 2.40 (s, 3H) ppm.

Synthesis of intermediate 1.710

3-Cyclopropyl-4-(trifluoromethoxy)benzaldehyde 1.710

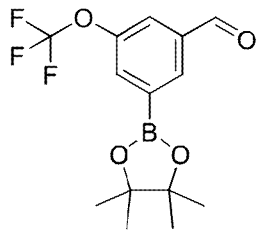


A mixture of 3-bromo-4-(trifluoromethoxy)benzaldehyde (500 mg, 1.86 mmol), cyclopropylboronic acid (239.48 mg, 2.79 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (151.78 mg, 185.86 μmol) and K_2CO_3 (513.76 mg, 3.72 mmol) in 1,4-dioxane (10 mL) and H_2O (1 mL) was stirred at 90 °C for 12 h under a nitrogen atmosphere. The mixture was concentrated *in vacuo* and the residue was purified by prep-TLC (SiO_2, PE/EA = 3/1) to afford **compound 1.710** (350 mg, 1.52 mmol, 81.8% yield) as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.94 (s, 1H), 7.79 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.44 (dd, *J* = 8.4, 1.6 Hz, 1H), 2.22-2.15 (m, 1H), 1.13-1.07 (m, 2H), 0.83-0.78 (m, 2H) ppm.

Synthesis of Intermediate 1.712

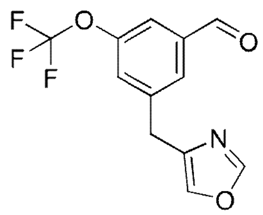
3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethoxy)benzaldehyde 1.711



A mixture of 3-bromo-5-(trifluoromethoxy)benzaldehyde (5 g, 18.59 mmol), KOAc (3.65 g, 37.19 mmol), Pin_2B_2 (5.65 g, 22.25 mmol) and Pd(dppf)Cl_2 (700 mg, 0.96 mmol) in 1,4-dioxane (100 mL) was degassed and purged with nitrogen three times. The reaction mixture was then heated to 80 °C and stirred for 16 h under a nitrogen atmosphere. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM7) to afford **compound 1.711** (6.1 g) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.05 (s, 1H), 8.23 (s, 1H), 7.88 (d, *J* = 1.2 Hz, 1H), 7.82-7.81 (m, 1H), 1.38 (s, 12H) ppm.

3-(Oxazol-4-ylmethyl)-5-(trifluoromethoxy)benzaldehyde 1.712

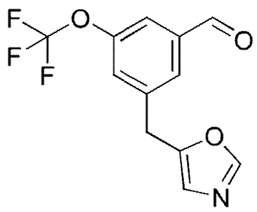


A mixture of **compound 1.711** (1.83 g, 5.79 mmol), 4-(chloromethyl)oxazole (680 mg, 5.79 mmol), K_2CO_3 (2.04 g, 14.76 mmol) and Pd(dppf)Cl_2 (212 mg, 0.29 mol) in 1,4-dioxane (16 mL) and H_2O (4 mL) was degassed and purged with nitrogen three times. The reaction mixture was then heated to 80 °C and stirred for 2 h under a nitrogen atmosphere. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM7) to afford **compound 1.712** (170 mg, 10.8% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.98 (s, 1H), 7.88 (s, 1H), 7.73 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 4.01 (s, 2H) ppm.

Synthesis of Intermediate 1.713

3-(Oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzaldehyde 1.713

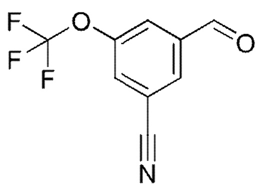


A mixture of **compound 1.711** (2.03 g, 6.41 mmol), 5-(chloromethyl)oxazole (750 mg, 6.38 mmol), K_2CO_3 (2.25 g, 16.28 mmol) and Pd(dppf)Cl_2 (240 mg, 0.33mmol) in 1,4-dioxane (16 mL) and H_2O (4 mL) was degassed and purged with nitrogen three times. The reaction mixture was then heated to 80 °C and stirred for 2 h under a nitrogen atmosphere. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM7) to afford **compound 1.713** (650 mg 37.6% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.99 (s, 1H), 7.84 (s, 1H), 7.70 (s, 1H), 7.64 (s, 1H), 7.35 (s, 1H), 6.89 (s, 1H), 4.13 (s, 2H) ppm.

Synthesis of intermediate 1.714

3-Formyl-5-(trifluoromethoxy)benzonitrile 1.714

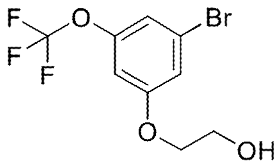


A mixture of 3-bromo-5-(trifluoromethoxy)benzaldehyde (700 mg, 2.60 mmol), $Zn(CN)_2$ (910 mg, 7.75 mmol) and $Pd(PPh_3)_4$ (300 mg, 0.26 mmol) in DMF (10 mL) was degassed and purged with nitrogen three times. The reaction mixture was heated to 90 °C and stirred for 1.5 h under nitrogen atmosphere. The reaction mixture was filtered and the filtrate was diluted with water (40 mL). The resultant mixture was extracted with EA (20 mL x 3) and the combined organic phase was washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM12) to afford **compound 1.714** (0.23 g, 41.1% yield) as a white solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.05 (s, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.76 (s, 1H) ppm.

Synthesis of Intermediate 1.718

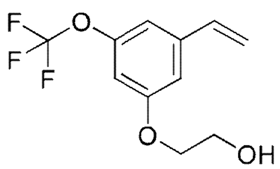
2-(3-Bromo-5-(trifluoromethoxy)phenoxy)ethanol 1.716



A mixture of 3-bromo-5-(trifluoromethoxy)phenol (930 mg, 3.62 mmol), 2-bromoethanol (500 mg, 4.00 mmol) and K_2CO_3 (1.00 g, 7.24 mmol) in DMF (10 mL) was stirred at 100 °C for 16 h. The reaction mixture was diluted with water (40 mL) and the resulting mixture was extracted with EA (10 mL x 3). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM7) to afford **compound 1.716** (1.1 g) as a colourless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.03-7.02 (m, 2H), 6.74 (s, 1H), 4.08 (t, *J* = 4.8 Hz, 2H), 3.97 (t, *J* = 4.8 Hz, 2H) ppm.

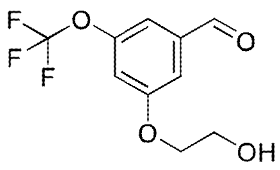
2-(3-(Trifluoromethoxy)-5-vinylphenoxy)ethanol 1.717



A mixture of **compound 1.716** (1.1 g, 3.65 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.1 g, 7.14 mmol), K_2CO_3 (1.01 g, 7.31 mmol) and Pd(dppf)Cl_2 (134 mg, 0.18 mmol) in 1,4-dioxane (10 mL) and H_2O (2 mL) was degassed and purged with nitrogen three times. The reaction mixture was heated to 80 °C and stirred under N_2 for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM4) to afford **compound 1.717** (630 mg, 69.5% yield) as a brown oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 6.89 (d, *J* = 2.0 Hz, 2H), 6.69-6.61 (m, 2H), 5.77 (d, *J* = 17.2 Hz, 1H), 5.34 (d, *J* = 10.8 Hz, 1H), 4.10 (t, *J* = 4.8 Hz, 2H), 3.98 (t, *J* = 4.8 Hz, 2H) ppm.

3-(2-Hydroxyethoxy)-5-(trifluoromethoxy)benzaldehyde 1.718

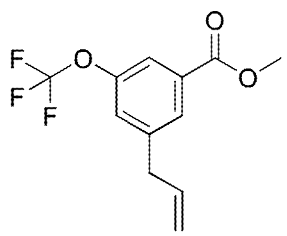


Ozone was bubbled through a solution of **compound 1.717** (630 mg, 2.54 mmol) in DCM (10 mL) at -70 °C until the colour of the solution turned blue. The excess ozone was purged with nitrogen and then DMS (1.58 g, 25.38 mmol) was added. The mixture was warmed to room temperature and stirred for 14 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM6) to afford **compound 1.718** (400 mg, 63.0% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.95 (s, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.34 (d, *J* = 0.8 Hz, 1H), 7.06 (d, *J* = 1.2 Hz, 1H), 4.17 (t, *J* = 4.4 Hz, 2H), 4.02 (t, *J* = 4.4 Hz, 2H) ppm.

Synthesis of Intermediate 1.723

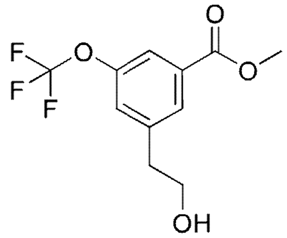
Methyl 3-allyl-5-(trifluoromethoxy)benzoate 1.720



A mixture of methyl 3-bromo-5-(trifluoromethoxy)benzoate (5 g, 16.72 mmol), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.21 g, 25.08 mmol), K_2CO_3 (4.62 g, 33.44 mmol) and Pd(dppf)Cl_2 (612 mg, 0.84 mmol) in 1,4-dioxane (40 mL) and H_2O (10 mL) was degassed and purged with nitrogen three times. The reaction mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM17) to afford **compound 1.720** (3.95 g, 90.8% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.83 (s, 1H), 7.74 (s, 1H), 7.24 (s, 1H), 6.00-5.90 (m, 1H), 5.17-5.10 (m, 2H), 3.94 (s, 3H), 3.46 (d, *J* = 5.6 Hz, 2H) ppm.

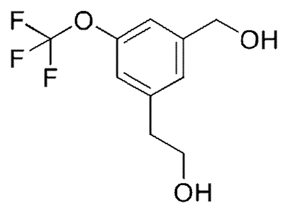
Methyl 3-(2-hydroxyethyl)-5-(trifluoromethoxy)benzoate 1.721



Ozone was bubbled through a solution of **compound 1.720** (3.95 g, 15.18 mmol) in DCM (40 mL) at - 70 °C until the colour of the reaction solution turned blue. After excess ozone was purged with nitrogen, $NaBH_4$ (2 g, 52.87 mmol) was added and the reaction mixture was warmed to 25 °C and stirred for 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (40 mL) and then extracted with DCM (40 mL x 3). The combined organic phase was washed with brine (120 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM7) to afford **compound 1.721** (1.7 g, 42.4% yield) as a yellow oil.

^1H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.86 (s, 1H), 7.75 (s, 1H), 7.30 (s, 1H), 3.95-3.89 (m, 5H), 2.93 (t, *J* = 6.4 Hz, 2H), 1.75 (br s, 1H) ppm.

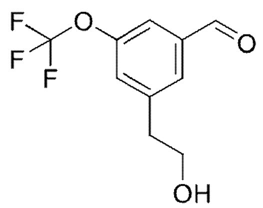
2-(3-(Hydroxymethyl)-5-(trifluoromethoxy)phenyl)ethanol 1.722



To a solution of **compound 1.721** (0.8 g, 3.03 mmol) in THF (10 mL) was added LAH (0.2 g, 5.27 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with aq. HCl (1 N, 30 mL) and the resulting mixture was extracted with EA (20 mL x 3). The combined organic phase was washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **compound 1.722** (0.67 g, 93.7% yield) as a yellow oil, which was used directly without further purification.

^1H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.16 (s, 1H), 7.08 (s, 1H), 7.00 (s, 1H), 4.65 (s, 2H), 3.84 (t, *J* = 6.4 Hz, 2H), 2.86 (t, *J* = 6.4 Hz, 2H), 2.45-2.05 (br s, 2H) ppm.

3-(2-Hydroxyethyl)-5-(trifluoromethoxy)benzaldehyde 1.723

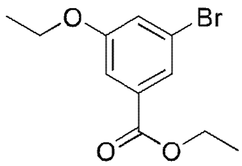


A mixture of **compound 1.722** (0.67 g, 2.84 mmol) and MnO_2 (2.47 g, 28.37 mmol) in DCM (20 mL) was stirred at 25 °C for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM2) to afford **compound 1.723** (520 mg, 78.3% yield) as a yellow oil.

^1H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.99 (s, 1H), 7.72 (s, 1H), 7.60 (s, 1H), 7.38 (s, 1H), 3.97-3.92 (m, 2H), 2.98 (t, *J* = 6.4 Hz, 2H) ppm.

Synthesis of Intermediate 1.741

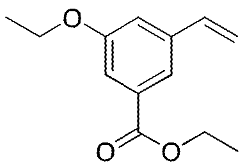
Ethyl 3-bromo-5-ethoxybenzoate 1.736



To a solution of 3-bromo-5-hydroxy-benzoic acid (2.8 g, 12.90 mmol) in ACN (50 mL) was added K_2CO_3 (8.92 g, 64.51 mmol) and iodoethane (5.03 g, 32.26 mmol) at ambient temperature. The resulting mixture was heated to 80 °C and stirred for 12 h. The mixture was filtered and concentrated *in vacuo* to afford **compound 1.736** (3.4 g, 12.45 mmol, 96.5% yield) as a light-yellow oil.

^1H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.74 (t, *J* = 1.6 Hz, 1H), 7.48 (t, *J* = 1.6 Hz, 1H), 7.22 (t, *J* = 2.0 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 1.44-1.40 (t, 3H), 1.40-1.36 (t, 3H) ppm.

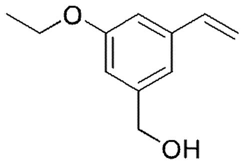
Ethyl 3-ethoxy-5-vinylbenzoate 1.737



To a solution of **compound 1.736** (3.6 g, 13.18 mmol) in DME (50 mL) was added CsF (4.00 g, 26.36 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (3.05 g, 19.77 mmol) and Pd(dppf)Cl_2 (964.45 mg, 1.32 mmol). The mixture was heated to 80 °C and stirred for 12 h under a nitrogen atmosphere. The mixture was concentrated *in vacuo* and the residue was purified (PM17) to afford **compound 1.737** (2.4 g, 10.90 mmol, 82.7% yield) as a light-yellow oil.

^1H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.68 (t, *J* = 1.2 Hz, 1H), 7.45 (t, *J* = 1.2 Hz, 1H), 7.13 (t, *J* = 2.0 Hz, 1H), 6.71 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.81 (d, *J* = 16.8 Hz, 1H), 5.31 (d, *J* = 11.2 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 1.45-1.41 (t, 3H), 1.41-1.37 (t, 3H) ppm.

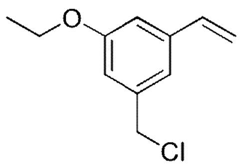
(3-Ethoxy-5-vinylphenyl)methanol 1.738



To a solution of **compound 1.737** (2.4 g, 10.90 mmol) in THF (30 mL) was added LAH (620.33 mg, 16.34 mmol) at 0 °C. The mixture was warmed to 25 °C and stirred for 1 h. The reaction was quenched by addition of aq. HCl (1 M) to pH = 3 at 0 °C. The mixture was diluted with water (50 mL) and extracted with EA (50 mL × 3). The combined organic phase was washed with brine (50 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford **compound 1.738** (2.2 g) as a light-yellow oil, which was used directly.

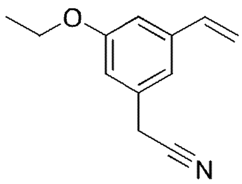
^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 6.99 (s, 1H), 6.88 (s, 1H), 6.83 (s, 1H), 6.68 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.75 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 4.66 (s, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H) ppm.

1-(Chloromethyl)-3-ethoxy-5-vinylbenzene 1.739



To a solution of **compound 1.738** (2.2 g, 12.34 mmol) in 1,4-dioxane (30 mL) was added $SOCl_2$ (3 g, 25.22 mmol) and the resulting mixture was stirred at 60 °C for 12 h. The mixture was concentrated *in vacuo* and the residue was diluted with EA (30 mL) and washed with saturated aq. $NaHCO_3$ solution (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give **compound 1.739** (2.2 g, 90.5% yield) as a brown oil, which was used directly without further purification.

2-(3-Ethoxy-5-vinylphenyl)acetonitrile 1.740

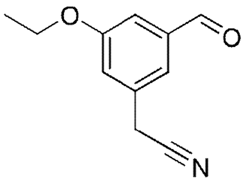


To a solution of **compound 1.739** (2.2 g, 11.19 mmol) in ACN (20 mL) was added TMSCN (4.44 g, 44.74 mmol) and TBAF (16.78 mL, 2 M in THF). The resulting mixture was heated to

80 °C and stirred for 1 h. The mixture was concentrated *in vacuo* and the residue was purified (PM11) to afford **compound 1.740** (1.4 g, 66.8% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 6.92 (s, 1H), 6.90 (s, 1H), 6.76 (s, 1H), 6.67 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.77 (d, *J*= 17.6 Hz, 1H), 5.30 (d, *J* = 11.2 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.71 (s, 2H), 1.43 (t, *J* = 7.2 Hz, 3H) ppm.

2-(3-Ethoxy-5-formylphenyl)acetonitrile 1.741

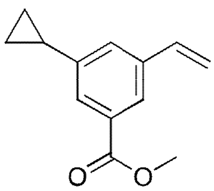


Ozone was bubbled through a solution of **compound 1.740** (1.4 g, 7.48 mmol) in DCM (20 mL) at -78 °C until the colour of the reaction mixture turned blue. After excess ozone was purged with nitrogen, DMS (8.46 g, 136.16 mmol) was added. The mixture was warmed to 20 °C and stirred for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM11) to afford **compound 1.741** (635 mg, 3.36 mmol, 44.9% yield) as a white solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.97 (s, 1H), 7.41 (s, 1H), 7.35 (s, 1H), 7.15 (s, 1H), 4.12 (q, *J* = 6.8 Hz, 2H), 3.81 (s, 2H), 1.46 (t, *J* = 6.8 Hz, 3H) ppm.

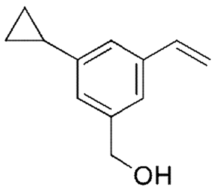
Synthesis of Intermediate 1.744

Methyl 3-cyclopropyl-5-vinylbenzoate 1.742



To a mixture of **compound 1.683** (4.4 g, 18.25 mmol) and cyclopropylboronic acid (1.72 g, 20.08 mmol) in 1,4-dioxane (44 mL) and H_2O (4.4 mL) was added K_2CO_3 (5.04 g, 36.50 mmol) and Pd(dppf)Cl_2 (667.72 mg, 912.56 μmol). The mixture was heated to 80 °C and stirred for 12 h under a nitrogen atmosphere. The mixture was concentrated *in vacuo* and the residue was purified (PM14, R_f = 0.43) to afford **compound 1.742** (1.45 g, 7.17 mmol, 39.3% yield) as a yellow oil, which was used directly.

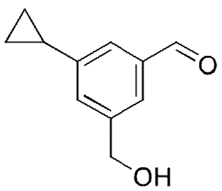
(3-Cyclopropyl-5-vinylphenyl)methanol 1.743



To a solution of LAH (251.47 mg, 6.63 mmol) in THF (20 mL) was added **compound 1.742** (1.34 g, 6.63 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction was quenched by addition of HCl (1 M) to pH = 3 at 0 °C. The mixture was diluted with water (50 mL) and extracted with EA (50 mL × 3). The combined organic phase was washed with brine (50 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford **compound 1.743** (1.2 g) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.22 (s, 1H), 7.07 (s, 1H), 7.01 (s, 1H), 6.71 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.76 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 4.68 (d, *J* = 3.6 Hz, 2H), 1.96-1.89 (m, 1H), 1.01-0.96 (m, 2H), 0.76-0.72 (m, 2H) ppm.

3-Cyclopropyl-5-(hydroxymethyl)benzaldehyde 1.744

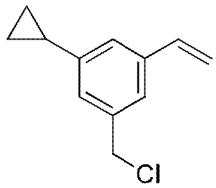


Ozone was bubbled through a solution of **compound 1.743** (300 mg, 1.72 mmol) in DCM (8 mL) at -78 °C until the colour of the reaction mixture turned blue. After excess ozone was purged with nitrogen, DMS (1.39 g, 22.38 mmol) was added. The mixture was warmed to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM11) to afford **compound 1.744** (200 mg, 1.14 mmol, 65.9% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.97 (s, 1H), 7.65 (s, 1H), 7.49 (s, 1H), 7.37 (s, 1H), 4.75 (s, 2H), 2.02-1.95 (m, 1H), 1.07-1.02 (m, 2H), 0.79-0.75 (m, 2H) ppm.

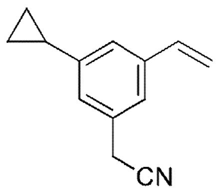
Synthesis of Intermediate 1.747

1-(Chloromethyl)-3-cyclopropyl-5-vinylbenzene 1.745



To a solution of **compound 1.743** (900 mg, 5.17 mmol) in 1,4-dioxane (10 mL) was added $SOCl_2$ (1.84 g, 15.50 mmol) at 0 ° C. The mixture was heated to 70 °C and stirred for 2 h. The reaction mixture was quenched by addition of saturated aq. $NaHCO_3$ solution (10 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **compound 1.745** (940 mg) as a yellow oil and taken on directly to the next step.

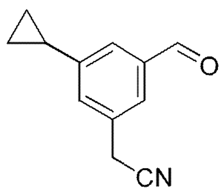
2-(3-Cyclopropyl-5-vinylphenyl)acetonitrile 1.746



A solution of **compound 1.745** (940 mg, 4.88 mmol), TMSCN (677.56 mg, 6.83 mmol) and TBAF (6.34 mL, 1 M in THF) in ACN (80 mL) was stirred at 25 °C for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM16) to afford **compound 1.746** (760 mg, 4.15 mmol, 85% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.06 (s, 1H), 6.99 (s, 1H), 6.84 (s, 1H), 6.57 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.68 (d, *J* = 17.6 Hz, 1H), 5.21 (d, *J* = 11.2 Hz, 1H), 3.63 (s, 2H), 1.86-1.78 (m, 1H), 0.94-0.89 (m, 2H), 0.66-0.62 (m, 2H) ppm.

2-(3-Cyclopropyl-5-formylphenyl)acetonitrile 1.747

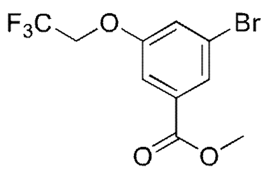


Ozone was bubbled through a solution of **compound 1.746** (760 mg, 4.15 mmol) in DCM (8 mL) at -78 °C until the colour of the mixture turned blue. After excess ozone was purged with nitrogen, DMS (3.35 g, 53.92 mmol) was added, The mixture was warmed to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* to give a residue that was purified (PM7) to afford **compound 1.747** (380 mg, 2.05 mmol, 49.5% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 9.91 (s, 1H), 7.53 (s, 1H), 7.45 (s, 1H), 7.27 (s, 1H), 3.73 (s, 2H), 1.96-1.89 (m, 1H), 1.04-0.98 (m, 2H), 0.73-0.69 (m, 2H) ppm.

Synthesis of Intermediate 1.754

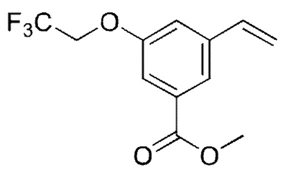
Methyl 3-bromo-5-(2,2,2-trifluoroethoxy)benzoate 1.749



To a solution of methyl 3-bromo-5-hydroxybenzoate (4.1 g, 17.75 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (4.12 g, 17.75 mmol) in DMF (40 mL) was added K_2CO_3 (3.68 g, 26.62 mmol). The mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (200mL × 3), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **compound 1.749** (5.75 g) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.74 (d, *J* = 1.6 Hz, 1H), 7.65 (t, *J* = 1.6 Hz, 1H), 7.56 (t, *J* = 1.6 Hz, 1H), 4.92 (q, *J* = 8.8 Hz, 2H), 3.87 (s, 3H) ppm.

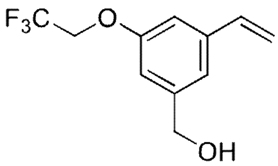
Methyl 3-(2,2,2-trifluoroethoxy)-5-vinylbenzoate 1.750



To a solution of **compound 1.749** (5.75 g, 18.37 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (4.53 g, 29.39 mmol, 4.98 mL) in DME (60 mL) was added Pd(dppf)Cl_2 (1.34 g, 1.84 mmol) and CsF (5.86 g, 38.57 mmol). The mixture was heated to 80 °C for 12 h under a nitrogen atmosphere. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM18) to afford **compound 1.750** (3 g, 11.53 mmol, 62.8% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.81 (s, 1H), 7.49 (t, *J* = 1.6 Hz, 1H), 7.22 (t, *J* = 2.0 Hz, 1H), 6.72 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.86 (d, *J* = 17.6 Hz, 1H), 5.38 (d, *J* = 10.8 Hz, 1H), 4.43 (q, *J* = 8.0 Hz, 2H), 3.95 (s, 3H) ppm.

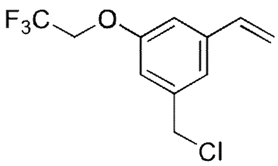
(3-(2,2,2-Trifluoroethoxy)-5-vinylphenyl)methanol 1.751



To a solution of LAH (481.34 mg, 12.68 mmol) in THF (40 mL) at 0 °C was added **compound 1.750** (3.3 g, 12.68 mmol). The mixture was stirred at 0 °C for 2 h. The reaction was quenched by addition of aq. HCl (1 M) to pH = 3 at 0 °C. The mixture was diluted with water (100 mL) and extracted with EA (100 mL × 3). The combined organic phase was washed with brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM7) to afford **compound 1.751** (2.4 g, 10.34 mmol, 81.5% yield) as a yellow oil.

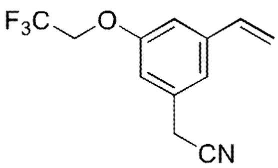
^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.09 (s, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 6.68 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.77 (d, *J* = 17.6 Hz, 1H), 5.30 (d, *J* = 10.8 Hz, 1H), 4.69 (s, 2H), 4.42-4.35 (m, 2H) ppm.

1-(Chloromethyl)-3-(2,2,2-trifluoroethoxy)-5-vinylbenzene 1.752



To a solution of **compound 1.751** (2.4 g, 10.34 mmol) in 1,4-dioxane (30 mL) was added $SOCl_2$ (3.69 g, 31.01 mmol, 2.25 mL) slowly at 0 °C. The mixture was then heated to 70 °C and stirred for 2 h. The reaction mixture was quenched by slow addition of saturated aq. $NaHCO_3$ solution (10 mL), then diluted with water (100 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **compound 1.752** (2.62 g) as a yellow oil, which was used directly without further purification.

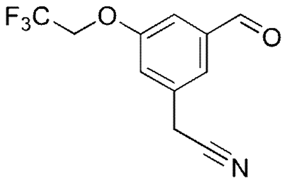
2-(3-(2,2,2-Trifluoroethoxy)-5-vinylphenyl)acetonitrile 1.753



A mixture of **compound 1.752** (2.62 g, 10.45 mmol), TMSCN (1.45 g, 14.63 mmol) and TBAF (13.59 mL, 1 M in THF) in ACN (80 mL) was stirred at 25 °C for 12 h. The mixture was concentrated *in vacuo* and purified (PM16) to afford **compound 1.753** (1.5 g, 6.22 mmol, 59.5% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.06 (s, 1H), 6.95 (s, 1H), 6.83 (s, 1H), 6.67 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.78 (d, *J* = 17.6 Hz, 1H), 5.35 (d, *J* = 10.8 Hz, 1H), 4.38 (q, *J* = 8.0 Hz, 2H), 3.74 (s, 2H) ppm.

2-(3-Formyl-5-(2,2,2-trifluoroethoxy)phenyl)acetonitrile 1.754

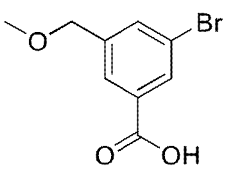


Ozone was bubbled through a solution of **compound 1.753** (1.5 g, 6.22 mmol) in DCM (15 mL) at -78 °C until the colour of mixture turned blue. After excess ozone was purged with nitrogen, DMS (5.02 g, 80.84 mmol) was added. The mixture was warmed to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM7) to afford **compound 1.754** (1 g, 4.11 mmol, 66.1% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.01 (s, 1H), 7.56 (s, 1H), 7.42 (d, *J* = 1.2 Hz, 1H), 7.27 (t, *J* = 1.6 Hz, 1H), 4.47 (q, *J* = 8.0 Hz, 2H), 3.86 (s, 2H) ppm.

<u>**Synthesis of intermediate 1.803**</u>

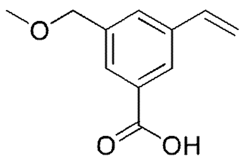
3-Bromo-5-(methoxymethyl)benzoic acid 1.797



To a mixture of methyl 3-bromo-5-(bromomethyl)benzoate (900 mg, 2.92 mmol) in MeOH (10 mL) was added NaOMe (1.58 g, 29.22 mmol). The mixture was heated to 65 °C and stirred for 4 h. The mixture was cooled to 25 °C and concentrated *in vacuo*. The residue was diluted with water (2 mL) and adjusted to pH = 5 with aq. HCl (1 M). The mixture was extracted with EA (20 mL × 2) and the combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford **compound 1.797** (700 mg) as a light yellow solid.

^{1}H NMR (400 MHz, MeOH-*d$_4$*) δ: 8.05 (s, 1H), 7.94 (s, 1H), 7.73 (s, 1H), 4.50 (s, 2H), 3.41 (s, 3H) ppm.

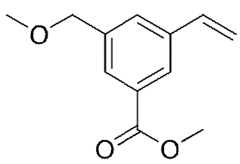
3-(Methoxymethyl)-5-vinylbenzoic acid 1.798



A mixture of **compound 1.797** (0.7 g, 2.86 mmol), CsF (867.75 mg, 5.71 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (659.87 mg, 4.28 mmol) and Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (116.63 mg, 142.82 µmol) in DME (10 mL) was stirred at 90 °C for 12 h under a nitrogen atmosphere. The mixture was filtered and concentrated and the residue was purified (PM7) to afford **compound 1.798** (400 mg, 2.08 mmol, 72.8% yield) as a yellow oil.

^{1}H NMR (400 MHz, MeOH-*d$_4$*) δ: 8.00 (s, 1H), 7.89 (s, 1H), 7.64 (s, 1H), 6.80 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.87 (d, *J* = 17.6 Hz, 1H), 5.33 (d, *J* = 11.2 Hz, 1H), 4.51 (s, 2H), 3.41 (s, 3H) ppm.

Methyl 3-(methoxymethyl)-5-vinylbenzoate 1.799

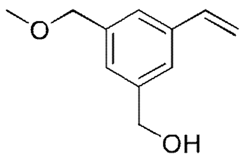


To a mixture of **compound 1.798** (400 mg, 2.08 mmol) in MeOH (30 mL) was added $SOCl_2$ (1.24 g, 10.41 mmol) at 0 °C and then the mixture was heated to 60 °C and stirred for 0.5 h. The mixture was cooled to 25 °C and poured into sat. aqueous $NaHCO_3$ solution (50 mL). The aqueous phase was extracted with EA (50 mL × 3) and the combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*.

The residue was purified (PM7) to afford **compound 1.799** (380 mg, 1.84 mmol, 88.5% yield) as a yellow oil.

^{1}H NMR (400 MHz, MeOH-*d₄*) δ: 7.98 (s, 1H), 7.87 (s, 1H), 7.64 (s, 1H), 6.79 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.87 (d, *J* = 17.6 Hz, 1H), 5.33 (d, *J* = 11.2 Hz, 1H), 4.50 (s, 2H), 3.91 (s, 3H), 3.40 (s, 3H) ppm.

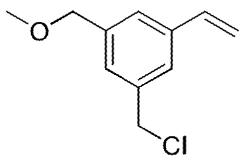
(3-(Methoxymethyl)-5-vinylphenyl)methanol 1.800



To a mixture of **compound 1.799** (380 mg, 1.84 mmol) in THF (20 mL) was added LAH (83.91 mg, 2.21 mmol) in one portion under nitrogen protection at 0 °C. The mixture was warmed to 25 °C and stirred for 0.5 h The mixture was cooled to 0 °C and diluted with EA (10 mL). The mixture was quenched by addition of water (0.2 mL) followed by aqueous NaOH solution (10% wt, 0.2 mL) and water (0.6 mL). After stirring for 0.5 h, Na_2SO_4 (1 g) was added and stirring continued for 0.5 h. The resulting suspension was filtered and concentrated *in vacuo.* The residue was purified (PM2) to afford **compound 1.800** (260 mg, 1.46 mmol, 79.2% yield) as a yellow oil.

^{1}H NMR (400 MHz, MeOH-*d₄*) δ: 7.36 (s, 1H), 7.31 (s, 1H), 7.23 (s, 1H), 6.75 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.80 (d, *J* = 17.6 Hz, 1H), 5.24 (d, *J* = 10.8 Hz, 1H), 4.60 (s, 2H), 4.46 (s, 2H), 3.38 (s, 3H) ppm.

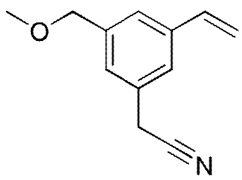
1-(Chloromethyl)-3-(methoxymethyl)-5-vinylbenzene 1.801



To a mixture of **compound 1.800** (250 mg, 1.40 mmol) in 1,4-dioxane (20 mL) was added $SOCl_2$ (333.76 mg, 2.81 mmol) at 0 °C. The mixture was then heated to 90 °C and stirred for 1 h. The mixture was concentrated *in vacuo* to afford **compound 1.801** (250 mg), which was used without purification.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 7.41 (s, 1H), 7.36 (s, 1H), 7.29 (s, 1H), 6.74 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.82 (d, *J* = 17.6 Hz, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 4.64 (s, 2H), 4.46 (s, 2H), 3.39 (s, 3H) ppm.

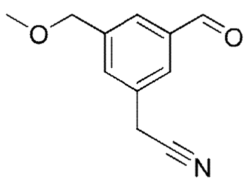
2-(3-(Methoxymethyl)-5-vinylphenyl)acetonitrile 1.802



A mixture of **compound 1.801** (250 mg, 1.27 mmol), TMSCN (189.16 mg, 1.91 mmol) and TBAF (2.54 mL, 1 M in THF) in ACN (50 mL) was stirred at 25 °C for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM6) to afford **compound 1.802** (100 mg, 534.08 µmol, 42.0% yield) as a yellow oil.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 7.37-7.35 (m, 2H), 7.24 (s, 1H), 6.74 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.83 (d, *J* = 17.6 Hz, 1H), 5.29 (d, *J* = 11.2 Hz, 1H), 4.46 (s, 2H), 3.89 (s, 2H), 3.39 (s, 3H) ppm.

2-(3-Formyl-5-(methoxymethyl)phenyl)acetonitrile 1.803

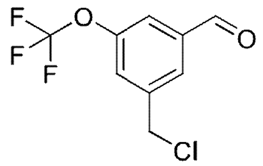


Ozone was bubbled into a solution of **compound 1.802** (100 mg, 534.08 µmol) in DCM (20 mL) at -78 °C until the colour of reaction turned blue. After excessive ozone was purged with nitrogen, DMS (331.83 mg, 5.34 mmol) was added. The mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM11) to afford **compound 1.803** (80 mg, 422.81 µmol, 79.2% yield) as a colorless oil.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.98 (s, 1H), 7.82-7.81 (m, 2H), 7.64 (s, 1H), 4.54 (s, 2H), 4.01 (s, 2H), 3.42 (s, 3H) ppm.

Synthesis of Intermediate 1.825

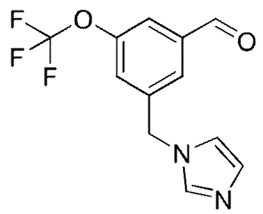
3-(Chloromethyl)-5-(trifluoromethoxy)benzaldehyde 1.824



Ozone was bubbled to a solution of **compound 1.502** (100 mg, 422.62 μmol) at -78 °C in DCM (5 mL) until the colour of the reaction turned blue. After excessive ozone was purged with nitrogen, DMS (0.44 g, 7.08 mmol) was added. The mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was concentrated *in vacuo* and the residue purified (PM7) to afford **compound 1.824** (60 mg, 251.48 μmol, 59.5% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.02 (s, 1H), 7.86 (s, 1H), 7.69 (s, 1H), 7.53 (s, 1H), 4.65 (s, 2H) ppm.

3-((1H-imidazol-1-yl)methyl)-5-(trifluoromethoxy)benzaldehyde 1.825

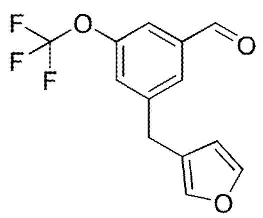


To a solution of **compound 1.824** (500 mg, 2.10 mmol) in ACN (5 mL) was added imidazole (713.33 mg, 10.48 mmol). The reaction mixture was then heated to 60 °C and stirred for 12 h. The mixture was concentrated and the crude product was purified (PM151) to afford **compound 1.825** (450 mg, 1.67 mmol, 79.5% yield) as a white solid.

LCMS (AM3): rt = 0.830 min, (271.0 [M+H]$^+$), 100% purity.

Synthesis of Intermediate 1.826

3-(Furan-3-ylmethyl)-5-(trifluoromethoxy)benzaldehyde 1.826

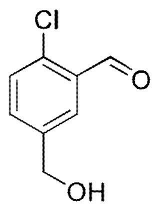


To a solution of **compound 1.824** (500 mg, 2.10 mmol) in 1,4-dioxane (1.5 mL), H_2O (0.15 mL) was added K_2CO_3 (579.28 mg, 4.19 mmol), furan-3-yl boronic acid (447.29 mg, 2.31 mmol) and Pd(dppf)Cl_2 (153.34 mg, 209.56 μmol). The reaction mixture was heated to 70 °C and stirred for 12 h under a nitrogen atmosphere The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified (PM150) to afford **compound 1.826** (360 mg, 1.24 mmol, 59.3% yield) as a yellow oil.

LCMS (AM3): rt = 1.001 min, (271.2 $[M+H]^+$), 94.4% purity.

<u>Synthesis of Intermediate 1.834</u>

2-Chloro-5-(hydroxymethyl)benzaldehyde 1.834

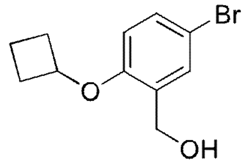


To a solution of (3-bromo-4-chloro-phenyl)methanol (1 g, 4.52 mmol) in THF (10 mL) was added *n*-BuLi (3.79 mL, 2.5 M) at -78 °C under a nitrogen atmosphere. After stirring for 0.5 h, DMF (330.01 mg, 4.52 mmol) was added and the mixture was stirred at -78 °C for 0.5 h.. The reaction mixture was diluted with water (200 mL) and extracted with EA (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by reverse-phase HPLC (AM46) to afford **compound 1.834** (200 mg, 1.17 mmol, 25.9% yield) as a white solid.

LCMS (AM3): rt = 0.570 min, (171.0 $[M+H]^+$), 39.0% purity

<u>Synthesis of Intermediate 1.64</u>

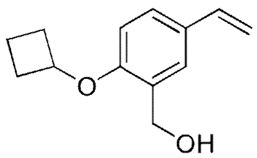
(5-bromo-2-cyclobutoxyphenyl)methanol, 1.62



[00360] To a mixture of 4-bromo-2-(hydroxymethyl)phenol (2.0 g, 9.95 mmol) and bromocyclobutane (2.66 g, 19.70 mmol) in DMF (10 mL) was added potassium carbonate (3.4 g, 24.63 mmol) under nitrogen protection at ambient temperature. The mixture was then heated to 80 °C and stirred for 12 h. The reaction mixture was poured into water (100 mL) and the aqueous phase was extracted with EA (50 mL × 2). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified (PM4) to afford **compound 1.62** (1.6 g, 6.22 mmol, 63.2% yield) as a white solid.

^{1}H NMR (400 MHz, MeOD) δ: 7.49 (d, *J* = 2.8 Hz, 1H), 7.28 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.67 (d, *J* = 8.8 Hz, 1H), 4.71–4.62 (m, 1H), 4.59 (s, 2H), 2.52–2.39 (m, 2H), 2.18–2.05 (m, 2H), 1.83–1.67 (m, 2H) ppm.

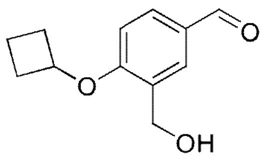
(2-cyclobutoxy-5-vinylphenyl)methanol, 1.63



[00361] To a mixture of tributyl(vinyl)stannane (1.85 g, 5.83 mmol) and **compound 1.62** (1.5 g, 5.83 mmol) in toluene (50 mL) was added tetrakis(triphenylphosphine) palladium (337.06 mg, 291.69 μmol) under nitrogen protection at ambient temperature. The mixture was then heated to 100 °C and stirred for 12 h. The mixture was cooled to room temperature and then poured into saturated aqueous KF solution (20 mL). The mixture was stirred for 30 min and then extracted with EA (50 mL × 4). The combined organic phases were washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM11) to afford **compound 1.63** (600 mg, 2.94 mmol, 50.4% yield) as a colorless oil.

^{1}H NMR (400 MHz, MeOH-*d₄*) δ: 7.48 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.71–6.62 (m, 2H), 5.62 (dd, *J* = 1.2, 17.6 Hz, 1H), 5.07 (dd, *J* = 1.2, 10.8 Hz, 1H), 4.71–4.64 (m, 1H), 4.62 (s, 2H), 2.50–2.38 (m, 2H), 2.21–2.07 (m, 2H), 1.86–1.68 (m, 2H) ppm.

4-cyclobutoxy-3-(hydroxymethyl)benzaldehyde, 1.64

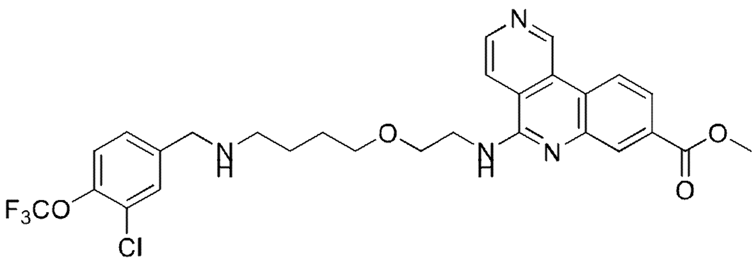


[00362] Ozone was bubbled into a solution of **compound 1.63** (600 mg, 2.94 mmol) in DCM (30 mL) at -78 °C until the reaction mixture turned blue, then the reaction mixture was warmed to 0 °C and DMS (1.82 g, 29.37 mmol) was added. The reaction mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was poured into water (50 mL) and the aqueous solution was extracted with EA (50 mL × 2). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified (PM11) to afford **compound 1.64** (250 mg, 1.21 mmol, 41.3% yield) as a yellow oil.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.83 (s, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 7.79 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 4.74–4.68 (m, 1H), 4.67 (s, 2H), 2.54–2.46 (m, 2H), 2.22–2.10 (m, 2H), 1.92–1.70 (m, 2H) ppm.

<u>Synthesis of Intermediate 1.155</u>

Methyl 5-((2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo [c][2,6]naphthyridine-8-carboxylate, 1.155

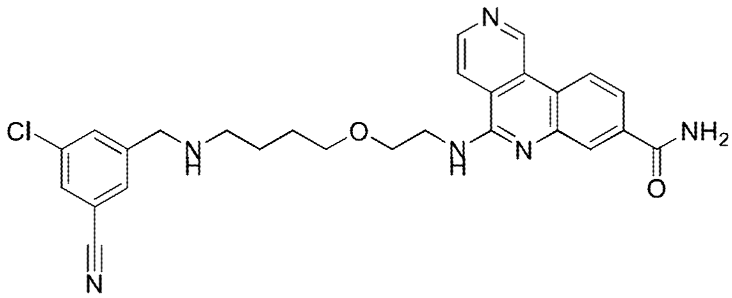


[00363] To a mixture of **compound 1.154** (180 mg, 444.57 μmol) and sodium acetate (109.41 mg, 1.33 mmol) in MeOH (15 mL) was added 3-chloro-4-(trifluoromethoxy)benzaldehyde (90 mg, 400.78 μmol) at 20 °C. The mixture was stirred at 20 °C for 2 h, then sodium triacetoxyborohydride (450.00 mg, 2.12 mmol) was added. The mixture was stirred at 20 °C for 12 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified (PM33) to afford **compound 1.155** (103 mg, 178.51 μmol, 36.5% yield) as a yellow oil.

LCMS (AM3): rt = 0.812 min, (577.1 [M+H]$^+$), 29% purity.

Synthesis of Intermediate 1.573

5-((2-(4-((3-Chloro-5-cyanobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6] naphthyridine-8-carboxamide 1.573

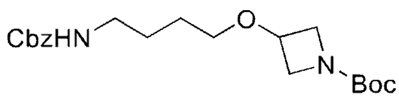


[00364] A mixture of **Intermediate E** (80 mg, 205.19 μmol), sodium acetate (67.33 mg, 820.76 μmol) and 3-chloro-5-formylbenzonitrile (33.97 mg, 205.19 μmol) in MeOH (3 mL) was stirred at 20 °C for 12.5 h, then sodium triacetoxyborohydride (130.47 mg, 615.57 μmol) was added. The reaction mixture was stirred at 20 °C for another 3 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo.* The residue was purified (PM57) to afford **compound 1.573** (60 mg, 119.29 μmol, 58.1% yield) as a white solid.

LCMS (AM7): rt = 0.865 min, (503.1 $[M+H]^+$), 66.1% purity.

Synthesis of Intermediate 1.399

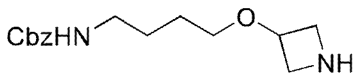
tert-Butyl 3-(4-(((benzyloxy)carbonyl)amino)butoxy)azetidine-1-carboxylate 1.395



[00365] A mixture of benzyl N-(4-bromobutyl)carbamate (3.30 g, 11.55 mmol), tert-butyl 3-hydroxyazetidine-1-carboxylate (1 g, 5.77 mmol), NaOH (2.31 g, 57.73 mmol) and TBAI (0.11 g, 298 mmol) in H_2O (5 mL) was stirred at room temperature for 20 h. The reaction mixture was diluted with water (50 mL) and extracted with MTBE (20 mL × 2). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM47) to afford **compound 1.395** (1.1 g, 50.3% yield) as light yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.37–7.28 (m, 5H), 5.10 (s, 2H), 4.86 (br s, 1H), 4.20–4.14 (m, 1H), 4.07–4.03 (m, 2H), 3.82–3.78 (m, 2H), 3.41–3.30 (m, 2H), 3.26–3.17 (m, 2H), 1.65–1.55 (m, 4H), 1.44 (s, 9H) ppm.

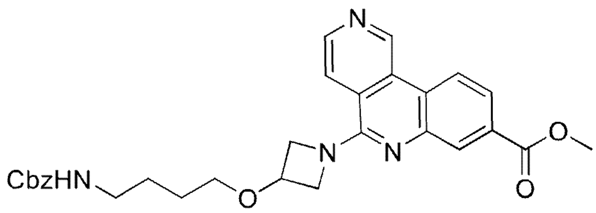
Benzyl (4-(azetidin-3-yloxy)butyl)carbamate 1.396



[00366] A mixture of **compound 1.395** (1.1 g, 2.91 mmol) and TFA (135.06 mmol, 10 mL) in DCM (10 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to afford **compound 1.396** (1.5 g, TFA salt) as a brown oil, which was used directly without further purification.

LCMS (AM3): rt = 0.334 min, (279.2 $[M+H]^+$), 71% purity.

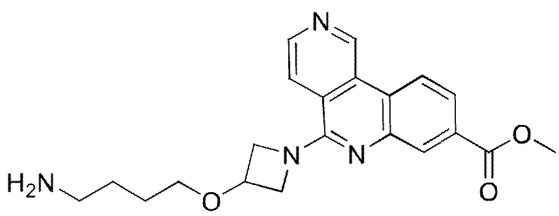
Methyl 5-(3-(4-(((benzyloxy)carbonyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6] naphthyridine -8-carboxylate 1.397



[00367] A mixture of **compound 1.396** (0.4 g, 1.44 mmol), **compound 1.1** (0.3 g, 1.10 mmol) and DIPEA (0.8 mL, 4.59 mmol) in DMSO (8 mL) was stirred at 90 °C for 16 h, a brown solid precipitated. The precipitate was collected by filtration and purified (PM47) to afford **compound 1.397** (0.4 g, 70.7% yield) as a brown solid.

LCMS (AM3): rt = 0.875 min, (515.3 $[M+H]^+$), 100% purity.

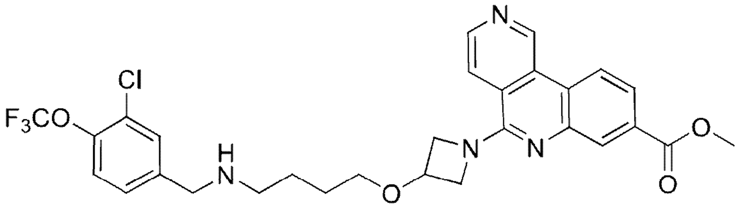
Methyl 5-(3-(4-aminobutoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylate 1.398



[00368] A mixture of **compound 1.397** (0.4 g, 0.777 mmol), palladium on carbon (0.05 g, 10% wt Pd/C) and ammonium hydroxide (0.5 mL, 3.25 mmol, 25%) in MeOH (20 mL) was hydrogenated under H_2 atmosphere (1 atm) at room temperature for 16 h. The reaction mixture was heated to 40 °C and stirred for 5 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to afford **compound 1.398** (0.29 g, 98.1% yield) as a yellow solid, which was used directly without further purification

LCMS (AM3): rt = 0.690 min, (381.2 [M+H]$^+$), 94.2% purity.

Methyl 5-(3-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylate 1.399

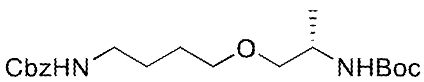


[00369] A mixture of 3-chloro-4-(trifluoromethoxy)benzaldehyde (0.17 g, 0.757 mmol) and **compound 1.398** (0.29 g, 0.762 mmol) in MeOH (10 mL) was stirred at room temperature for 16 h, then sodium triacetoxyborohydride (0.7 g, 3.30 mmol) was added. The reaction mixture was then stirred for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM67) to afford **compound 1.399** (0.17 g, 38.1% yield) as a yellow solid.

LCMS (AM3): rt = 0.815 min, (589.2 [M+H]$^+$), 100% purity.

<u>**Synthesis of intermediate 1.625**</u>

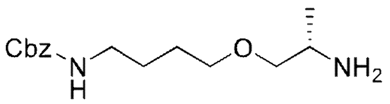
Tert-butyl N-[(1*S*)-2-[4-(benzyloxycarbonylamino)butoxy]-1-methyl-ethyl]carbamate 1.621



[00370] A mixture of tert-butyl N-[(1*S*)-2-hydroxy-1-methyl-ethyl]carbamate (2 g, 11.41 mmol), benzyl (4-bromobutyl)carbamate (6.6 g, 23.06 mmol), NaOH (4.57 g, 114.14 mmol) and TBAI (0.21 g, 0.569 mmol) in H_2O (11 mL) was stirred at room temperature for 18 h. The reaction mixture was added to water (80 mL) and the resulting mixture was extracted with EA (20 mL × 3). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM47) to afford **compound 1.621** (0.93 g, 1.83 mmol, 16.1% yield) as a colorless oil.

LCMS (AM3): rt = 0.968 min, (403.2 [M+Na]$^+$), 75.3% purity.

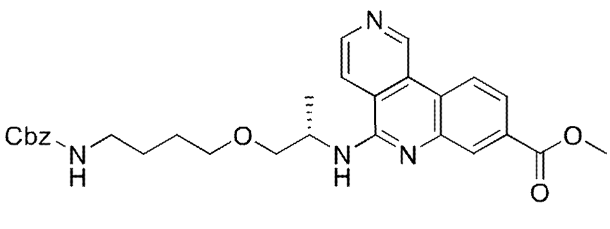
(*S*)-Benzyl (4-(2-aminopropoxy)butyl)carbamate 1.622



[00371] A mixture of **compound 1.621** (820 mg, 2.16 mmol) in a solution of HCl in 1,4-dioxane (20 mL, 4 M) was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM123) to afford **compound 1.622** (460 mg, 1.64 mmol, 76.1% yield, HCl salt) as a colorless oil.

LCMS (AM3): rt = 0.658 min, (281.1 $[M+H]^+$), 100% purity.

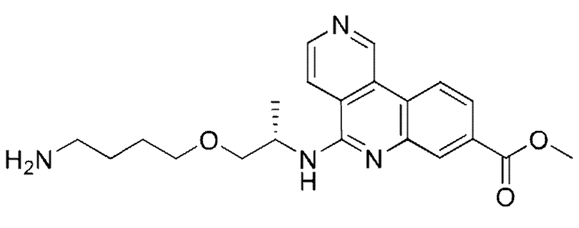
(*S*)-Methyl 5-((1-(4-(((benzyloxy)carbonyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.623



[00372] A mixture of **compound 1.622** (440 mg, 1.57 mmol, HCl salt), **compound 1.1** (480.36 mg, 1.73 mmol) and DIPEA (608.50 mg, 4.71 mmol) in DMSO (10 mL) was stirred at 80 °C for 12 h. The reaction mixture was filtered and the filtrate was purified (PM122) to afford **compound 1.623** (400 mg, 723.26 μmol, 46.1% yield) as a yellow gum.

LCMS (AM3): rt = 0.849 min, (517.4 $[M+H]^+$), 98.9% purity.

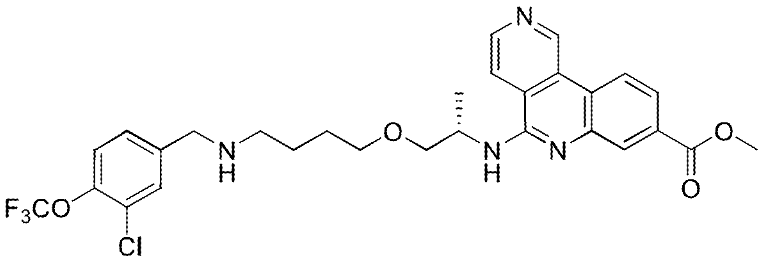
(*S*)-Methyl 5-((1-(4-aminobutoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.624



[00373] To a mixture of **compound 1.623** (400 mg, 723.26 μmol, HCl salt) and aq. ammonium hydroxide solution (1.00 mL, 25%) in MeOH (10 mL) was added 10% palladium on charcoal catalyst (0.2 g) under nitrogen protection. The resulting suspension was hydrogenated under one atmosphere H_2 at room temperature for 1 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to afford **compound 1.624** (170 mg, 61.5% yield) as a yellow solid, which was used directly without further purification.

LCMS (AM3): rt = 0.599 min, (383.3 [M+H]+), 88.7% purity.

(*S*)-Methyl 5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.625

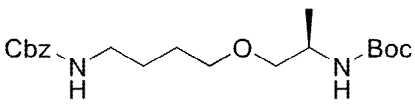


[00374] A mixture of 3-chloro-4-(trifluoromethoxy)benzaldehyde (60 mg, 267.18 μmol), **compound 1.624** (120 mg, 241.70 μmol, TFA salt) and DIPEA (93.72 mg, 725.11 μmol) in MeOH (4 mL) was stirred at room temperature for 12 h, then sodium cyanoborohydride (45 mg, 716.08 μmol) was added. The reaction mixture was then stirred at room temperature for another 1 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified (PM91) to afford **compound 1.625** (50 mg, 29.3% yield, TFA salt) as a yellow solid.

LCMS (AM3): rt = 0.852 min, (591.2 [M+H]+), 98.5% purity.

<u>**Synthesis of Intermediate 1.609**</u>

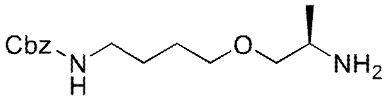
Tert-butyl N-[(1*R*)-2-[4-(benzyloxycarbonylamino)butoxy]-1-methyl-ethyl]carbamate 1.605



[00375] A mixture of tert-butyl N-[(1*R*)-2-hydroxy-1-methyl-ethyl]carbamate (2 g, 11.41 mmol), benzyl (4-bromobutyl)carbamate (6.6 g, 23.06 mmol) (Journal of the American Chemical Society, 2004, 126 (14), 4543–4549), NaOH (4.57 g, 114.14 mmol) and TBAI (0.21 g, 0.569 mmol) in H_2O (11 mL) was stirred at room temperature for 16 h. The reaction mixture was diluted with water (80 mL) and the resulting mixture was extracted with EA (20 mL x 3). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM47) to afford **compound 1.605** (0.86 g) as a colorless oil.

LCMS (AM3): rt = 0.977 min, (281.2 [M-tBuCO$_2$+2H]+), 49.7% purity.

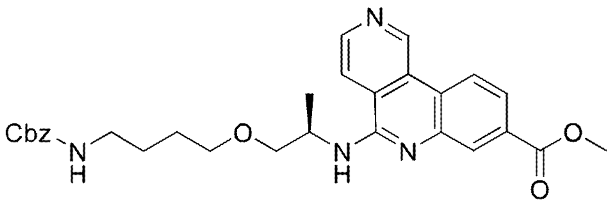
(*R*)-benzyl (4-(2-aminopropoxy)butyl)carbamate 1.606



[00376] A mixture of **compound 1.605** (0.86 g, 2.26 mmol) in a solution of HCl in 1,4-dioxane (10 mL, 4 M) was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM120) to afford **compound 1.606** (0.41 g, 57.3% yield, HCl salt) as a colorless oil

LCMS (AM3): rt = 0.719 min, (281.2 $[M+H]^+$), 100% purity.

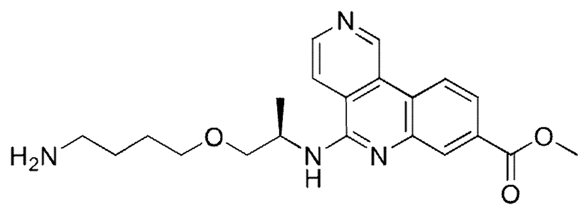
(*R*)-methyl 5-((1-(4-(((benzyloxy)carbonyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.607



[00377] A mixture of **compound 1.606** (0.41 g, 1.29 mmol, HCl salt), **compound 1.1** (0.36 g, 1.32 mmol) and DIPEA (4.02 mmol, 0.7 mL) in DMSO (4 mL) was stirred at 90 °C for 18 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* and purified (PM22) to afford **compound 1.607** (0.5 g, 67.8% yield, HCl salt) as a yellow solid.

LCMS (AM3): rt = 0.878 min, (517.3 $[M+H]^+$), 97.2% purity.

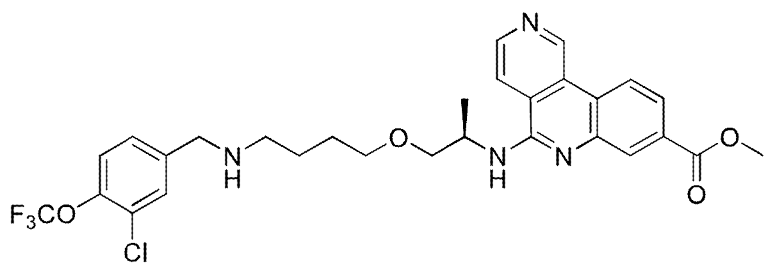
(*R*)-methyl 5-((1-(4-aminobutoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.608



[00378] A mixture of **compound 1.607** (0.5 g, 0.904 mmol, HCl salt), 10% palladium on carbon catalyst (0.1 g) and aqueous ammonia hydroxide solution (1.39 mL, 25%) in MeOH (20 mL) was hydrogenated under one atmosphere H_2 pressure at room temperature for 2 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to afford **compound 1.608** (0.34 g, 98.3% yield) as a yellow solid, which was used directly without purification.

LCMS (AM3): rt = 0.703 min, (383.3 $[M+H]^+$), 90.9% purity.

(*R*)-methyl 5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.609



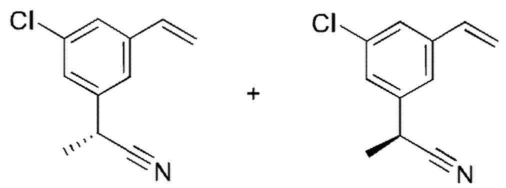
[00379] A mixture of 3-chloro-4-(trifluoromethoxy)benzaldehyde (0.2 g, 0.891 mmol) and **compound 1.608** (0.34 g, 0.889 mmol) in MeOH (4 mL) was stirred at room temperature for 1 h, then sodium cyanoborohydride (0.22 g, 3.50 mmol) was added. The reaction mixture was then stirred at room temperature for additional 1 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was (PM119) to afford **compound 1.609** (0.15 g, 17.89% yield, TFA salt) as a yellow solid.

LCMS (AM3): rt = 0.838 min, (591.2 $[M+H]^+$), 98.9% purity.

Synthesis of Intermediates 1.837 and 1.838

Intermediates 1.837 and 1.838 have been assigned the following stereochemical nomenclature but could be defined as either enantiomer as definitive stereochemistry has not been fully elucidated by analytical techniques.

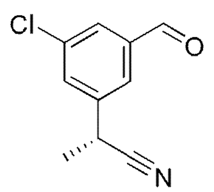
(R)-2-(3-chloro-5-vinylphenyl)propanenitrile 1.835 and (S)-2-(3-chloro-5-vinylphenyl)propanenitrile 1.836



To a solution of **compound 1.365** (1.15 g, 6.47 mmol) in THF (15 mL) was added NaHMDS (6.47 mL, 1 M) at -78 °C. After stirring for 1 h, MeI (918.93 mg, 6.47 mmol) was added slowly and the mixture was stirred at -78 °C for 2 h. The mixture was concentrated *in vacuo* to give a residue that was purified (PM47) to afford 430 mg of racemic product, which was separated by SFC (column: DAICEL CHIRALCEL OD 250 mm × 30 mm× 10 μm; mobile phase: [0.1% ammonium hydroxide-IPA]; B%: 15%-15%, 2.4 min; 35 min) to afford **compound 1.835** (160 mg, 826.48 μmol, Peak 1) and **compound 1.836** (130 mg, 671.51 μmol, Peak 2) as yellow oils.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.37 (t, *J* = 1.6 Hz, 1H), 7.26 (d, *J* = 1.2 Hz, 1H), 7.23 (t, *J* = 1.2 Hz, 1H), 6.66 (dd, *J* = 17.2, 10.8 Hz 1H), 5.81 (d, *J* = 17.2 Hz, 1H), 5.38 (d, *J* = 10.8 Hz, 1H), 3.91-3.86 (q, 1H), 1.66 (d, *J* = 7.2 Hz, 3H) ppm.

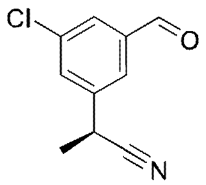
(R)-2-(3-chloro-5-formylphenyl)propanenitrile 1.837



Ozone was bubbled into a solution of **compound 1.835** (160 mg, 834.83 μmol) in DCM (10 mL) at -78 °C until the colour of the reaction mixture turned blue. After excessive ozone was purged with nitrogen, DMS (674.28 mg, 10.85 mmol) was added. The mixture was warmed to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM7) to afford **compound 1.837** (70 mg, 361.52 μmol, 43.3% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.00 (s, 1H), 7.84 (t, *J* = 1.6 Hz, 1H), 7.78 (d, *J* = 1.2 Hz, 1H), 7.65 (t, *J* = 1.6 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 1H), 1.71 (d, *J* = 7.2 Hz, 3H) ppm.

(S)-2-(3-chloro-5-formylphenyl)propanenitrile 1.838

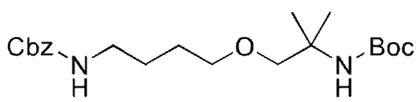


Ozone was bubbled into a solution of **compound 1.836** (130 mg, 678.30 µmol) in DCM (15 mL) at -78 °C until the colour of the reaction mixture turned blue. After excessive ozone was purged with nitrogen, DMS (547.85 mg, 8.82 mmol) was added. The mixture was warmed to 25 °C and stirred for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM7) to afford **compound 1.838** (80 mg, 361.52 µmol, 43.3% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.00 (s, 1H), 7.84 (t, *J* = 1.6 Hz, 1H), 7.78 (s, 1H), 7.64 (t, *J* = 1.6 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 1H), 1.71 (d, *J* = 7.6 Hz, 3H) ppm.

Synthesis of Intermediate 1.734

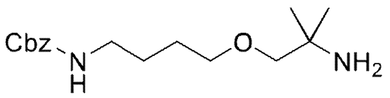
Tert-butyl N-[2-[4-(benzyloxycarbonylamino)butoxy]-1,1-dimethyl-ethyl]carbamate 1.730



A mixture of benzyl (4-bromobutyl)carbamate (12 g, 41.93 mmol), tert-butyl (1-hydroxy-2-methylpropan-2-yl)carbamate (4 g, 21.14 mmol), NaOH (8.45 g, 211.36 mmol) and TBAI (0.4 g, 1.08 mmol) in H_2O (20 mL) was stirred at room temperature for 14 h. Water (100 mL) was added and the resulting mixture was extracted with MTBE (30 mL x 3). The combined organic phase was washed with brine (90 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM22) to afford **compound 1.730** (0.73 g, 8.2% yield) as a colourless oil.

LCMS (AM3): rt = 1.027 min, (417.4 $[M+Na]^+$), 94.3% purity.

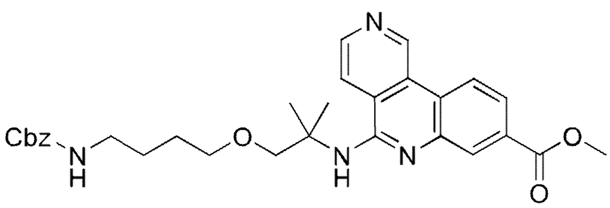
Benzyl (4-(2-amino-2-methylpropoxy)butyl)carbamate 1.731



A mixture of **compound 1.730** (730 mg, 1.85 mmol) and TFA (5 mL, 67.53 mmol) in DCM (5 mL) was stirred at room temperature for 0.5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM47) to afford **compound 1.731** (0.69 g, 91.3% yield, TFA salt) as colourless oil.

LCMS (AM3): rt = 0.660 min, (295.3 $[M+H]^+$), 98.9% purity.

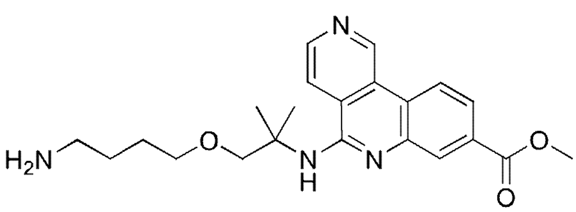
Methyl 5-((1-(4-(((benzyloxy)carbonyl)amino)butoxy)-2-methylpropan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.732



A mixture of **compound 1.731** (690 mg, 1.69 mmol, TFA salt), **compound 1.1** (550 mg, 2.02 mmol) and DIPEA (1 mL, 5.74 mmol) in DMSO (9 mL) was stirred at 120 °C for 20 h. The reaction mixture was filtered and the filtrate was purified (PM22) to afford **compound 1.732** (250 mg, 20.9% yield) as a yellow solid.

LCMS (AM3): rt = 0.915 min, (531.5 $[M+H]^+$), 75.8% purity.

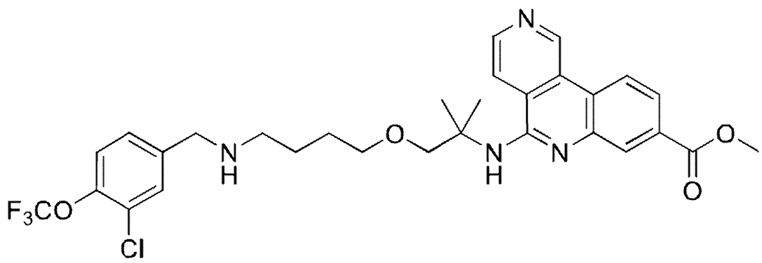
Methyl 5-((1-(4-aminobutoxy)-2-methylpropan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.733



A mixture of **compound 1.732** (250 mg, 0.47 mmol), 10% palladium on carbon (0.1 g) and aq. ammonium hydroxide solution (0.3 mL, 1.95 mmol, 25% wt.) in MeOH (10 mL) was hydrogenated under 1 atmosphere H_2 at room temperature for 16 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified (PM47) to afford **compound 1.733** (90 mg, 34.1% yield, TFA salt) as a yellow oil.

LCMS (AM3): rt = 0.726 min, (397.0 $[M+H]^+$), 91.2% purity.

Methyl 5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)-2-methylpropan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.734

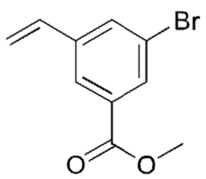


A mixture of 3-chloro-4-(trifluoromethoxy)benzaldehyde (44 mg, 0.20 mmol), **compound 1.733** (90 mg, 0.18 mmol, TFA salt) and DIPEA (0.1 mL, 0.54 mmol) in MeOH (2 mL) was stirred at room temperature for 15 h, then sodium triacetoxyborohydride (112 mg, 0.53 mmol) was added. The reaction mixture was then stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM144) to afford **compound 1.734** (25 mg, 21.9% yield, FA salt) as a white solid.

LCMS (AM3): rt = 0.871 min, (605.4 $[M+H]^+$), 94.6% purity.

__Synthesis of Intermediate 1.689__

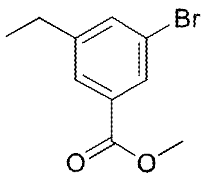
Methyl 3-bromo-5-vinylbenzoate 1.683



To a solution of methyl 3-bromo-5-iodo-benzoate (25.7 g, 75.38 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (11.73 g, 76.13 mmol) in DME (300 mL) was added Pd(dppf)Cl_2 (5.52 g, 7.54 mmol) and CsF (22.90 g, 150.76 mmol). The mixture was heated to 80 °C and stirred for 12 h under a nitrogen atmosphere. The mixture was poured into water (300 mL) and extracted with EA (200 mL × 2). The combined organic phase was washed with brine (300 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM1) to afford **compound 1.683** (13.5 g, 56.00 mmol, 74.3% yield) as a light yellow oil.

^1H NMR (400 MHz, $CHCl_3$-*d*) δ: 8.05 (s, 1H), 8.00 (s, 1H), 7.72 (s, 1H), 6.66 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.84 (d, *J* = 17.6 Hz, 1H), 5.39 (d, *J* = 10.8 Hz, 1H), 3.94 (s, 3H) ppm.

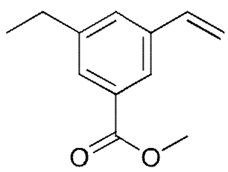
Methyl 3-bromo-5-ethylbenzoate 1.684



To a solution of **compound 1.683** (2.5 g, 10.37 mmol) in MeOH (50 mL) was added PtO_2 (588.70 mg, 2.59 mmol) under a nitrogen atmosphere. The suspension was degassed under vacuum and purged with hydrogen three times. The mixture was stirred under 15 psi pressure of H_2 at 25 °C for 0.5 h. The catalyst was removed by filtration and the filtrate was concentrated to afford **compound 1.684** (2.3 g) as a yellow oil, which was used directly without purification.

LCMS (AM3): rt = 0.982 min, (243.0 $[M+H]^+$), 86.4 % purity.

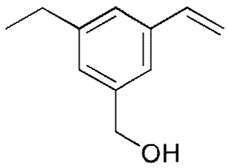
Methyl 3-ethyl-5-vinylbenzoate 1.685



To a solution of **compound 1.684** (2.3 g, 9.46 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.19 g, 14.19 mmol) in DME (50 mL) was added Pd(dppf)Cl_2 (692.29 mg, 946.12 μmol) and CsF (2.87 g, 18.92 mmol). The mixture was heated to 80 °C and stirred for 12 h under a nitrogen atmosphere. The mixture was poured into water (100 mL) and extracted with EA (80 mL × 3). The combined organic phase was washed with brine (100 mL × 3), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM1) to afford **compound 1.685** (1.4 g, 7.36 mmol, 77.8% yield) as a yellow oil.

^1H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.92 (s, 1H), 7.78 (s, 1H), 7.43 (s, 1H), 6.75 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.83 (d, *J* = 17.6 Hz, 1H), 5.31 (d, *J* = 10.8 Hz, 1H), 3.93 (s, 3H), 2.70 (q, *J* = 5.2 Hz, 2H), 1.27 (t, *J* = 5.2 Hz, 3H) ppm.

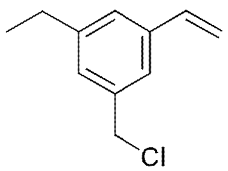
(3-Ethyl-5-vinylphenyl)methanol 1.686



To a solution of **compound 1.685** (1.4 g, 7.36 mmol) in THF (20 mL) was added LAH (430 mg, 11.33 mmol) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. The reaction mixture was cooled to 0°C and then diluted with H_2O (0.45 mL), 10% aq. NaOH solution (0.45 mL) and H_2O (1.35 mL). After stirring for 0.5 h, Na_2SO_4 (3 g) was added. The mixture was stirred at 20 °C for another 0.5 h and then filtered and the filter cake was washed with EA (50 mL × 3). The filtrate was concentrated *in vacuo* to afford **compound 1.686** (1.1 g, 6.78 mmol, 92.1% yield) as a yellow oil.

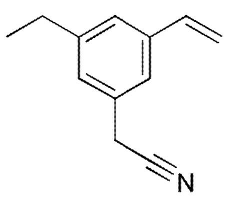
^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.29 (s, 1H), 7.22 (s, 1H), 7.15 (s, 1H), 6.76 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.81 (d, *J* = 17.6 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 4.72 (s, 2H), 2.74-2.67 (q, 2H), 1.32-1.27 (t, 3H) ppm.

1-(Chloromethyl)-3-ethyl-5-vinylbenzene 1.687



To a solution of **compound 1.686** (1 g, 6.16 mmol) in 1,4-dioxane (15 mL) was added $SOCl_2$ (1.64 g, 13.78 mmol) at 0 °C slowly. The reaction mixture was then heated to 90 °C and stirred for 2 h. The reaction mixture was diluted with iced water (80 mL) slowly at 0 °C and then extracted with EA (50 mL × 2). The organic layer was washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **compound 1.687** (1.1 g, 6.09 mmol, 98.8% yield) as a yellow oil, which was used directly in next step.

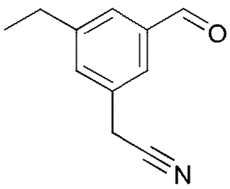
2-(3-Ethyl-5-vinylphenyl)acetonitrile 1.688



To a solution of **compound 1.687** (1 g, 5.53 mmol) in ACN (20 mL) was added TMSCN (1.10 g, 11.07 mmol) and TBAF (11.07 mL, 1 M) at 20 °C. The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified (PM7) to afford **compound 1.688** (900 mg, 5.26 mmol, 94.9% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.20-7.18 (m, 2H), 7.05 (s, 1H), 6.69 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.77 (d, *J* = 17.6 Hz, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 3.72 (s, 2H), 2.68-2.62 (q, 2H), 1.26-1.23 (t, 3H) ppm.

2-(3-Ethyl-5-formylphenyl)acetonitrile 1.689

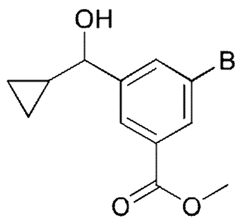


To a solution of **compound 1.688** (0.9 g, 5.26 mmol) in DCM (15 mL) cooled to -78 °C was bubbled ozone until the colour of mixture turned blue. DMS (4.90 g, 78.84 mmol) was added slowly. The reaction mixture was warmed up to 20 °C and stirred for 12 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified (PM7) to afford **compound 1.689** (750 mg, 4.33 mmol, 82.38% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.01 (s, 1H), 7.69 (s, 1H), 7.66 (s, 1H), 7.45 (s, 1H), 3.82 (s, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H) ppm.

Synthesis of Intermediate 1.697

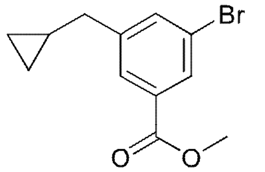
Methyl 3-bromo-5-(cyclopropyl(hydroxy)methyl)benzoate 1.691



To a solution of methyl 3-bromo-5-formyl-benzoate (1.5 g, 6.17 mmol) in THF (70 mL) was added cyclopropylmagnesium bromide (18.51 mL, 0.5 M) slowly at 0 °C. The mixture was stirred at 0 °C for 0.5 h. The mixture was poured into saturated aq. NH_4Cl solution (100 mL) and extracted with EA (50 mL × 2). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified (PM12) to afford **compound 1.691** (570 mg, 2.00 mmol, 32.4% yield) as a red oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 8.09 (s, 1H), 8.02 (s, 1H), 7.81 (s, 1H), 4.04 (d, *J* = 8.1 Hz, 1H), 3.95 (s, 3H), 2.12 (br s, 1H), 1.23-1.13 (m, 1H), 0.71-0.55 (m, 2H), 0.55-0.33 (m, 2H) ppm.

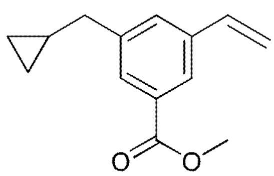
Methyl 3-bromo-5-(cyclopropylmethyl)benzoate 1.692



To a mixture of TFA (1.73 g, 15.13 mmol) and Et_3SiH (815.60 mg, 7.01 mmol) was added **compound 1.691** (1 g, 3.51 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified (PM1) to afford **compound 1.692** (700 mg, 2.60 mmol, 74.2% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 8.00 (s, 1H), 7.85 (s, 1H), 7.60 (s, 1H), 3.92 (s, 3H), 2.56 (d, *J* = 6.8 Hz, 2H), 1.02-0.92 (m, 1H), 0.58-0.54 (m, 2H), 0.24-0.19 (m, 2H) ppm.

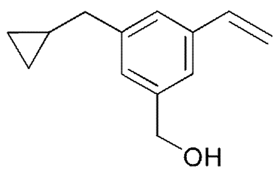
Methyl 3-(cyclopropylmethyl)-5-vinylbenzoate 1.693



To a solution of **compound 1.692** (600 mg, 2.23 mmol) in 1,4-dioxane (6 mL) and water (0.6 mL) was added K_2CO_3 (616.23 mg, 4.46 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (686.71 mg, 4.46 mmol) and Pd(dppf)Cl_2 (163.12 mg, 222.94 μmol). The reaction mixture was then heated to 80 °C and stirred for 12 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified (PM13) to afford **compound 1.693** (330 mg, 1.53 mmol, 68.4% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.93 (s, 1H), 7.82 (s, 1H), 7.47 (s, 1H), 6.74 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.82 (d, *J* = 17.6 Hz, 1H), 5.31 (d, *J* = 10.8 Hz, 1H), 3.92 (s, 3H), 2.58 (d, *J* = 6.8 Hz, 2H), 1.05-0.96 (m, 1H), 0.57-0.53 (m, 2H), 0.24-0.20 (m, 2H) ppm.

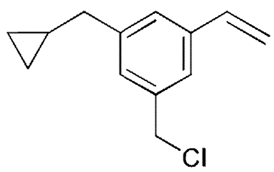
(3-(Cyclopropylmethyl)-5-vinylphenyl)methanol 1.694



To a solution of **compound 1.693** (330 mg, 1.53 mmol) in THF (5 mL) was added LAH (57.91 mg, 1.53 mmol) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with water (0.1 mL) followed by addition of 10% aq. NaOH solution (0.1 mL) and water (0.3 mL). After being stirred for 0.5 h, Na_2SO_4 (3 g) was added and stirred at 20 °C for 0.5 h. The mixture was filtered and concentrated *in vacuo* to give **compound 1.694** (300 mg) as a colorless oil.

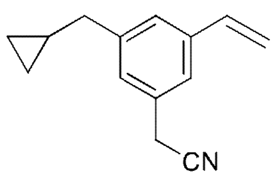
^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.27 (s, 1H), 7.23 (s, 1H), 7.17 (s, 1H), 6.72 (dd, *J* = 17.6, 11.2 Hz 1H), 5.76 (d, *J* = 17.6 Hz, 1H), 5.25 (d, *J* = 11.2, 1H), 4.69 (s, 2H), 2.55 (d, *J* = 6.8 Hz, 2H), 1.64 (br s, 1H), 1.04-0.96 (m, 1H), 0.56-0.51 (m, 2H), 0.23-0.19 (m, 2H) ppm.

1-(Chloromethyl)-3-(cyclopropylmethyl)-5-vinylbenzene 1.695



To a solution of **compound 1.694** (300 mg, 1.59 mmol) in 1,4-dioxane (5 mL) was added $SOCl_2$ (492.00 mg, 4.14 mmol) slowly at 0 °C. The reaction mixture was then heated to 80 °C and stirred for 2 h. The mixture was diluted with H_2O (10 mL) and then extracted with EA (50 mL × 2). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **compound 1.695** (300 mg, 1.45 mmol, 91.1% yield) as a yellow oil, which was used directly.

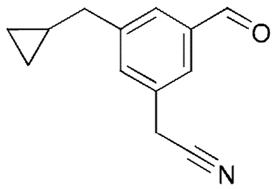
2-(3-(Cyclopropylmethyl)-5-vinylphenyl)acetonitrile 1.696



To a solution of **compound 1.695** (300 mg, 1.45 mmol) in ACN (20 mL) was added TMSCN (287.96 mg, 2.90 mmol) and TBAF (2.90 mL, 1 M in THF) at 20 °C. The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified (PM7) to afford **compound 1.696** (300 mg) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 7.27 (s, 1H), 7.20 (s, 1H), 7.12 (s, 1H), 6.70 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.77 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 3.72 (s, 2H), 2.55 (d, *J* = 6.8 Hz, 2H), 1.04-0.95 (m, 1H), 0.55-0.50 (m, 2H), 0.23-0.19 (m, 2H) ppm.

2-(3-(Cyclopropylmethyl)-5-formylphenyl)acetonitrile 1.697

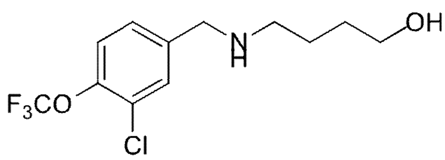


To a solution of **compound 1.696** (300 mg, 1.52 mmol) in DCM (8 mL) cooled to -78 °C was bubbled ozone until the color of mixture turned blue. After excess ozone was purge with nitrogen, DMS (2.31 g, 37.18 mmol) was added. The mixture was warmed up to 20 °C and stirred for 12 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified (PM11) to afford **compound 1.697** (230 mg, 1.15 mmol, 75.9% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 10.02 (s, 1H), 7.76 (s, 1H), 7.70 (s, 1H), 7.52 (s, 1H), 3.83 (s, 2H), 2.64 (d, *J* = 6.8 Hz, 2H), 1.06-0.96 (m, 1H), 0.62-0.57 (q, 2H), 0.26-0.23 (q, 2H) ppm.

Synthesis of Intermediate 1.782

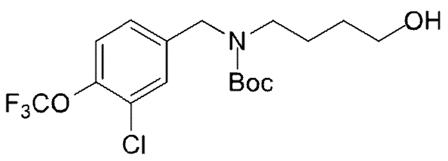
4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butan-1-ol 1.157



A solution of 3-chloro-4-(trifluoromethoxy)benzaldehyde (1 g, 4.45 mmol) and 4-aminobutan-1-ol (1.19 g, 13.36 mmol) in MeOH (10 mL) was stirred at 20 °C for 12 h, then sodium cyanoborohydride (1.12 g, 17.81 mmol) was added. The resulting mixture was stirred at 20 °C for 1 h. The mixture was concentrated *in vacuo* and purified (PM150) to give **compound 1.157** (1.2 g, FA salt) as a white solid.

LCMS (AM3): rt = 0.911 min, (298.1 $[M+H]^+$), 96.6% purity.

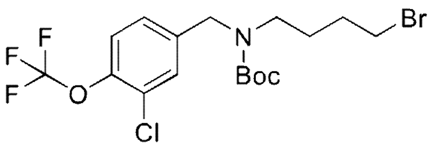
tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(4-hydroxybutyl)carbamate 1.158



To a solution of **compound 1.157** (1.2 g, 3.49 mmol) in THF (10 mL) and water (10 mL) was added $NaHCO_3$ (439.92 mg, 5.24 mmol) and Boc_2O (914.32 mg, 4.19 mmol) at 20 °C. The mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted water (50 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic phase was washed with brine (90 mL× 3), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM6) to afford **compound 1.158** (890 mg, 2.21 mmol, 63.2% yield) as a light yellow oil.

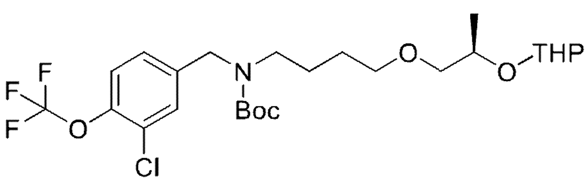
LCMS (AM3): rt = 1.049 min, (420.1 $[M+Na]^+$), 73.2% purity.

Tert-butyl (4-bromobutyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate 1.778



To a solution of **compound 1.158** (3.1 g, 7.79 mmol) and CBr_4 (3.10 g, 9.35 mmol) in DCM (40 mL) was added PPh_3 (2.45 g, 9.35 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM7) to afford **compound 1.778** (2 g, 55.7% yield) as a colorless oil, which was used directly.

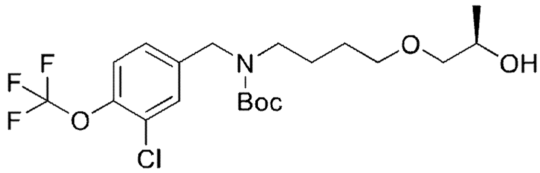
Tert-butyl 3-chloro-4-(trifluoromethoxy)benzyl(4-((2R)-2-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)butyl)carbamate 1.779



A mixture of **compound 1.778** (2 g, 4.34 mmol), (2R)-2-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol (Tetrahedron Letters, 2003, 44 (32), 6149–6151), (0.7 g, 4.37 mmol), NaOH (1.74 g, 43.41 mmol) and TBAI (160 mg, 0.43 mmol) in H_2O (4 mL) was stirred at 25 °C for 14 h. The reaction mixture was diluted with water (40 mL) and the resulting mixture was extracted with MTBE (20 mL × 2). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified (PM47) to afford **compound 1.779** (700 mg, 20.9% yield) as a brown oil.

LCMS (AM3): rt = 1.071 min, (456.2 [M-THP+2H]$^+$), 69.8% purity.

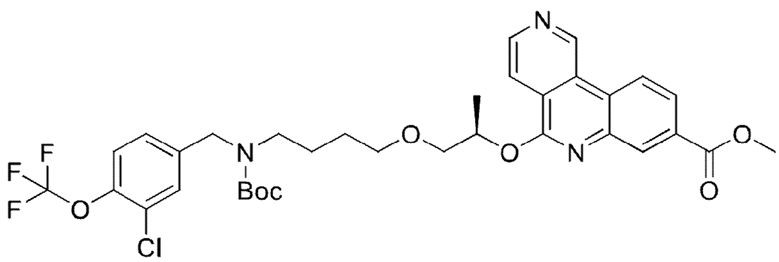
(R)-tert-butyl 3-chloro-4-(trifluoromethoxy)benzyl(4-(2-hydroxypropoxy)butyl)carbamate 1.780



A mixture of **compound 1.779** (0.7 g, 1.30 mmol) and TsOH·H_2O (50 mg, 0.26 mmol) in MeOH (15 mL) was stirred at room temperature for 1 h. K_2CO_3 (1 g) was added and the mixture was stirred for 10 min. The mixture was then filtered and the filtrate was concentrated *in vacuo* to give a residue that was purified (PM6) to afford **compound 1.780** (0.5 g, 84.6% yield) as a light yellow oil.

LCMS (AM3): rt = 1.065 min, (478.1 [M+Na]$^+$), 43.3% purity.

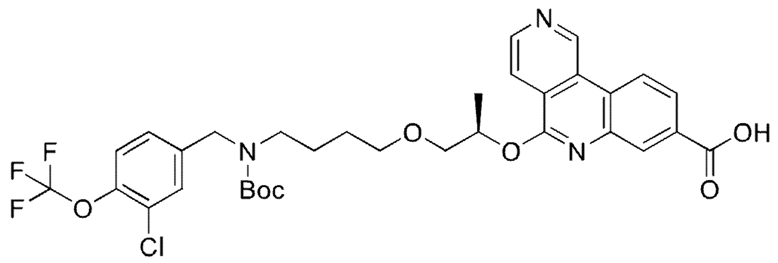
(R)-methyl 5-((1-(4-((tert-butoxycarbonyl)(3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylate 1.781



To a solution of **compound 1.780** (500 mg, 1.10 mmol) in THF (10 mL) was added NaH (60 mg, 1.50 mmol, 60% dispersion in oil) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h, then **compound 1.1** (450 mg, 1.65 mmol) was added. The reaction mixture was then heated to 60 °C and stirred for 20 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue that was purified (PM47) to afford **compound 1.781** (100 mg, 12.5% yield) as a colorless oil.

LCMS (AM3): rt = 1.247 min, (692.3 [M+H]$^+$), 96.8% purity.

(R)-5-((1-(4-((tert-butoxycarbonyl)(3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid 1.782

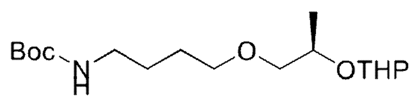


A mixture of **compound 1.781** (100 mg, 0.14 mmol) and lithium hydroxide monohydrate (50 mg, 1.19 mmol) in THF (8 mL) and H_2O (2 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM150) to afford **compound 1.782** (67 mg, 68.4% yield) as a white solid.

LCMS (AM3): rt = 1.153 min, (678.2 $[M+H]^+$), 100% purity.

__Synthesis of Intermediate 1.729__

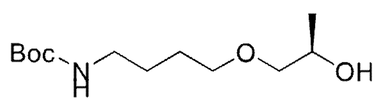
Tert-butyl (4-((2R)-2-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)butyl)carbamate 1.725



A mixture of tert-butyl (4-bromobutyl)carbamate (29.27 g, 116.10 mmol), (2R)-2-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol (Tetrahedron Letters, 2003, 44 (32), 6149–6151), (9.3 g, 58.05 mmol), NaOH (23.22 g, 580.49 mmol) and TBAI (2.14 g, 5.79 mmol) in H_2O (58 mL) was stirred at room temperature for 12 h. The reaction mixture was poured into water (200 mL) and the resulting mixture was extracted with MTBE (100 mL x 3). The combined organic phase was washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified (PM6) to afford **compound 1.725** (6.5 g) as a colourless oil.

^1H NMR (400 MHz, $CHCl_3$-*d*) δ: 4.78-4.67 (m, 1H), 4.01-3.77 (m, 2H), 3.57-3.33 (m, 5H), 3.17-3.07 (m, 2H), 1.86-1.73 (m, 2H), 1.63-1.52 (m, 8H), 1.43 (s, 9H), 1.22-1.10 (m, 3H) ppm.

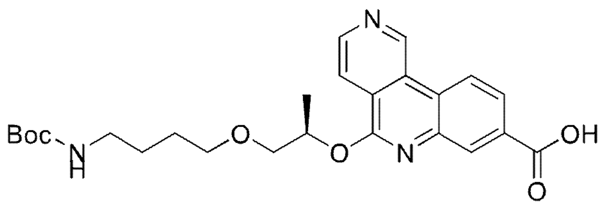
(R)-Tert-butyl (4-(2-hydroxypropoxy)butyl)carbamate 1.726



A mixture of **compound 1.725** (5.6 g, 16.90 mmol) and TsOH·H_2O (321 mg, 1.69 mmol) in MeOH (50 mL) was stirred at room temperature for 1 h. K_2CO_3 (1 g) was added and the resulting mixture was concentrated *in vacuo*. The residue was purified (PM3) to afford **compound 1.726** (1.1 g) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 4.80-4.60 (br s, 1H), 3.99-3.87 (m, 1H), 3.67-3.45 (m, 2H), 3.43-3.40 (m, 1H), 3.24-3.20 (m, 1H), 3.13 (t, *J* = 6.4 Hz, 2H), 1.65-1.52 (m, 4H), 1.44 (s, 9 H), 1.14 (d, *J* = 6.4 Hz, 3H) ppm.

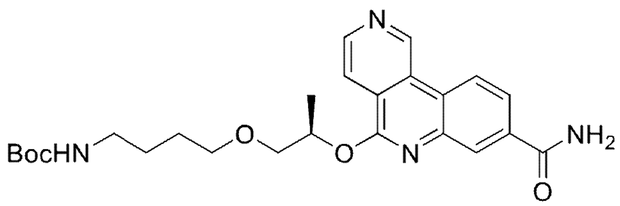
(R)-5-((1-(4-((Tert-butoxycarbonyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid 1.727



To a solution of **compound 1.726** (1.1 g, 4.45 mmol) in THF (20 mL) was added NaH (0.22 g, 5.50 mmol, 60% dispersion in oil) at 0 °C. After stirring at 0 °C for 0.5 h, **compound 1.1** (1.46 g, 5.34 mmol) was added. The reaction mixture was then warmed to room temperature and stirred for 16 h. The reaction mixture was quenched by water (1 mL) and concentrated *in vacuo* and the residue was purified (PM47) to afford **compound 1.727** (0.66 g) as a brown solid.

LCMS (AM3): rt = 0.931 min, (470.4 $[M+H]^+$), 68.6% purity.

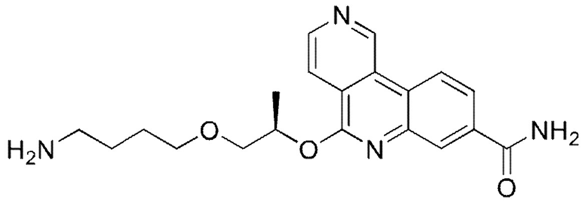
(R)-Tert-butyl (4-(2-((8-carbamoylbenzo[c][2,6]naphthyridin-5-yl)oxy)propoxy)butyl)carbamate 1.728



To a mixture of **compound 1.727** (0.66 g, 1.41 mmol), DIPEA (1.22 mL, 7.03 mmol), EDCI (540 mg, 2.82 mmol) and HOBt (380 mg, 2.81 mmol) in DMF (7 mL) was added NH_4Cl (300 mg, 5.61 mmol) at ambient temperature. The reaction mixture was heated to 70 °C and stirred for 15 h. The reaction mixture was filtered and the filtrate was purified (PM150) to afford **compound 1.728** (0.26 g, 39.1% yield) as a brown solid.

LCMS (AM3): rt = 0.906 min, (469.2 [M+H]$^+$), 98.9% purity.

(R)-5-((1-(4-Aminobutoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxamide 1.729

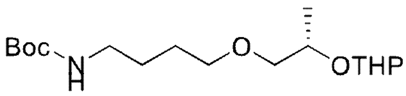


A mixture of **compound 1.728** (260 mg, 0.55 mmol) in a solution of HCl in 1,4-dioxane (10 mL, 2 M) was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to afford **compound 1.729** (0.25 g, HCl salt) as a brown solid, which was used directly without further purification.

LCMS (AM3): rt = 0.723 min, (369.4 [M+H]$^+$), 93.3% purity.

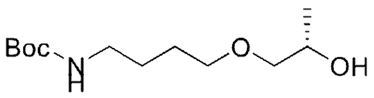
<u>**Synthesis of Intermediate 1.681**</u>

Tert-butyl (4-((2S)-2-((tetrahydro-2H-pyran-2-yl)oxy)propoxy)butyl)carbamate 1.677



To a solution of NaOH (13.23 g, 330.81 mmol) in H_2O (33.08 mL) was added (2S)-2-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol (5.3 g, 33.08 mmol) (Journal of the American Chemical Society, 1984, 106, (17) 4916-4922), tert-butyl (4-bromobutyl)carbamate (20 g, 79.32 mmol) and TBAI (610.96 mg, 1.65 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with H_2O (100 mL) and then extracted with MTBE (100 mL × 2). The combined organic layer was washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified (PM7) to afford **compound 1.677** (3 g, 9.05 mmol, 27.4% yield) as a colorless oil, which was used directly.

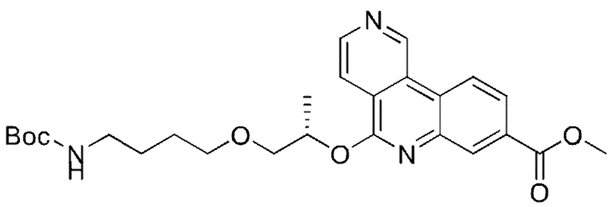
(S)-Tert-butyl (4-(2-hydroxypropoxy)butyl)carbamate 1.678



To a solution of **compound 1.677** (3 g, 9.05 mmol) in MeOH (25 mL) was added TsOH·H_2O (200 mg, 1.16 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated *in vacuo* to give the crude product which was purified (PM4) to afford **compound 1.678** (940 mg, 3.80 mmol, 42% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 4.71 (br s, 1H), 4.00-3.92 (m, 1H), 3.54-3.44 (m, 2H), 3.42-3.39 (m, 1H), 3.24-3.19 (t, 1H), 3.15-3.05 (m, 2H), 1.96 (br s, 1H), 1.65-1.51 (m, 4H), 1.44 (s, 9H), 1.14 (d, *J* = 6.4 Hz, 3H) ppm.

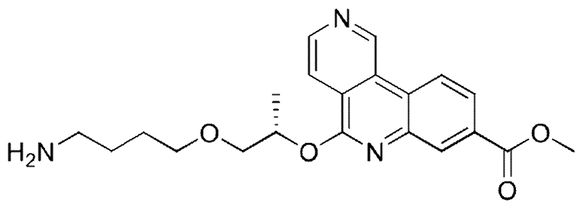
(S)-Methyl 5-((1-(4-((tert-butoxycarbonyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylate 1.679



To a solution of **compound 1.678** (820 mg, 3.32 mmol) in THF (20 mL) was added NaH (198.92 mg, 4.97 mmol, 60% dispersion in oil) at 20 °C. After being stirred at 20 °C for 0.5 h, **compound 1.1** (904.07 mg, 3.32 mmol) was added. The reaction mixture was stirred at 20 °C for another 2 h. The reaction mixture was diluted with H_2O (80 mL) and then extracted with EA (60 mL × 2). The organic layer was washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified (PM47) to afford **compound 1.679** (460 mg, 951.29 μmol, 28.7% yield) as a brown solid.

LCMS (AM3): rt = 1.029 min, (484.2 [M+H]$^+$), 94.8% purity.

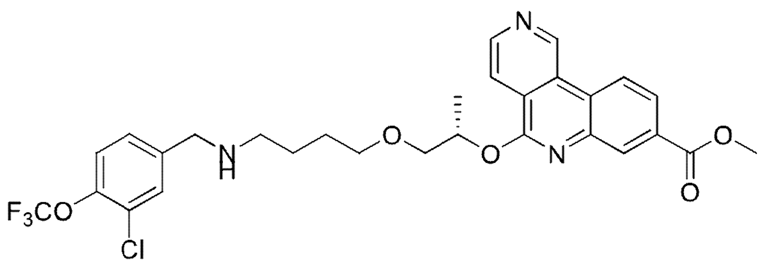
(S)-Methyl 5-((1-(4-aminobutoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylate 1.680



To a solution of **compound 1.679** (220 mg, 454.96 μmol) in 1,4-dioxane (1 mL) was added a solution of HCl in 1,4-dioxane (11.0 mL, 4 M). The reaction mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated *in vacuo* to give the crude product, which was purified (PM150) to afford **compound 1.680** (240 mg, FA salt) as a yellow solid.

LCMS (AM5): rt = 0.987 min, (384.2 $[M+H]^+$), 69.9 % purity.

(S)-Methyl 5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylate 1.681

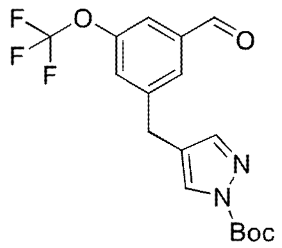


A mixture of **compound 1.680** (240 mg, 481.95 μmol), sodium acetate (118.61 mg, 1.45 mmol) and 3-chloro-4-(trifluoromethoxy)benzaldehyde (108.23 mg, 481.95 μmol) in MeOH (3 mL) was stirred at 20 °C for 12 h, then sodium triacetoxyborohydride (306.44 mg, 1.45 mmol) was added. The reaction mixture was stirred at 20 °C for another 3.5 h. The crude product was purified (PM143) to afford **compound 1.681** (200 mg, 337.84 μmol, 70.1% yield) as a white solid.

LCMS (AM3): rt = 0.907 min, (592.2 $[M+H]^+$), 99.2 % purity.

Synthesis of Intermediate 1.828

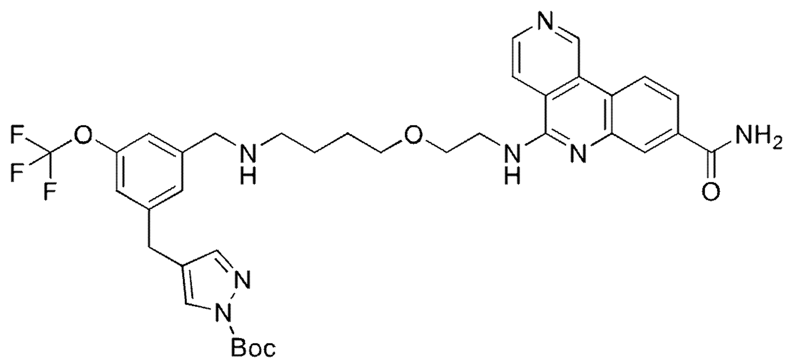
Tert-butyl 4-(3-formyl-5-(trifluoromethoxy)benzyl)-1H-pyrazole-1-carboxylate 1.827



To a mixture of **compound 1.824** (500 mg, 2.10 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) was added K_2CO_3 (579.28 mg, 4.19 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (678.08 mg, 2.31 mmol) and Pd(dppf)Cl_2 (153.34 mg, 209.56 μmol). The reaction mixture was then heated to 70 °C and stirred for 12 h under a nitrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated *in vacuo.* The crude product was purified (PM150) to afford **compound 1.827** (400 mg, 1.02 mmol, 48.8% yield) as a yellow oil.

LCMS (AM3): rt = 0.975 min, (392.9 $[M+Na]^+$), 97.1% purity.

Tert-butyl 4-(3-(((4-(2-((8-carbamoylbenzo[c][2,6]naphthyridin-5-yl)amino)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)benzyl)-1H-pyrazole-1-carboxylate 1.828

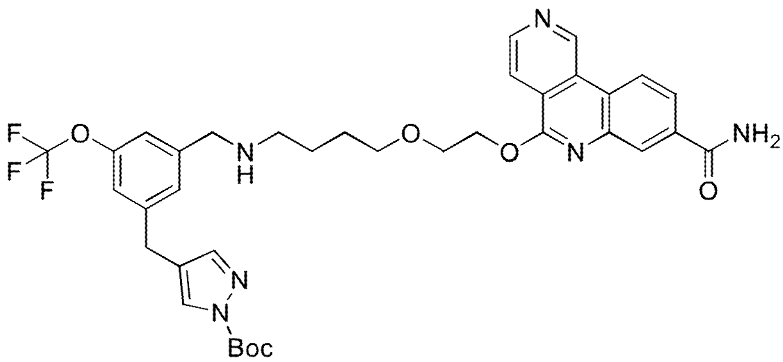


A mixture of **Intermediate E** (210.56 mg, 540.07 μmol, HCl salt), DIPEA (209.40 mg, 1.62 mmol) and **compound 1.827** (200 mg, 540.07 μmol) in MeOH (3 mL) was stirred at 20 °C for 12 h, then sodium cyanoborohydride (101.81 mg, 1.62 mmol) was added. The reaction mixture was stirred at 20 °C for 3 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* and purified (PM168) to afford **compound 1.828** (100 mg, 129.45 μmol, 23.9% yield) as a white solid.

LCMS (AM3): rt = 0.809 min, (708.3 $[M+H]^+$), 86.0% purity.

Synthesis of Intermediate 1.829

Tert-butyl 4-(3-(((4-(2-((8-carbamoylbenzo[c][2,6]naphthyridin-5-yl)oxy)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)benzyl)-1H-pyrazole-1-carboxylate 1.829

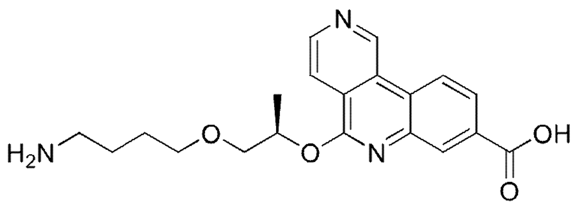


A mixture of **compound 1.57** (216.26 mg, 540.07 μmol, FA salt), DIPEA (209.40 mg, 1.62 mmol) and **compound 1.827** (200 mg, 540.07 μmol) in MeOH (3 mL) was stirred at 20 °C for 3 h, then sodium cyanoborohydride (101.82 mg, 1.62 mmol) was added. The reaction mixture was stirred at 20 °C for 0.5 h. The reaction mixture was filtered and the filtrate was purified (PM171) to afford **compound 1.829** (150 mg, 211.65 μmol, 39.2% yield) as a white solid.

LCMS (AM3): rt = 0.873 min, (709.3 $[M+H]^+$), 78.5% purity.

Synthesis of Intermediate 1.832

(R)-5-((1-(4-aminobutoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid 1.832

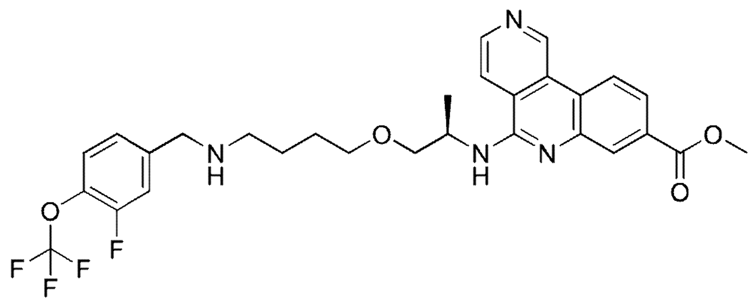


A mixture of **compound 1.727** (880 mg, 1.87 mmol) and TFA (10 mL, 135.06 mmol) in DCM (20 mL) was stirred at room temperature for 0.5 h. The reaction mixture was concentrated *in vacuo* to afford **compound 1.832** (680 mg, 83.8% yield, TFA salt) as a white solid, which was used directly without further purification.

LCMS (AM3): rt = 0.773 min, (370.4 $[M+H]^+$), 96.0% purity.

Synthesis of Intermediate 1.831

(R)-methyl 5-((1-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.831

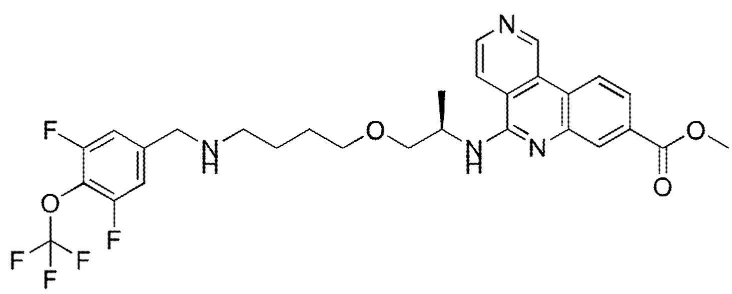


A mixture of 3-fluoro-4-(trifluoromethoxy)benzaldehyde (75 mg, 0.36 mmol), **compound 1.608** (170 mg, 0.35 mmol, HCl salt) and DIPEA (1.44 mmol, 0.25 mL) in MeOH (10 mL) was stirred at room temperature for 16 h, then sodium triacetoxyborohydride (306 mg, 1.44 mmol) was added. The reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was filtered and the filtrate was purified (PM158) to afford **compound 1.831** (130 mg, 55.6% yield, FA salt) as a yellow solid.

LCMS (AM3): rt = 0.832 min, (575.2 $[M+H]^+$), 95.7% purity.

Synthesis of Intermediate 1.830

(R)-methyl 5-((1-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylate 1.830

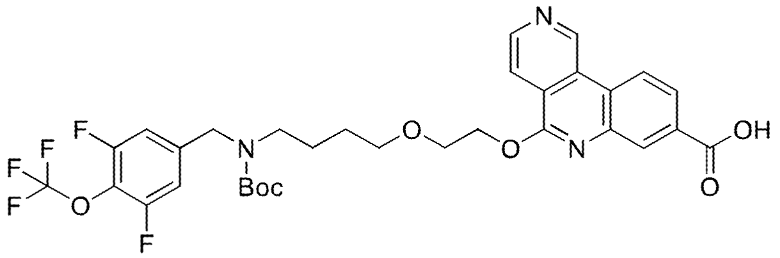


A mixture of **compound 1.608** (140 mg, 284.65 μmol, HCl salt), DIPEA (147.15 mg, 1.14 mmol) and **compound 1.507** (90.10 mg, 398.51 μmol) in MeOH (3 mL) was stirred at 40 °C for 12 h, then sodium triacetoxyborohydride (241.31 mg, 1.14 mmol) was added. The reaction mixture was stirred at 40 °C for 3 h. The reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified (PM170) to afford **compound 1.830** (100 mg, 156.60 μmol, 55.0% yield, FA salt) as a yellow solid.

LCMS (AM3): rt = 0.827 min, (593.2 $[M+H]^+$), 95.6% purity.

Synthesis of Intermediate 1.840

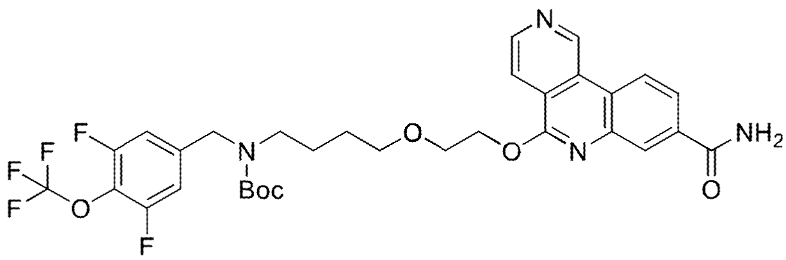
5-(2-(4-((Tert-butoxycarbonyl)(3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid 1.839



To a solution of **Example 116** (3 g, 4.91 mmol, FA salt) in EtOH (30 mL) was added DIPEA (1.86 g, 14.35 mmol) and Boc_2O (1.43 g, 6.53 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated *in vacuo* to give the residue. The residue was purified (PM150) to afford **compound 1.839** (2.6 g, 3.01 mmol, 61.42% yield) as white solid.

LCMS (AM3): rt = 1.076 min, (666.1 $[M+H]^+$), 77.1% purity.

Tert-butyl (4-(2-((8-carbamoylbenzo[c][2,6]naphthyridin-5-yl)oxy)ethoxy)butyl)(3,5-difluoro-4-(trifluoromethoxy)benzyl)carbamate 1.840



To a mixture of **compound 1.839** (500 mg, 744.56 μmol), NH_4Cl (398.28 mg, 7.45 mmol) and HATU (339.73 mg, 893.47 μmol) in DMF (5 mL) was added DIPEA (192.45 mg, 1.49 mmol) at 25 °C. The resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated *in vacuo* to give the residue. The residue was purified (PM150) to afford **compound 1.840** (420 mg, 619.3 μmol, 83.2% yield) as white solid.

LCMS (AM3): rt = 1.027 min, (665.2 $[M+H]^+$), 98.9% purity.

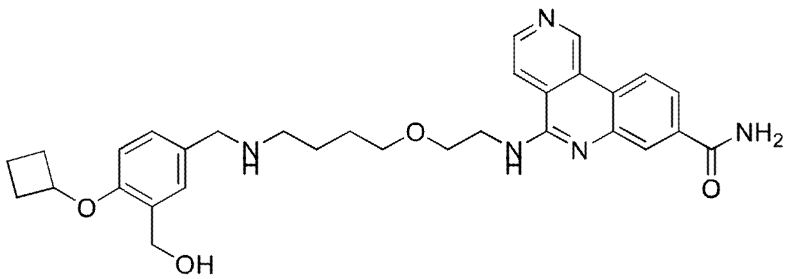
Example compounds

[00380] The Examples are prepared according to the methods below using the Preparations hereinbefore. Wherein additional materials have been prepared, preparations are included for each Example. Alternatively, wherein commercially available materials are used, only the final steps are included, and no intermediate reference number is necessary.

[00381]

Example 1

5-((2-(4-((4-cyclobutoxy-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



[00382] A mixture of **compound 1.64** (40 mg, 193.95 μmol), **Intermediate E** (75.62 mg, 193.95 μmol, HCl salt) and DIPEA (50.13 mg, 387.90 μmol) in MeOH (1 mL) was stirred at 25 °C for 1 h, then sodium triacetoxyborohydride (205.53 mg, 969.76 μmol) was added. The reaction mixture was stirred at 25 °C for 11 h. The reaction mixture was concentrated *in vacuo* to give a residue which was purified (PM23) to afford **Example 1** (26.71 mg, 49.13 μmol, 25.3% yield, 100% purity) as an off-white solid.

LCMS (AM3): rt = 0.726 min, (544.2 $[M+H]^+$), 100% purity.

^{1}H NMR (400MHz, MeOH-d_4) δ: 9.90 (s, 1H), 8.75 (d, *J* = 5.6 Hz, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 2.0 Hz, 1H), 8.11 (d, *J* = 5.6 Hz, 1H), 7.82 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 4.62 (t, *J* = 7.2 Hz, 1H), 4.59 (s, 2H), 3.90–3.87 (t, 2H), 3.80–3.77 (t, 2H), 3.61 (s, 2H), 3.55–3.51 (m, 2H), 2.60–2.53 (m, 2H), 2.47–2.36 (m, 2H), 2.09 (tt, *J* = 2.4, 9.6 Hz, 2H), 1.87–1.60 (m, 2H), 1.60–1.56 (m, 4H) ppm.

The following examples in Table 1 were made with non-critical changes or substitutions to the exemplified procedure in Example 1, that would be understood by one skilled in the art using intermediate E and compounds of formula (III)

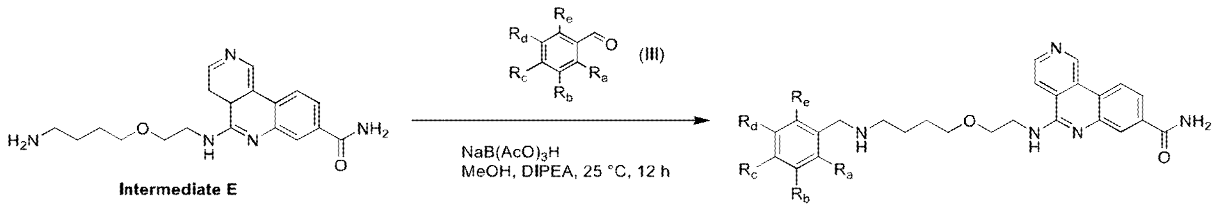
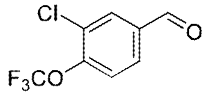
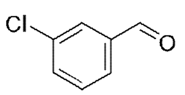
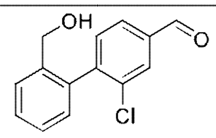
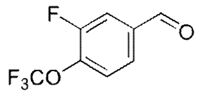
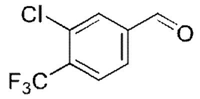
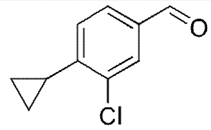
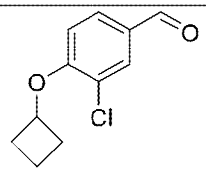
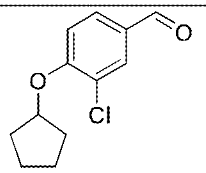
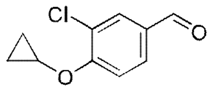
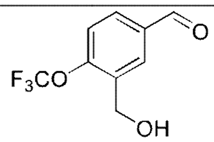
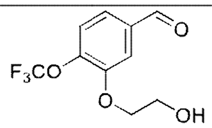
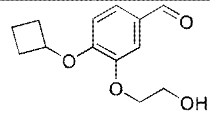
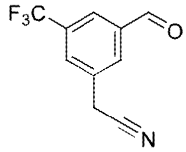
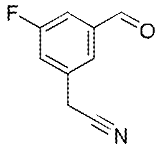
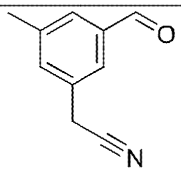


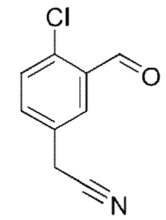
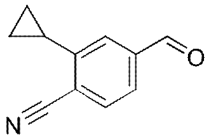
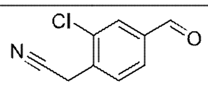
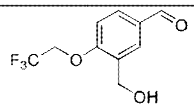
Table 1

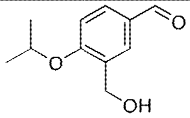
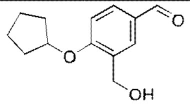
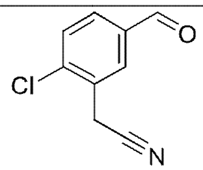
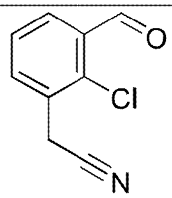
Example No.	Chemical IUPAC name	Compound (III)	Analytical
Example 3	5-((2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-chloro-4-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ 10.06 (s, 1H), 8.96 (d, J = 5.7 Hz, 1H), 8.75 (d, J = 8.6 Hz, 1H), 8.39 (d, 1H), 8.36-8.35 (d, 1H), 8.00 (dd, J = 1.7, 8.4 Hz, 1H), 7.73 (s, 1H), 7.51 (s, 2H), 4.18 (s, 2H), 4.05 (t, J = 5.1 Hz, 2H), 3.90-3.88 (t, 2H), 3.61 (t, J = 6.1 Hz, 2H), 3.09-3.05 (t, 2H), 1.85-1.75 (quintet, 2H), 1.73-1.62 (quintet, 2H) ppm. LCMS (AM3): rt = 0.739 min, (562.0 [M+H]$^+$), 100% purity. Purification Method 25
Example 4	5-((2-(4-((3-chlorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-chlorobenzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.04 (s, 1H), 8.92 (d, J = 5.6 Hz, 1H), 8.73 (d, J = 8.6 Hz, 1H), 8.34 (d, J = 1.7 Hz, 1H), 8.29 (d, J = 5.6 Hz, 1H), 7.96 (dd, J = 1.7, 8.3 Hz, 1H), 7.50 (s, 1H), 7.46-7.34 (m, 3H), 4.13 (s, 2H), 4.03-4.01 (t, 2H), 3.88-3.86 (m, 2H), 3.62 (t, J = 6.0 Hz, 2H), 3.07-3.03 (m, 2H), 1.83-1.75 (quintet, 2H), 1.71-1.63 (m, 2H) ppm. LCMS (AM3): rt = 0.683 min, (478.0 [M+H]$^+$), 100% purity. Purification Method 26
Example 6	5-((2-(4-(((2-chloro-2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)methyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-Chloro-2'-(hydroxymethyl)-[1,1'-biphenyl]-4-carbaldehyde **1.345**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.06 (s, 1H), 8.96 (d, J = 5.6 Hz, 1H), 8.76 (d, J = 8.8 Hz, 1H), 8.39 (s, 1H), 8.35 (d, J = 5.6 Hz, 1H), 8.00 (dd, J = 1.6, 8.4 Hz, 1H), 7.63 (s, 1H), 7.61–7.58 (d, 1H), 7.44–7.39 (t, 2H), 7.38–7.30 (m, 2H), 7.08 (d, J = 7.4 Hz, 1H), 4.41 (d, J = 13.2 Hz, 1H), 4.27 (d, J = 13.2 Hz, 1H), 4.19 (s, 2H), 4.06 (t, J = 5.2 Hz, 2H), 3.90 (t, J = 5.2 Hz, 2H), 3.63 (t, J = 6.0 Hz, 2H), 3.09 (t, J = 8.0 Hz, 2H), 1.87–1.79 (quin, 2H), 1.73–1.66 (quin, 2H) ppm. LCMS (AM3): rt = 0.719 min, (584.0 [M+H]$^+$), 99.5% purity Purification Method 28

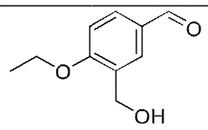
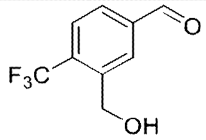
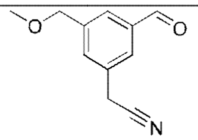
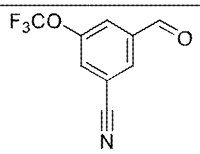
Example 7	5-((2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-fluoro-4-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.07 (s, 1H), 8.95 (d, *J* = 5.5 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.37 (d, *J* = 1.6 Hz, 1H), 8.34-8.32 (d, 1H), 8.00 (dd, *J* = 1.7, 8.5 Hz, 1H), 7.55-7.47 (m, 2H), 7.38-7.36 (m, 1H), 4.19 (s, 2H), 4.06-4.03 (t, 2H), 3.90-3.87 (t, 2H), 3.62 (t, *J* = 6.1 Hz, 2H), 3.09-3.05 (dd, 2H), 1.85-1.77 (m, 2H), 1.70-1.64 (quintet, 2H) ppm. LCMS (AM3): rt = 0.746 min, (546.4 $[M+H]^+$), 100% purity. Purification Method 27
Example 8	5-((2-(4-((3-chloro-4-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-chloro-4-(trifluoromethyl)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.08 (s, 1H), 8.97 (d, *J* = 5.7 Hz, 1H), 8.77 (d, *J* = 8.6 Hz, 1H), 8.38-8.37 (d, 1H), 8.35 (d, *J* = 5.5 Hz, 1H), 8.01 (dd, *J* = 1.8, 8.5 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.76 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 4.24 (s, 2H), 4.07-4.05 (t, 2H), 3.90-3.88 (t, 2H), 3.64-3.61 (t, 2H), 3.10-3.06 (dd, 2H), 1.87-1.79 (m, 2H), 1.71-1.63 (m, 2H) ppm. LCMS (AM3): rt = 0.755 min, (546.4 $[M+H]^+$), 100% purity. Purification Method 27
Example 9	5-((2-(4-((3-chloro-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Chloro-4-cyclopropylbenzaldehyde **1.202**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.06 (s, 1H), 8.95 (d, *J* = 5.8 Hz, 1H), 8.76 (d, *J* = 8.5 Hz, 1H), 8.37 (d, *J* = 1.8 Hz, 1H), 8.33 (d, *J* = 5.8 Hz, 1H), 8.00 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.26 (dd, *J* = 1.9, 7.9 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 4.07 (s, 2H), 4.04 (t, *J* = 5.3 Hz, 2H), 3.90–3.86 (t, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.05–2.99 (m, 2H), 2.23–2.15 (m, 1H), 1.84–1.74 (m, 2H), 1.72–1.62 (m, 2H), 1.08–1.01 (m, 2H), 0.71–0.66 (m, 2H) ppm. LCMS (AM3): rt = 0.727 min, (518.1 $[M+H]^+$), 100% purity. Purification Method 29
Example 10	5-((2-(4-((3-chloro-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-chloro-4-cyclobutoxybenzaldehyde **1.32**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.06 (s, 1H), 8.96 (d, *J* = 5.8 Hz, 1H), 8.76 (d, *J* = 8.5 Hz, 1H), 8.40-8.30 (m, 2H), 8.00 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.47 (d, *J* = 2.3 Hz, 1H), 7.28 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.73 (m, *J* = 7.0 Hz, 1H), 4.05-4.03 (m, 4H), 3.88 (t, *J* = 5.2 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.02-2.98 (m, 2H), 2.53-2.43 (m, 2H), 2.23-2.09 (m, 2H), 1.94-1.62 (m, 6H) ppm. LCMS (AM3): rt = 0.737 min, (548.1 $[M+H]^+$), 100% purity. Purification Method 27

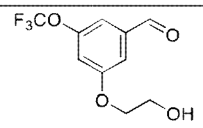
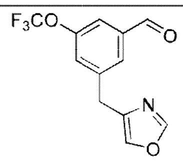
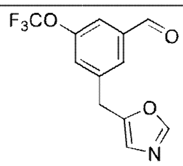
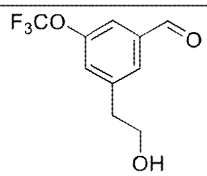
Example 11	5-((2-(4-((3-chloro-4-(cyclopentyloxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-chloro-4-(cyclopentyloxy)benzaldehyde **1.33**	[1]H NMR (400 MHz, MeOH-d_4) δ: 10.06 (s, 1H), 8.95 (d, *J* = 5.6 Hz, 1H), 8.76 (d, *J* = 8.6 Hz, 1H), 8.37 (d, *J* = 1.6 Hz, 1H), 8.32 (d, *J* = 5.6 Hz, 1H), 8.00 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.30 (dd, *J* = 2.2, 8.4 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 4.90-4.89 (m, 1H), 4.04-4.04 (m, 4H), 3.89-3.86 (t, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.03-2.99 (t, 2H), 1.97-1.90 (m, 2H), 1.86-1.73 (m, 6H), 1.70-1.62 (m, 4H) ppm. LCMS (AM3): rt = 0.779 min, (562.1 $[M+H]^+$), 100% purity Purification Method 30
Example 12	5-((2-(4-((3-chloro-4-cyclopropoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Chloro-4-cyclopropoxybenzaldehyde **1.90**	[1]H NMR (400 MHz, MeOH-d_4) δ: 10.06 (s, 1H), 8.95 (d, *J* = 5.6 Hz, 1H), 8.76 (d, *J* = 8.6 Hz, 1H), 8.37-8.36 (d, 1H), 8.33-8.31 (d, 1H), 7.99 (dd, *J* = 1.7, 8.3 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.43-7.41 (m, 1H), 7.36-7.35 (m, 1H), 4.05-4.03 (m, 4H), 3.91-3.84 (m, 3H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.05-2.98 (m, 2H), 1.84-1.74 (m, 2H), 1.74-1.64 (m, 2H), 0.89-0.81 (m, 2H), 0.75-0.70 (m, 2H) ppm. LCMS (AM3): rt = 0.737 min, (534.1 $[M+H]^+$), 100% purity Purification Method 37
Example 23	5-((2-(4-((3-(hydroxymethyl)-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Hydroxymethyl)-4-(trifluoromethoxy)benzaldehyde, **1.153**	[1]H NMR (400 MHz, MeOH-d_4) δ: 10.02 (s, 1H), 8.95 (d, *J* = 5.6 Hz, 1H), 8.72 (d, *J* = 8.6 Hz, 1H), 8.39-8.35 (m, 2H), 8.00 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.74 (d, *J* = 2.1 Hz, 1H), 7.50-7.44 (m, 1H), 7.37-7.33 (m, 1H), 4.70 (s, 2H), 4.18 (s, 2H), 4.06 (t, *J* = 5.0 Hz, 2H), 3.89 (t, *J* = 5.1 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.08-3.03 (t, 2H), 1.87-1.77 (m, 2H), 1.71-1.61 (m, 2H) ppm. LCMS (AM3): rt = 0.712 min, (558.2 $[M+H]^+$), 99.3% purity Purification Method 41
Example 35	5-((2-(4-((3-(2-hydroxyethoxy)-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(2-Hydroxyethoxy)-4-(trifluoromethoxy)benzaldehyde **1.402**	[1]H NMR (400 MHz, MeOH-d_4) δ: 10.05 (br s, 1H), 8.98 (d, *J* = 3.6 Hz, 1H), 8.74 (d, *J* = 8.4 Hz, 1H), 8.41–8.40 (m, 2H), 8.01 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.34–7.30 (m, 2H), 7.08 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 4.18–4.14 (t, 4H), 4.07 (t, *J* = 4.8 Hz, 2H), 3.93–3.86 (m, 4H), 3.60 (t, *J* = 4.8 Hz, 2H), 3.05 (t, *J* = 8.0 Hz, 2H), 1.85–1.76 (quin, 2H), 1.71–1.62 (quin, 2H) ppm. LCMS (AM3): rt = 0.708 min, (588.2 $[M+H]^+$), 100% purity. Purification Method 50

Example 36	5-((2-(4-((4-cyclobutoxy-3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 4-Cyclobutoxy-3-(2-hydroxyethoxy)benzaldehyde **1.410**	^{1}H NMR (400 MHz, MeOH-*d$_4$*) δ: 9.92 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 8.14 (d, *J* = 5.6 Hz. 1H), 7.83 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 6.91 (d, *J* = 1.6 Hz, 1H), 6.75–6.68 (m, 2H), 4.66–4.58 (quin, 1H), 4.04 (t, *J* = 4.8 Hz, 2H), 3.91–3.84 (m, 4H), 3.79 (t, *J* = 5.6 Hz, 2H), 3.60–3.53 (m, 4H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.44–2.36 (m, 2H), 2.18–2.07 (m, 2H), 1.85–1.76 (m, 1H), 1.72–1.55 (m, 5H) ppm. LCMS (AM3): rt = 0.708 min, (574.3 [M+H]$^+$), 96.9 % purity. Purification Method 51
Example 56	5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-(trifluoromethyl)phenyl)acetonitrile **1.469**	^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ: 10.06 (s, 1H), 8.85 (d, *J* = 5.6 Hz, 1H), 8.69 (d, *J* = 8.8 Hz, 1H), 8.27 (d, *J* = 5.6 Hz, 1H), 8.22 (s, 1H), 8.17 (br s, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.98 (t, *J* = 5.2 Hz, 1H), 7.80 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.65 (s, 1H), 7.61 (s, 1H), 7.57 (s, 1H), 7.42 (br s, 1H), 4.15 (s, 2H), 3.80–3.77 (m, 2H), 3.76 (s, 2H), 3.77 (t, *J* = 6.4 Hz, 2H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.52–2.51 (m, 2H), 1.58–1.44 (m, 4H) ppm. LCMS (AM3): rt = 0.714 min, (551.3 [M+H]$^+$), 99.4% purity Purification Method 68
Example 57	5-((2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Fluoro-5-formylphenyl)acetonitrile **1.472**	^{1}H NMR (400 MHz, MeOH-*d$_4$*) δ: 9.89 (s, 1H), 8.76 (d, *J* = 6.0 Hz, 1H), 8.57 (d, *J* = 8.4 Hz, 1H), 8.48 (br s, 1H), 8.18 (d, *J* = 1.6 Hz, 1H), 8.10 (d, *J* = 5.6 Hz, 1H), 7.80 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.25 (s, 1H), 7.17 (d, *J* = 9.2 Hz, 2H), 4.09 (s, 2H), 3.95 (s, 2H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 6.0 Hz, 2H), 1.84–1.76 (quin, 2H), 1.72–1.66 (quin, 2H) ppm. LCMS (AM3): rt = 0.672min, (501.3 [M+H]$^+$), 100% purity Purification Method 68
Example 58	5-((2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-methylphenyl)acetonitrile **1.475**	^{1}H NMR (400 MHz, MeOH-*d$_4$*) δ: 9.91 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.52 (br s, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 8.11 (d, *J* = 5.6 Hz, 1H), 7.81 (dd, *J* = 8.4, 1.6, Hz, 1H), 7.21–7.16 (m, 3H), 4.01 (s, 2H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.86 (s, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 5.8 Hz, 2H), 3.02 (t, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 1.84–1.75 (quin, 2H), 1.72–1.65 (quin, 2H) ppm LCMS (AM3): rt = 0.705 min, (497.3 [M+H]$^+$), 100% purity. Purification Method 68

Example 59	5-((2-(4-((2-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(4-Chloro-3-formylphenyl)acetonitrile **1.521**	^{1}H NMR (400 MHz, MeOH-d_4, broad peaks) δ: 9.72 (s, 1H), 8.67 (d, *J* = 5.2 Hz, 1H), 8.48 (s, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.07–7.99 (m, 2H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.49 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 4.18 (s, 2H), 3.89 (s, 2H), 3.84–3.80 (m, 4H), 3.61 (t, *J* = 5.6 Hz, 2H), 3.09 (t, *J* = 7.6 Hz, 2H), 1.92–1.81 (m, 2H), 1.73–1.67 (m, 2H) ppm LCMS (AM3): rt = 0.719 min, (517.3 [M+H]$^+$), 98.6% purity. Purification Method 69
Example 60	5-((2-(4-((4-cyano-3-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-Cyclopropyl-4-formylbenzonitrile **1.526**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.91 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.47 (s, 1H), 8.18 (d, *J* = 1.6 Hz, 1H), 8.11 (d, *J* = 5.6 Hz, 1H), 7.81 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.10 (s, 1H), 4.07 (s, 2H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.83 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.26–2.19 (m,1H), 1.83–1.76 (quin, 2H), 1.72–1.65 (quin, 2H), 1.17–1.13 (m, 2H), 0.84–0.80 (m, 2H) ppm LCMS (AM3): rt = 0.709 min, (509.3 [M+H]$^+$), 98.4% purity Purification Method 63
Example 61	5-((2-(4-((3-chloro-4-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(2-Chloro-4-formylphenyl)acetonitrile **1.524**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.86 (s, 1H), 8.74 (d, *J* = 5.6 Hz, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.45 (br s, 1H), 8.15 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 5.6 Hz, 1H), 7.78 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.55–7.53 (m, 2H), 7.38 (d, *J* = 7.8 Hz, 1H), 4.08 (s, 2H), 3.95 (s, 2H), 3.87 (t, *J* = 4.8 Hz, 2H), 3.82 (t, *J* = 5.2 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 1.84–1.77 (quin, 2H), 1.72–1.63 (quin, 2H) ppm LCMS (AM3): rt = 0.721 min, (517.3 [M+H]$^+$), 100% purity Purification Method 69
Example 62	5-((2-(4-((3-(hydroxymethyl)-4-(2,2,2-trifluoroethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Hydroxymethyl)-4-(2,2,2-trifluoroethoxy)benzaldehyde **1.530**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.92 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 8.54 (s, 1H), 8.20 (s, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.51 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz,1H), 4.66 (s, 2H), 4.54 (q, *J* = 8.4 Hz, 2H), 4.00 (s, 2H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 7.6 Hz, 2H), 1.82–1.74 (quin, 2H), 1.71–1.64 (quin, 2H) ppm LCMS (AM3): rt = 0.723 min, (572.4 [M+H]$^+$), 100% purity Purification AM70

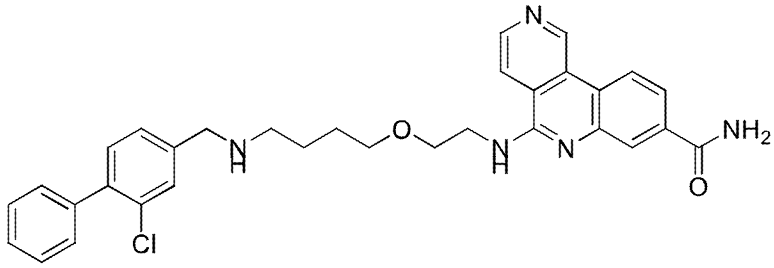
Example 63	5-((2-(4-((3-(hydroxymethyl)-4-isopropoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Hydroxymethyl)-4-isopropoxybenzaldehyde **1.668**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.90 (s, 1H), 8.76 (d, *J* = 5.6 Hz, 1H), 8.57 (d, *J* = 8.4 Hz, 1H), 8.42 (br s, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 8.11 (d, *J* = 6.0 Hz, 1H), 7.81 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.60-4.56 (m, 3H), 4.01 (s, 2H), 3.89 (t, *J* = 5.2 Hz, 2H), 3.81 (t, *J* = 5.2 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.01 (t, *J* = 7.6 Hz, 2H), 1.82-1.76 (m, 2H), 1.72-1.67 (m, 2H), 1.29 (d, *J* = 6.0 Hz, 6H) ppm LCMS (AM3): rt = 0.734 min, (532.3 [M+H]$^+$), 100% purity Purification AM70
Example 64	5-((2-(4-((4-(cyclopentyloxy)-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 4-(Cyclopentyloxy)-3-(hydroxymethyl)benzaldehyde **1.671**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.90 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.52 (br s, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.42 (d, *J* = 1.6 Hz, 1H), 7.22 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 4.80-4.76 (m, 1H), 4.58 (s, 2H), 4.01 (s, 2H), 3.89 (t, *J* = 6.4 Hz, 2H), 3.81 (t, *J* = 6.4 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.01 (t, *J* = 7.6 Hz, 2H), 1.92-1.85 (m, 2H), 1.83-1.55 (m, 10H) ppm LCMS (AM3): rt = 0.563 min, (558.3 [M+H]$^+$), 100% purity. Purification AM71
Example 65	5-((2-(4-((4-chloro-3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(2-Chloro-5-formylphenyl)acetonitrile **1.478**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.05 (s, 1H), 8.97 (d, *J* = 5.6 Hz, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 1.2 Hz, 1H), 8.38 (d, *J* = 5.6 Hz, 1H), 8.01 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64 (d, *J* = 1.6 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.48–7.45 (m, 1H), 4.17 (s, 2H), 4.07 (t, *J* = 4.8 Hz, 2H), 4.01 (s, 2H), 3.90 (t, *J* = 5.2 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.05 (t, *J* = 8.0 Hz, 2H), 1.84–1.77 (quin, 2H), 1.70–1.62 (quin, 2H) ppm LCMS (AM3): rt = 0.721min, (517.3 [M+H]$^+$), 98.5% purity Purification Method 50
Example 66	5-((2-(4-((2-chloro-3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(2-Chloro-3-formylphenyl)acetonitrile **1.483**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.84 (s, 1H), 8.73 (d, *J* = 6.0 Hz, 1H), 8.53–8.45 (m, 2H), 8.15 (d, *J* = 1.6 Hz, 1H), 8.08 (d, *J* = 5.6 Hz, 1H), 7.77 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 6.8 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 4.20 (s, 2H), 3.97 (s, 2H), 3.89 (t, *J* = 6.8 Hz, 2H), 3.82 (t, *J* = 5.2 Hz, 2H), 3.63 (t, *J* = 5.8 Hz, 2H), 3.08 (t, *J* = 8.0 Hz, 2H), 1.88–1.79 (quin, 2H), 1.74–1.66 (quin, 2H) ppm LCMS (AM3): rt = 0.701 min, (517.2 [M+H]$^+$), 100% purity Purification AM72

Example 68	5-((2-(4-((4-ethoxy-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 4-Ethoxy-3-(hydroxymethyl)benzaldehyde **1.635**	^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 10.07 (s, 1H), 8.86 (d, *J* = 5.6 Hz, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.34 (s, 1H), 8.29 (d, *J* = 5.6 Hz, 1H), 8.19 (br s, 1H), 8.15 (d, *J* = 1.6 Hz, 1H), 8.02 (t, *J* = 5.2 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.43-7.40 (m, 2H), 7.18-7.15 (m, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.48 (s, 2H), 3.99 (q, *J* = 7.2 Hz, 2H), 3.80-3.77 (m, 4H), 3.70 (t, *J* = 5.6 Hz, 2H), 3.46 (t, *J* = 5.6 Hz, 2H), 2.68-2.62 (m, 2H), 1.60-1.50 (m, 4H), 1.30 (t, *J* = 6.8 Hz, 3H) ppm LCMS (AM3): rt = 0.710 min, (518.3 [M+H]$^+$), 100% purity Purification Method 68
Example 85	5-((2-(4-((3-(hydroxymethyl)-4-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Hydroxymethyl)-4-(trifluoromethyl)benzaldehyde **1.589**	^{1}H NMR (400 MHz, MeOH-*d*$_4$) δ: 9.89 (s, 1H), 8.78 (d, *J* = 5.6 Hz, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.47 (br s, 1H), 8.18 (d, *J* = 1.6 Hz, 1H), 8.10 (d, *J* = 5.6 Hz, 1H), 7.87 (s, 1H), 7.80 (dd, *J* = 8.4, 2.0, Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 4.80 (s, 2H), 4.17 (s, 2H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H), 1.86-1.78 (quin, 2H), 1.73-1.66 (quin, 2H) ppm LCMS (AM3): rt = 0.707 min, (542.2 [M+H]$^+$), 98.8% purity Purification Method 92 then 72
Example 153	5-((2-(4-((3-(cyanomethyl)-5-(methoxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-(methoxymethyl)phenyl)acetonitrile **1.803**	^{1}H NMR (400 MHz, MeOH-*d*$_4$) δ: 9.86 (s, 1H), 8.74 (d, *J* = 5.6 Hz, 1H), 8.54 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 2.0 Hz, 1H), 8.09 (d, *J* = 5.6 Hz, 1H), 7.80 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.20-7.17 (m, 3H), 4.41 (s, 2H), 3.88 (t, *J* = 5.6 Hz, 2H), 3.85 (s, 2H), 3.79 (t, *J* = 5.6 Hz, 2H), 3.64 (s, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 3.36 (s, 3H), 2.55 (t, *J* = 6.8 Hz, 2H), 1.61-1.57 (m, 4H) ppm LCMS (AM3): rt = 0.689 min, (527.1 [M+H]$^+$), 98.4% purity Purification Method 149
Example 156	5-((2-(4-((3-cyano-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Formyl-5-(trifluoromethoxy)benzonitrile **1.714**	^{1}H NMR (400 MHz, MeOH-*d*$_4$) δ: 9.87 (s, 1H), 8.74 (d, *J* = 5.6 Hz, 1H), 8.55 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 1.6 Hz, 1H), 8.09 (d, *J* = 5.6 Hz, 1H), 7.80 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.65 (s, 1H), 7.55 (s, 2H), 3.89 (t, *J* = 5.6 Hz, 2H), 3.80 (t, *J* = 5.6 Hz, 2H), 3.73 (s, 2H), 3.57 (t, *J* = 6.0 Hz, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 1.65-1.55 (m, 4H) ppm LCMS (AM3): rt = 0.748 min, (553.2 [M+H]$^+$), 99.2% purity Purification Method 153

Example 157	5-((2-(4-((3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(2-Hydroxyethoxy)-5-(trifluoromethoxy)benzaldehyde **1.718**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.94 (s, 1H), 8.78 (d, *J* = 5.6 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.47 (s, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 8.13 (dd, *J* = 5.6 Hz, 0.8 Hz, 1H), 7.82 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 4.08-4.06 (m, 4H), 3.92 (t, *J* = 5.6 Hz, 2H), 3.87 (J = 5.6 Hz, 2H), 3.82 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 6.8 Hz, 2H), 1.84-1.76 (quin, 2H), 1.72-1.66 (quin, 2H) ppm LCMS (AM3): rt = 0.729 min, (588.3 $[M+H]^+$), 99.4% purity Purification Method 154
Example 158	5-((2-(4-((3-(oxazol-4-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Oxazol-4-ylmethyl)-5-(trifluoromethoxy)benzaldehyde **1.712**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.92 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.46 (s, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 8.16 (s, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 7.81 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.77 (s, 1H), 7.33 (s, 1H), 7.24 (d, *J* = 6.4 Hz, 2H), 4.09 (s, 2H), 3.94 (s, 2H), 3.92 (t, *J* = 5.6 Hz, 2H), 3.83 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 1.84-1.76 (quin, 2H), 1.74-1.66 (quin, 2H) ppm LCMS (AM3): rt = 0.765 min, (609.2 $[M+H]^+$), 100% purity. Purification Method 155
Example 159	5-((2-(4-((3-(oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzaldehyde **1.713**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.93 (s, 1H), 8.78 (d, *J* = 5.6 Hz, 1H), 8.62 (d, *J* = 8.4 Hz, 1H), 8.48 (s, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.13-8.10 (m, 2H), 7.82 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.31-7.25 (m, 3H), 6.93 (s, 1H), 4.13 (s, 2H), 4.08 (s, 2H), 3.92 (t, *J* = 5.6 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.02 (t, *J* = 7.2 Hz, 2H), 1.82-1.75 (m, 2H), 1.71-1.64 (m, 2H) ppm LCMS (AM3): rt = 0.755 min, (609.2 $[M+H]^+$), 100% purity Purification Method 155
Example 165	5-((2-(4-((3-(2-hydroxyethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(2-Hydroxyethyl)-5-(trifluoromethoxy)benzaldehyde **1.723**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.92 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.46 (br s, 1H), 8.20 (d, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 4.4 Hz, 1H), 7.81 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.29 (s, 1H), 7.23 (s, 2H), 4.10 (s, 2H), 3.91 (t, *J* = 5.6 Hz, 2H), 3.83-3.80 (t, 2H), 3.80-3.77 (t, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.05 (t, *J* = 7.6 Hz, 2H), 2.86 (t, *J* = 6.4 Hz, 2H), 1.84-1.76 (quin, 2H), 1.72-1.66 (quin, 2H) ppm LCMS (AM3): rt = 0.732 min, (572.2 $[M+H]^+$), 100% purity Purification Method 160

Example 2

5-((2-(4-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)butoxy)ethyl)amino)benzo[c][2,6] naphthyridine-8-carboxamide



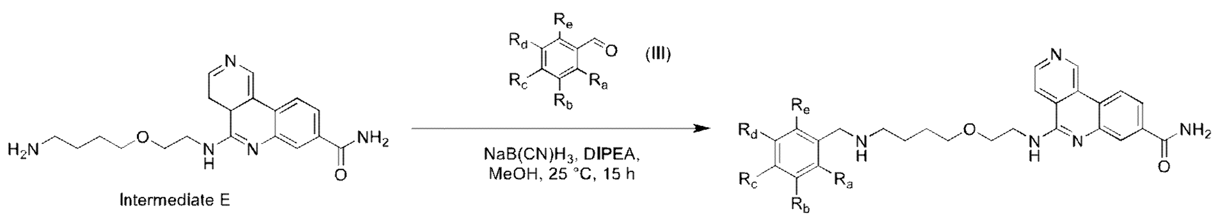
[00383] A mixture of **Intermediate E** (150 mg, 0.385 mmol, HCl salt), DIPEA (44.52 mg, 0.344 mmol) and 3-chloro-4-phenylbenzaldehyde (83 mg, 0.383 mmol) in MeOH (4 mL) was stirred at 25 °C for 12 h, then sodium cyanoborohydride (75 mg, 1.19 mmol) was added. The mixture was stirred at 25 °C for 3 h. The mixture was concentrated *in vacuo* and purified (PM24) to afford **Example 2** (63.38 mg, 0.0949 mmol, 24.7% yield, TFA salt) as a yellow solid.

LCMS (AM3): rt = 0.786 min, (554.1 $[M+H]^+$), 100% purity.

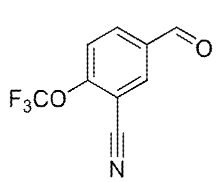
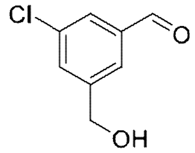
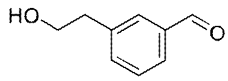
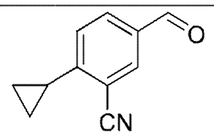
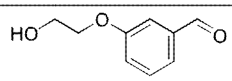
^{1}H NMR (400 MHz, MeOD) δ: 10.07 (s, 1H), 8.98 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.8 Hz, 1H), 8.43–8.37 (m, 2H), 8.03 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.46–7.35 (m, 7H), 4.19 (s, 2H), 4.07 (t, *J* = 5.2 Hz, 2H), 3.92–3.87 (t, 2H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.12–3.05 (m, 2H), 1.88–1.77 (m, 2H), 1.75–1.64 (m, 2H) ppm

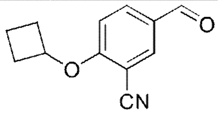
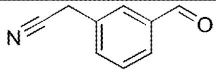
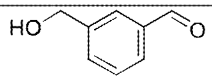
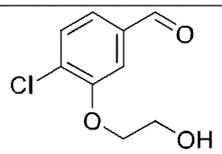
The following examples in Table 2 were made with non-critical changes or substitutions to the exemplified procedure in Example 2, that would be understood by one skilled in the art using intermediate E and compounds of formula (III).

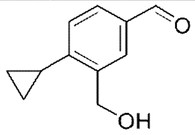
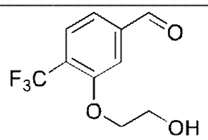
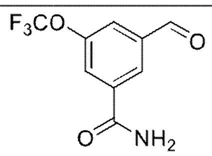
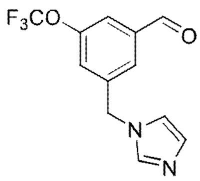
Table 2

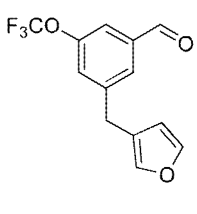


Example No.	Chemical IUPAC name	Compound (III)	Analytical

Example 5	5-((2-(4-((3-cyano-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 5-Formyl-2-(trifluoromethoxy)benzonitrile **1.136**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.06 (s, 1H), 8.94 (d, *J* = 4.6 Hz, 1H), 8.76 (d, *J* = 8.8 Hz, 1H), 8.35 (s, 1H), 8.31-8.29 (d, 1H), 7.99 (d, *J* = 2.2 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 4.25 (s, 2H), 4.04 (t, *J* = 4.8 Hz, 2H), 3.90-3.87 (t, 2H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.11-3.07 (dd, 2H), 1.85-1.78 (quintet, 2H), 1.72-1.63 (quintet, 2H) ppm. LCMS (AM3): rt = 0.715 min, (553.1 [M+H]$^+$), 98.1% purity. Purification Method 27
Example 13	5-((2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Chloro-5-(hydroxymethyl)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.06 (s, 1H), 8.97 (d, *J* = 5.4 Hz, 1H), 8.76 (d, *J* = 8.3 Hz, 1H), 8.43-8.35 (m, 2H), 8.02 (dd, *J* = 1.5, 8.6 Hz, 1H), 7.43 (m, 1H), 7.37 (d, *J* = 9.3 Hz, 2H), 4.62 (s, 2H), 4.13 (s, 2H), 4.07 (t, *J* = 5.0 Hz, 2H), 3.89 (t, *J* = 5.1 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.06-3.02 (m, 2H), 1.85-1.75 (m, 2H), 1.70-1.60 (m, 2H) ppm. LCMS (AM3): rt = 0.663 min, (508.0 [M+H]$^+$), 100% purity. Purification Method 31
Example 14	5-((2-(4-((3-(2-hydroxyethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(2-hydroxyethyl)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ:10.07 (br s, 1H), 8.98 (s, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.41 (s, 1H), 8.41-8.39 (d, 1H), 8.02 (dd, *J* = 1.8, 8.5 Hz, 1H), 7.37-7.26 (m, 4H), 4.12 (s, 2H) 4.12-4.06 (t, 2H), 3.89 (t, *J* = 5.2 Hz, 2H), 3.77 (t, *J* = 6.8 Hz, 2H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.02 (m, *J* = 6.0 Hz, 2H), 2.84 (t, *J* = 6.8 Hz, 2H), 1.85-1.74 (m, 2H), 1.69-1.61 (m, 2H) ppm. LCMS (AM3): rt = 0.648 min, (488.1 [M+H]$^+$), 99.2% purity Purification Method 32
Example 18	5-((2-(4-((3-cyano-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-cyclopropyl-5-formylbenzonitrile **1.52**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.08 (s, 1H), 8.99 (d, *J* = 5.1 Hz, 1H), 8.78 (d, *J* = 8.6 Hz, 1H), 8.41 (s, 1H), 8.41-8.39 (d, 1H), 8.04 (dd, *J* = 1.3, 8.4 Hz, 1H), 7.75 (d, *J* = 1.7 Hz, 1H), 7.64-7.61 (dd, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 4.15 (s, 2H), 4.08 (t, *J* = 5.0 Hz, 2H), 3.91-3.88 (t, 2H), 3.61 (t, *J* = 6.1 Hz, 2H), 3.06-3.02 (t, 2H), 2.30-2.21 (septet, 1H), 1.85-1.75 (quintet, 2H), 1.69-1.61 (quintet, 2H), 1.20-1.15 (m, 2H), 0.88-0.82 (m, 2H) ppm. LCMS (AM3): rt = 0.703 min, (509.1 [M+H]$^+$), 97.4% purity. Purification Method 37
Example 19	5-((2-(4-((3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(2-hydroxyethoxy)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.04 (br s, 1H), 8.97 (br s, 1H), 8.73 (d, *J* = 8.6 Hz, 1H), 8.41 (br s, 2H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.05-6.94 (m, 3H), 4.10-4.05 (m, 6H), 3.90-3.85 (m, 4H), 3.60 (t, *J* = 5.5 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 1.85-1.72 (m, 2H), 1.70-1.58 (m, 2H) ppm. LCMS (AM3): rt = 0.647 min, (504.1 [M+H]$^+$), 100% purity Purification Method 31

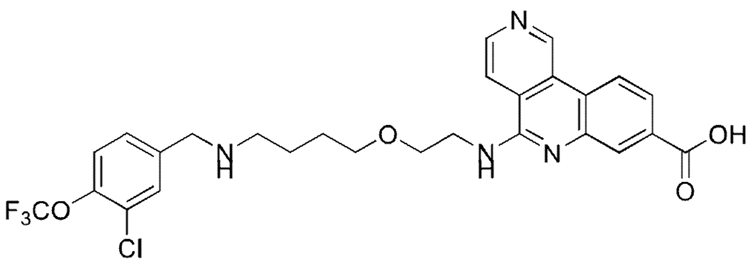
Example 20	5-((2-(4-((3-cyano-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-cyclobutoxy-5-formylbenzonitrile **1.47**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.06 (s, 1H), 8.95 (d, *J* = 5.6 Hz, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 8.36 (d, *J* = 1.6 Hz, 1H), 8.32 (d, *J* = 5.6 Hz, 1H), 7.99 (dd, *J* = 1.7, 8.5 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.64 (dd, *J* = 2.3, 8.7 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 4.84-4.79 (m, 1H), 4.10 (s, 2H), 4.04 (t, *J* = 5.2 Hz, 2H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.02 (t, *J* = 8.0 Hz, 2H), 2.55–2.47 (m, 2H), 2.24–2.14 (quin, 2H), 1.95–1.74 (m, 4H), 1.72–1.64 (m, 2H) ppm. LCMS (AM3): rt = 0.740 min, (539.4 [M+H]$^+$), 98.6% purity Purification Method 21
Example 21	5-((2-(4-((3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formylphenyl)acetonitrile	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.08 (s, 1H), 8.97 (d, *J* = 5.8 Hz, 1H), 8.78 (d, *J* = 8.5 Hz, 1H), 8.39 (d, *J* = 1.6 Hz, 1H), 8.35 (d, *J* = 5.6 Hz, 1H), 8.02 (dd, *J* = 1.7, 8.5 Hz, 1H), 7.50–7.40 (m, 4H), 4.15 (s, 2H), 4.06 (t, *J* = 5.1 Hz, 2H), 3.95 (s, 2H), 3.86 (t, *J* = 5.1 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 8.0 Hz, 2H), 1.84–1.76 (m, 2H), 1.70–1.62 (m, 2H) ppm. LCMS (AM3): rt = 0.677 min, (483.4 [M+H]$^+$), 98.7% purity. Purification Method 39
Example 22	5-((2-(4-((3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(hydroxymethyl)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.05 (s, 1H), 8.97 (d, *J* = 5.6 Hz, 1H), 8.75 (d, *J* = 8.6 Hz, 1H), 8.42 (s, 1H), 8.40–8.38 (d, 1H), 8.02 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.44–7.31 (m, 4H), 4.63 (s, 2H), 4.12 (s, 2H), 4.07 (t, *J* = 5.2 Hz, 2H), 3.89 (t, *J* = 4.8 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.02 (t, *J* = 8.0 Hz, 2H), 1.83–1.73 (quin, 2H), 1.69–1.60 (quin, 2H) ppm. LCMS (AM3): rt = 0.548 min, (474.3 [M+H]$^+$), 97.5% purity. Purification Method 40
Example 24	5-((2-(4-((4-chloro-3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 4-Chloro-3-(2-hydroxyethoxy)benzaldehyde, **1.412**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.10 (s, 1H), 9.00 (d, *J* = 5.6 Hz, 1H), 8.80 (d, *J* = 8.8 Hz, 1H), 8.42–8.38 (m, 2H), 8.04 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz. 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 7.00 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 4.16–4.12 (m, 4H), 4.08 (t, *J* = 4.8 Hz, 2H), 3.94–3.88 (m, 4H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 8.0 Hz, 2H), 1.84–1.76 (m, 2H), 1.70–1.63 (m, 2H) ppm. LCMS (AM3): rt = 0.660 min, (538.2 [M+H]$^+$), 100% purity. Purification Method 42

Example 29	5-((2-(4-((4-cyclopropyl-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 4-Cyclopropyl-3-(hydroxymethyl)benzaldehyde **1.537**	^{1}H NMR (400 MHz, MeOH-d_4) δ:10.05 (s, 1H), 8.93 (d, *J* = 5.6 Hz, 1H), 8.75 (d, *J* = 8.8 Hz, 1H), 8.35 (d, *J* = 1.6 Hz, 1H), 8.30 (d, *J* = 5.6 Hz, 1H), 7.98 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.22 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 4.84 (s, 2H), 4.07 (s, 2H), 4.01 (t, *J* = 4.8 Hz, 2H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.00–1.94 (m, 1H), 1.80–1.72 (quin, 2H), 1.70–1.64 (quin, 2H), 0.98–0.94 (m, 2H), 0.65–0.61 (m, 2H) ppm. LCMS (AM3): rt = 0.731 min, (514.5 [M+H]$^+$), 100% purity. Purification Method 42
Example 38	5-((2-(4-((3-(2-hydroxyethoxy)-4-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(2-Hydroxyethoxy)-4-(trifluoromethyl)benzaldehyde **1.406**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.03 (s, 1H), 8.97 (d, *J* = 5.6 Hz, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 8.41–8.39 (m, 2H), 8.01 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.13 (d, *J* = 8.0 Hz. 1H), 4.21–4.17 (m, 4H), 4.07 (t, *J* = 5.2 Hz, 2H), 3.92–3.86 (m, 4H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.07 (t, *J* = 8.0 Hz, 2H), 1.86–1.78 (quin, 2H), 1.71–1.63 (quin, 2H) ppm. LCMS (AM3): rt = 0.736 min, (572.3 [M+H]$^+$), 100 % purity. Purification Method 50
Example 168	5-((2-(4-((3-carbamoyl-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Formyl-5-(trifluoromethoxy)benzamide **1.675**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.92 (s, 1H), 8.76 (d, *J* = 6.0 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 8.13 (d, *J* = 5.6 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.79 (s, 1H), 7.66 (s, 1H), 7.43 (s, 1H), 3.88 (t, *J* = 5.6 Hz, 2H), 3.80 (t, *J* = 5.6 Hz, 2H), 3.74 (s, 2H), 3.56 (t, *J* = 5.6 Hz, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 1.64-1.56 (m, 4H) ppm LCMS (AM7): rt = 0.844 min, (571.2 [M+H]$^+$), 100% Purification Method 117
Example 172	5-((2-(4-((3-((1H-imidazol-1-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-((1H-imidazol-1-yl)methyl)-5-(trifluoromethoxy)benzaldehyde **1.825**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.93 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.61 (d, *J* = 8.8 Hz, 1H), 8.30 (s, 2H), 8.20 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 6.0 Hz, 1H), 7.84-7.81 (m, 2H), 7.36 (s, 1H), 7.28 (s, 1H), 7.26 (s, 1H), 7.16 (s, 1H), 7.05 (s, 1H), 5.31 (s, 2H), 4.12 (s, 2H), 3.91 (t, *J* = 5.6 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 1.83-1.75 (quin, 2H), 1.72-1.64 (m, 2H) ppm LCMS (AM3): rt = 0.661 min, (608.2 [M+H]$^+$), 96.9% purity Purification Method 167

Example 173	5-((2-(4-((3-(furan-3-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Furan-3-ylmethyl)-5-(trifluoromethoxy)benzaldehyde **1.826**	[1]H NMR (400 MHz, MeOH-*d4*) δ: 9.92 (s, 1H), 8.78 (d, *J* = 6.0 Hz, 1H), 8.60 (d, *J* = 8.8 Hz, 1H), 8.52 (s, 1H), 8.20 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 5.6 Hz, 1H), 7.83 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.43 (t, *J* = 1.6 Hz, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 7.24 (s, 1H), 7.20 (s, 1H), 6.26 (s, 1H), 4.09 (s, 2H), 3.92 (t, *J* = 5.6 Hz, 2H), 3.84-3.81 (m, 4H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 1.84-1.77 (quin, 2H), 1.74-1.67 (quin, 2H) ppm LCMS (AM3): rt = 0.786 min, (608.1 [M+H] +), 97.5% purity Purification Method 175

Example 15

5-((2-(4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6] naphthyridine-8-carboxylic acid



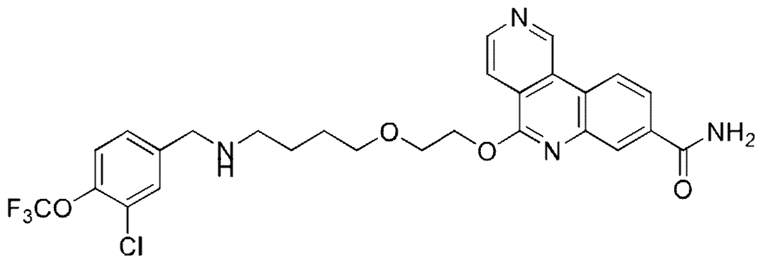
[00384] To a mixture of **compound 1.155** (50 mg, 86.66 μmol) in THF (3 mL), MeOH (3 mL) and water (3 mL) was added LiOH.H_2O (18.18 mg, 433.28 μmol) at 20 °C. The resulting mixture was stirred at 20 °C for 4 h. The mixture was acidified with aq. HCl (1 N) to pH4. The resulting mixture was concentrated *in vacuo* and purified (PM34) to afford **Example 15** (26.77 mg, 39.54 μmol, 45.6% yield, TFA salt) as a yellow solid.

LCMS (AM3): rt = 0.781 min, (563.1 $[M+H]^+$), 100% purity.

[1]H NMR (400 MHz, MeOH-*d4*) δ: 10.07 (s, 1H), 8.95 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.5 Hz, 1H), 8.50 (d, *J* = 1.5 Hz, 1H), 8.33 (d, *J* = 5.8 Hz, 1H), 8.13 (dd, *J* = 1.6, 8.5 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.50–7.49 (m, 2H), 4.16 (s, 2H), 4.03 (t, *J* = 5.3 Hz, 2H), 3.88 (t, *J* = 5.3 Hz, 2H), 3.64–3.61 (t, 2H), 3.07–3.04 (m, 2H), 1.83–1.75 (m, 2H), 1.75–1.65 (m, 2H) ppm.

Example 16

5-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide



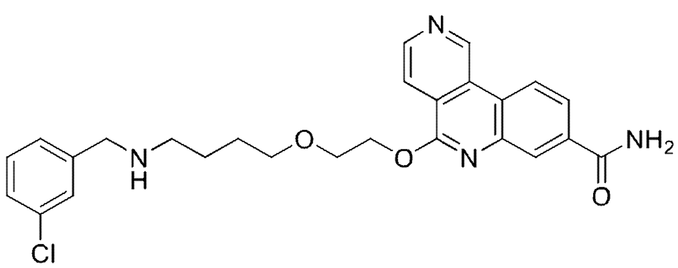
[00385] A mixture of 3-chloro-4-(trifluoromethoxy)benzaldehyde (33.08 mg, 147.30 μmol), **compound 1.57** (75 mg, 147.30 μmol, TFA salt) and sodium acetate (24.17 mg, 294.60 μmol) in methanol (1 mL) was stirred at 25 °C for 1 h, then sodium cyanoborohydride (92.56 mg, 1.47 mmol) was added. The reaction mixture was stirred at 25 °C for 11 h. The reaction mixture was concentrated *in vacuo* to give a residue which was purified (PM35) to afford **Example 16** (40.09 mg, 58.63 μmol, 39.8% yield, 99.08% purity, TFA salt) as a yellow solid.

LCMS (AM3): rt = 0.819 min, (563.2 $[M+H]^+$), 99.08% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.06 (s, 1H), 8.88 (d, J = 5.6 Hz, 1H), 8.81 (m, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.26 (dd, J = 0.8, 5.6 Hz, 1H), 8.08 (dd, J = 2.0, 8.4 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.53–7.45 (m, 2H), 4.87–4.83 (m, 2H), 4.17 (s, 2H), 4.01–3.99 (m, 2H), 3.69 (t, J = 6.0 Hz, 2H), 3.14–3.06 (m, 2H), 1.89–1.80 (m, 2H), 1.78–1.69 (m, 2H) ppm.

Example 17

5-(2-(4-((3-chlorobenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide



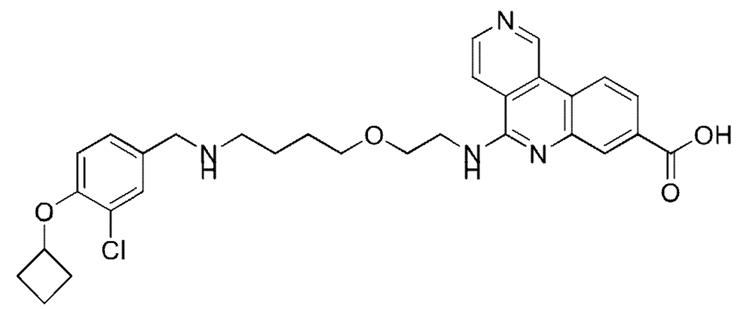
[00386] A mixture of 3-chlorobenzaldehyde (20.71 mg, 147.30 μmol, 16.70 μL), **compound 1.57** (75 mg, 147.30 μmol, TFA salt) and sodium acetate (24.17 mg, 294.60 μmol) in methanol (1 mL) was stirred at 25 °C for 1 h, and then sodium cyanoborohydride (92.56 mg, 1.47 mmol) was added. The mixture was stirred at 25 °C for 11 h. The reaction mixture was concentrated *in vacuo* to give a residue which was purified (PM37) to afford **Example 17** (41.86 mg, 70.59 μmol, 47.9% yield, 100% purity, TFA salt) as a yellow gum.

LCMS (AM3): rt = 0.663 min, (479.2 $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz, MeOD) *δ*: 9.98 (s, 1H), 8.85 (d, *J* = 5.6 Hz, 1H), 8.68 (d, *J* = 8.8 Hz, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 5.6 Hz, 1H), 8.03 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.49 (d, *J* = 0.8 Hz, 1H), 7.44–7.33 (m, 3H), 4.85–4.80 (m, 2H), 4.16 (s, 2H), 4.01–3.99 (m, 2H), 3.70 (t, *J* = 6.0 Hz, 2H), 3.12–3.08 (m, 2H), 1.92–1.81 (m, 2H), 1.79–1.73 (m, 2H) ppm.

Example 25

5-((2-(4-((3-Chloro-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6] naphthyridine-8-carboxylic acid



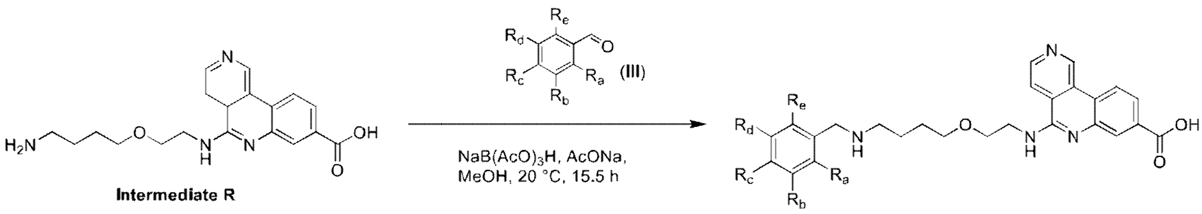
[00387] A mixture of **Intermediate R** (70 mg, 179.09 μmol), **compound 1.32** (37.73 mg, 179.09 μmol) and sodium acetate (58.77 mg, 716.36 μmol) in MeOH (3 mL) was stirred at 20 °C for 12.5 h before sodium triacetoxyborohydride (113.87 mg, 537.27 μmol) was added. The reaction mixture was stirred at 20 °C for another 3 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo.* The residue was purified (PM43) to afford **Example 25** (25.42 mg, 46.30 μmol, 25.9% yield) as a yellow gum.

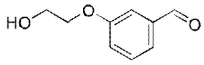
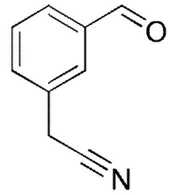
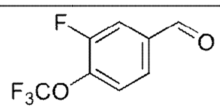
LCMS (AM3): rt = 0.790 min, (549.3 $[M+H]^+$), 100% purity.

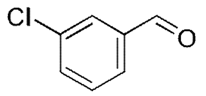
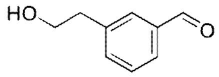
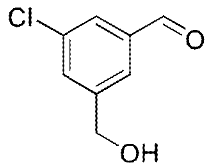
^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.04 (s, 1H), 8.84 (d, *J* = 5.6 Hz, 1H), 8.66 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 7.98 (t, *J* = 5.4 Hz, 1H), 7.83 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.39 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.72–4.64 (quin, 1H), 3.78–3.74 (m, 2H), 3.67 (t, *J* = 5.8 Hz, 2H), 3.63 (s, 2H), 3.46 (t, *J* = 5.6 Hz, 2H), 2.53–2.51 (m, 2H), 2.43–2.35 (m, 2H), 2.08–1.98 (quin, 2H), 1.83–1.74 (q, 1H), 1.66–1.54 (quin, 1H), 1.57–1.47 (m, 4H) ppm.

The following examples in Table 3 were made with non-critical changes or substitutions to the exemplified procedure in Example 25, that would be understood by one skilled in the art using intermediate R and compounds of formula (III).

Table 3

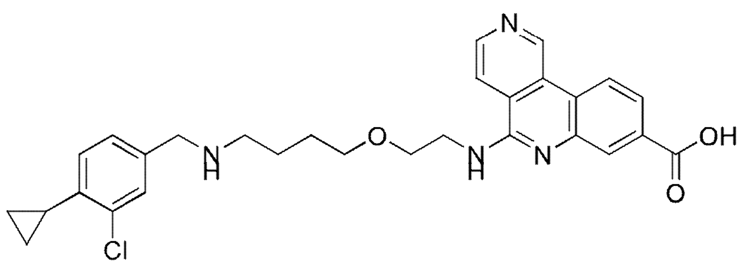


Example No.	Chemical IUPAC name	Compound (III)	Analytical
Example 26	5-((2-(4-((3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-(2-hydroxyethoxy)benzaldehyde	[1]H NMR (400 MHz, DMSO-d_6) δ: 9.99 (s, 1H), 8.78 (d, J = 5.6 Hz, 1H), 8.58 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 5.6 Hz, 1H), 8.15 (d, J = 1.2 Hz, 1H), 7.97–7.92 (m, 1H), 7.85 (dd, J = 8.4, 1.2 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.07 (s, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.83 (dd, J = 8.4, 2.0 Hz, 1H), 3.94 (t, J = 4.8 Hz, 2H), 3.88 (s, 2H), 3.74–3.70 (m, 2H), 3.68–3.65 (m, 4H), 3.43 (t, J = 6.0 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H), 1.66–1.57 (m, 2H), 1.55–1.48 (m, 2H) ppm. LCMS (AM3): rt = 0.689 min, (505.4 $[M+H]^+$), 98.4% purity. Purification Method 44
Example 27	5-((2-(4-((3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Formylphenyl)acetonitrile **1.134**	[1]H NMR (400 MHz, DMSO-d_6) δ:10.03 (s, 1H), 8.83 (d, J = 5.6 Hz, 1H), 8.65 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 5.6 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 7.98 (t, J = 5.2 Hz, 1H), 7.83 (dd, J = 8.4, 1.6 Hz, 1H), 7.34–7.29 (m, 3H), 7.24–7.19 (m, 1H), 4.01 (s, 2H), 3.77–3.74 (m, 4H), 3.68 (t, J = 5.6Hz, 2H), 3.45 (t, J = 5.6Hz, 2H), 2.60–2.53 (m, 2H), 1.57–1.51 (m, 4H) ppm. LCMS (AM3): rt = 0.694 min, (484.4 $[M+H]^+$), 95.5% purity. Purification Method 45
Example 28	5-((2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-fluoro-4-(trifluoromethoxy)benzaldehyde	[1]H NMR (400 MHz, DMSO-d_6) δ: 10.10 (s, 1H), 8.92 (d, J = 5.6 Hz, 1H), 8.84 (br s, 2H), 8.77 (d, J = 8.4 Hz, 1H), 8.34 (d, J = 5.2 Hz, 1H), 8.22 (br s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.69–7.61 (m, 2H), 7.41 (d, J = 8.4 Hz, 1H), 4.16 (t, J = 5.4 Hz, 2H), 3.84 (t, J = 5.2 Hz, 2H), 3.73 (t, J = 5.6 Hz, 2H), 3.49 (t, J = 6.0 Hz, 2H), 2.97–2.90 (m, 2H), 1.70–1.52 (m, 4H) ppm. LCMS (AM3): rt = 0.791 min, (547.3 $[M+H]^+$), 100% purity. Purification Method 46

Example 30	5-((2-(4-((3-chlorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-chlorobenzaldehyde	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.11 (s, 1H), 8.93 (d, *J* = 6.0 Hz, 1H), 8.85-8.77 (m, 3H), 8.36 (d, *J* = 5.6 Hz, 1H), 8.25 (br s, 1H), 7.88 (dd, *J* = 1.6, 8.4 Hz 1H), 7.57 (s, 1H), 7.52-7.39 (m, 3H), 4.10 (t, *J* = 6.0 Hz, 2H), 3.82 (t, *J* = 5.2 Hz, 2H), 3.73 (t, *J* = 5.2 Hz, 2H), 3.49 (t, *J* = 6.0 Hz, 2H), 2.95-2.88 (m, 2H), 1.69-1.62 (m, 2H), 1.60-1.54 (m, 2H) ppm. LCMS (AM3): rt = 0.759 min, (479.4 [M+H]$^+$), 100% purity. Purification Method 48
Example 32	5-((2-(4-((3-(2-hydroxyethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-(2-hydroxyethyl)benzaldehyde	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.18 (br s, 1H), 9.10-8.86 (br m, 4H), 8.78 (d, *J* = 8.4 Hz, 1H), 8.43 (br s, 1H), 8.31 (s, 1H), 7.90 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.33-7.19 (m, 4H), 4.04 (t, *J* = 5.6 Hz, 2H), 3.90-3.83 (m, 2H), 3.74 (t, *J* = 5.6 Hz, 2H), 3.60 (t, *J* = 6.8 Hz, 2H), 3.48 (t, *J* = 6.0 Hz, 2H), 2.95-2.86 (m, 2H), 2.72 (t, *J* = 6.8 Hz, 2H), 1.70-1.60 (m, 2H), 1.60-1.50 (m, 2H) ppm. LCMS (AM3): rt = 0.704 min, (489.5 [M+H]$^+$), 97.7% purity. Purification Method 48
Example 31	5-((2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Chloro-5-(hydroxymethyl)benzaldehyde **1.102**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.10 (s, 1H), 8.94 (d, *J* = 5.4 Hz, 1H), 8.88-8.77 (m, 3H), 8.37 (d, *J* = 5.6 Hz, 1H), 8.27 (br s, 1H), 7.89 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.36 (s, 1H), 4.52 (s, 2H), 4.09 (t, *J* = 5.6 Hz, 2H), 3.85 (t, *J* = 5.2 Hz, 2H), 3.74 (t, *J* = 5.6 Hz, 2H), 3.49 (t, *J* = 6.0 Hz, 2H), 2.95-2.89 (m, 2H), 1.70-1.52 (m, 4H), ppm. LCMS (AM3): rt = 0.718 min, (509.4 [M+H]$^+$), 98.3% purity. Purification Method 48

Example 33

5-((2-(4-((3-Chloro-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6] naphthyridine-8-carboxylic acid



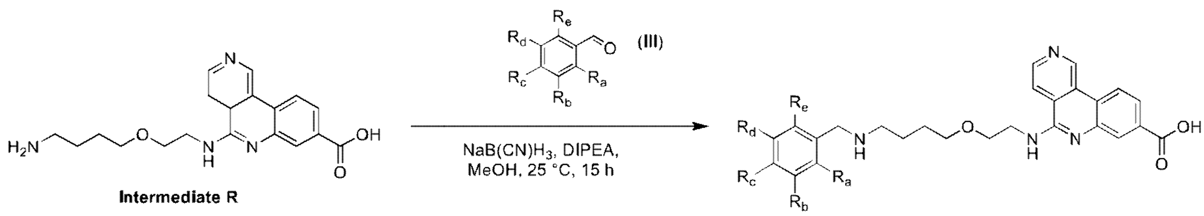
[00388] A mixture of **Intermediate R** (70 mg, 179.09 μmol), **compound 1.202** (32.35 mg, 179.09 μmol) and DIPEA (46.29 mg, 358.18 μmol) in MeOH (3 mL) was stirred at 20 °C for 12 h, then sodium cyanoborohydride (33.76 mg, 537.27 μmol) was added. The reaction mixture was stirred at 20 °C for another 3 h. The reaction concentrated mixture was filtered and *in vacuo*. The residue was purified (PM24) to afford **Example 33** 45.05 mg, 71.16 μmol, 39.7% yield, TFA salt) as a yellow oil.

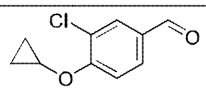
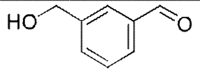
LCMS (AM3): rt = 0.759 min, (519.4 [M+H]$^+$), 96.8% purity.

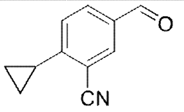
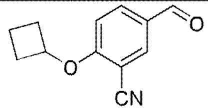
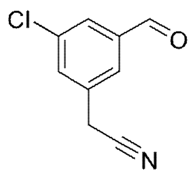
^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.10 (s, 1H), 8.93 (d, *J* = 5.6 Hz, 1H), 8.79–8.73 (m, 3H), 8.36 (d, *J* = 5.6 Hz, 1H), 8.26 (s, 1H), 7.88 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.30 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 4.05 (t, *J* = 5.6 Hz 2H), 3.83 (t, *J* = 4.8 Hz, 2H), 3.73 (t, *J* = 5.6 Hz, 2H), 3.48 (t, *J* = 6.0 Hz, 2H), 2.93–2.86 (m, 2H), 2.16–2.10 (m, 1H), 1.68–1.54 (m, 4H), 1.04–0.98 (m, 2H), 0.71–0.66 (m, 2H) ppm.

The following examples in Table 4 were made with non-critical changes or substitutions to the exemplified procedure in Example 33, that would be understood by one skilled in the art using intermediate R and compounds of formula (III).

Table 4

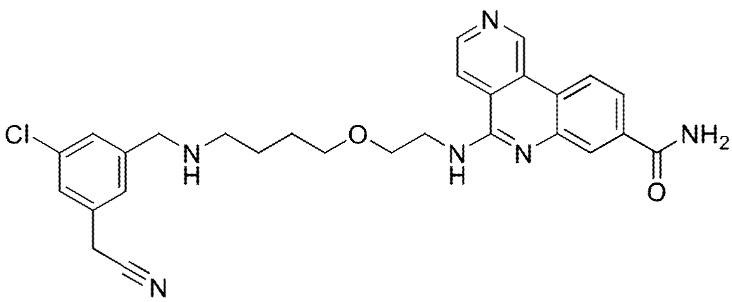


Example No.	Chemical IUPAC name	Compound (III)	Analytical
Example 34	5-((2-(4-((3-chloro-4-cyclopropoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Chloro-4-cyclopropoxybenzaldehyde **1.90**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.10 (s, 1H), 8.92 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.8 Hz, 1H), 8.64 (br s, 2H), 8.32 (d, *J* = 5.6 Hz, 1H), 8.21 (s, 1H), 7.86 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.46-7.37 (m, 2H), 4.03 (t, *J* = 5.6 Hz, 2H), 3.98-3.93 (m, 1H), 3.82 (t, *J* = 4.8 Hz, 2H), 3.72 (t, *J* = 5.6 Hz, 2H), 3.50-3.47 (m, 2H), 2.95-2.85 (br m, 2H), 1.68-1.53 (m, 4H), 0.85–0.80 (q, 2H), 0.70-0.66 (m, 2H) ppm. LCMS (AM3): rt = 0.754 min, (535.4 [M+H]$^+$), 96.8% purity. Purification Method 49
Example 37	5-((2-(4-((3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-(hydroxymethyl)benzaldehyde	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.12 (br s, 1H), 8.94 (br s, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.73-8.67 (br m, 2H), 8.34 (d, *J* = 5.2 Hz, 1H), 8.22 (br s, 1H), 7.87 (dd, *J* =8.4, 1.2 Hz, 1H), 7.41-7.26 (m, 4H), 4.52 (s, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.73 (t, *J* = 5.6 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.95-2.88 (m, 2H), 1.68-1.53 (m, 4H) ppm. LCMS (AM3): rt = 0.684 min, (475.2 [M+H]$^+$), 100% purity. Purification Method 52

Example 39	5-((2-(4-((3-cyano-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-cyclopropyl-5-formylbenzonitrile **1.52**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.03 (s, 1H), 8.84 (d, *J* = 5.6 Hz, 1H), 8.66 (d, *J* = 8.8 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 8.13 (d, *J* = 1.2 Hz, 1H), 7.97 (t, *J* = 5.2 Hz, 1H), 7.83 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.50 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 3.76 (t, *J* = 5.2 Hz, 2H), 3.69-3.65 (m, 4H), 3.45 (t, *J* = 6.0 Hz, 2H), 2.48-2.45 (m, 2H), 2.15-2.08 (m, 1H), 1.56-1.44 (m, 4H), 1.09-1.04 (m, 2H), 0.78-0.74 (m, 2H) ppm. LCMS (AM3): rt = 0.719 min, (510.2 [M+H]$^+$), 95.6% purity. Purification Method 53
Example 41	5-((2-(4-((3-cyano-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-cyclobutoxy-5-formylbenzonitrile **1.47**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.04 (s, 1H), 8.85 (d, *J* = 5.4 Hz, 1H), 8.68 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 5.6 Hz, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 7.99 (t, *J* = 5.2 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 4.82-4.74 (quin, 1H), 3.76 (t, *J* = 5.6 Hz, 2H), 3.67 (t, *J* = 5.6 Hz, 2H), 3.65 (s, 2H), 3.46 (t, *J* = 6.0 Hz, 4H), 2.45-2.40 (m, 2H), 2.10-2.00 (m, 2H), 1.83-1.75 (m, 1H), 1.68-1.58 (m, 1H), 1.54-1.47 (m, 4H) ppm. LCMS (AM3): rt = 0.780 min, (540.6 [M+H]$^+$), 99.0% purity. Purification Method 55
Example 42	5-((2-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Chloro-5-formylphenyl)acetonitrile **1.366**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.08 (s, 1H), 8.97 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.8 Hz, 1H), 8.52 (d, *J* = 1.6 Hz, 1H), 8.39 (d, *J* = 5.6 Hz, 1H), 8.15 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.48 (s, 2H), 7.40 (s, 1H), 4.14 (s, 2H), 4.06 (t, *J* = 5.2 Hz, 2H), 3.96 (s, 2H), 3.89 (t, *J* = 5.2 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.05 (t, *J* = 7.6 Hz 2H), 1.83-1.74 (quin, 2H), 1.71-1.64 (quin, 2H) ppm. LCMS (AM3): rt = 0.728 min, (518.4 [M+H]$^+$), 100% purity. Purification Method 175

Example 40

5-((2-(4-((3-Chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6] naphthyridine-8-carboxamide



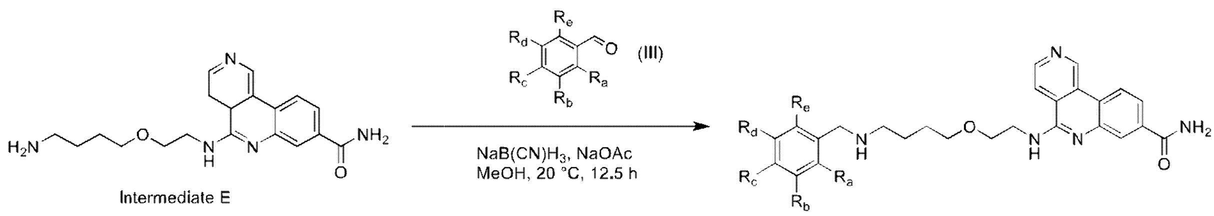
[00389] A mixture of **Intermediate E** (80 mg, 205.19 μmol), **compound 1.366** (36.85 mg, 205.19 μmol) and sodium acetate (67.33 mg, 820.77 μmol) in MeOH (3 mL) was stirred at 20 °C for 12 h, then sodium cyanoborohydride (38.68 mg, 615.58 μmol) was added. The mixture was stirred at 20 °C for another 0.5 h, The reaction mixture was concentrated *in vacuo* and purified (PM54) to afford **Example 40** (31.75 mg, 61.19 μmol, 29.8% yield) as a yellow oil.

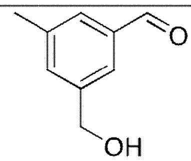
LCMS (AM7): rt = 0.853 min, (517.2 $[M+H]^+$), 99.5% purity.

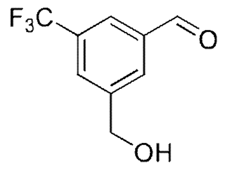
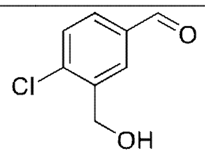
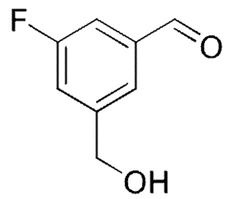
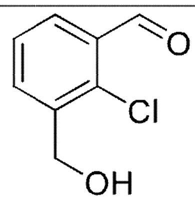
^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.05 (s, 1H), 8.85 (d, *J* = 5.2 Hz, 1H), 8.69 (d, *J* = 8.8 Hz, 1H), 8.27 (d, *J* = 5.6 Hz, 1H), 8.18 (br s, 1H), 8.14 (d, *J* = 1.2 Hz, 1H), 7.98 (t, *J* = 5.2 Hz, 1H), 7.81 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.42 (br s, 1H), 7.30 (s, 1H), 7.23 (d, *J* = 4.4 Hz, 2H), 4.02 (s, 2H), 3.78 (t, *J* = 5.6 Hz, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.61 (s, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.42 (t, *J* = 6.8 Hz, 2H), 1.57–1.50 (m, 2H), 1.50–1.40 (m, 2H) ppm.

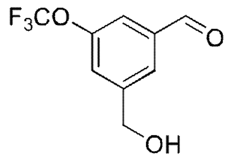
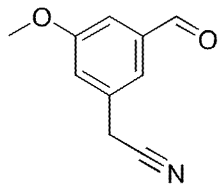
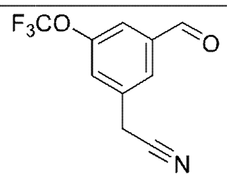
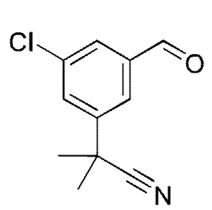
The following examples in Table 5 were made with non-critical changes or substitutions to the exemplified procedure in Example 40, that would be understood by one skilled in the art using intermediate E and compounds of formula (III).

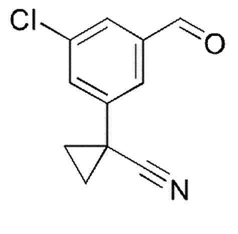
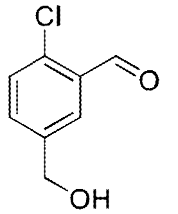
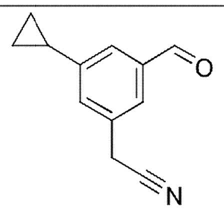
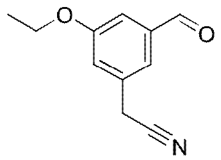
Table 5

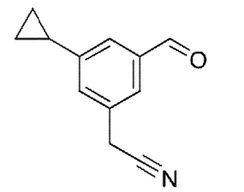
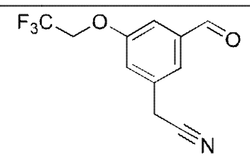


Example No.	Chemical IUPAC name	Compound (III)	Analytical
Example 47	5-((2-(4-((3-(hydroxymethyl)-5-methylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(hydroxymethyl)-5-methylbenzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.93 (s, 1H), 8.79 (d, *J* = 5.6 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.52 (br s, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.14 (d, *J* = 6.0 Hz, 1H), 7.83 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.22 (s, 1H), 7.18 (s, 1H), 7.11 (s, 1H), 4.59 (s, 2H), 4.03 (s, 2H), 3.93 (t, *J* = 6.0 Hz, 2H), 3.83 (t, *J* = 6.0 Hz, 2H), 3.64 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.35 (s, 3H), 1.85-1.75 (quin, 2H), 1.74-1.66 (quin, 2H) ppm. LCMS (AM3): rt = 0.701 min, (488.3 $[M+H]^+$), 100% purity. Purification Method 62

Example 48	5-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Hydroxymethyl)-5-(trifluoromethyl)benzaldehyde **1.501**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.07 (s, 1H), 8.86 (d, *J* = 5.6 Hz, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 5.6 Hz, 1H), 8.24 (s, 1H), 8.18 (br s, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.99 (t, *J* = 5.6 Hz, 1H), 7.81 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.55 (s, 2H), 7.53 (s, 1H), 7.43 (br s, 1H), 4.57 (s, 2H), 3.80-3.78 (m, 4H), 3.72 (t, *J* = 4.8 Hz, 2H), 3.46 (t, *J* = 4.8 Hz, 2H), 2.55-2.53 (m, 2H), 1.60-1.45 (m, 4H) ppm LCMS (AM3): rt = 0.727 min, (542.2 [M+H]$^+$), 100% purity. Purification Method 63
Example 49	5-((2-(4-((4-chloro-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 4-Chloro-3-(hydroxymethyl)benzaldehyde **1.661**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.85 (s, 1H), 8.74 (d, *J* = 5.6 Hz, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.48 (br s, 1H), 8.16 (d, *J* = 1.6 Hz, 1H), 8.08 (d, *J* = 5.6 Hz, 1H), 7.80 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 10.0 Hz, 2.4 Hz, 1H), 4.70 (s, 2H), 4.11 (s, 2H), 3.89 (t, *J* = 5.6 Hz, 2H), 3.82 (t, *J* = 5.6 Hz, 2H), 3.63 (t, *J* = 5.6 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H), 1.87-1.79 (m, 2H), 1.74-1.66 (m, 2H) ppm. LCMS (AM3): rt = 0.717 min, (508.2 [M+H]$^+$), 96.2% purity Purification Method 62
Example 55	5-((2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Fluoro-5-(hydroxymethyl)benzaldehyde **1.500**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.92 (s, 1H), 8.78 (d, *J* = 5.6 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 8.14 (d, *J* = 5.6 Hz, 1H), 7.83 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.16 (s, 1H), 7.09 (d, *J* = 9.2 Hz, 1H), 7.02 (d, *J* = 9.2 Hz, 1H), 4.60 (s, 2H), 3.94 (s, 2H), 3.91 (t, *J* = 5.6 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 1.77-1.63 (m, 4H) ppm. LCMS (AM3): rt = 0.672 min, (492.3 [M+H]$^+$), 100% purity Purification Method 62
Example 67	5-((2-(4-((2-chloro-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-Chloro-3-(hydroxymethyl)benzaldehyde **1.485**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.92 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 8.48 (br s, 1H), 8.21 (s, 1H), 8.13 (d, *J* = 5.6 Hz, 1H), 7.82 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.62 (t, *J* = 4.8 Hz, 1H), 7.37 (d, *J* = 4.8 Hz, 2H), 4.67 (s, 2H), 4.19 (s, 2H), 3.92 (t, *J* = 5.6 Hz, 2H), 3.83 (t, *J* = 6.0 Hz, 2H), 3.64 (t, *J* = 5.6 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 1.86–1.78 (quin, 2H), 1.74–1.66 (quin, 2H) ppm LCMS (AM3): rt = 0.679 min, (508.2 [M+H]$^+$), 99.3% purity Purification Method 73

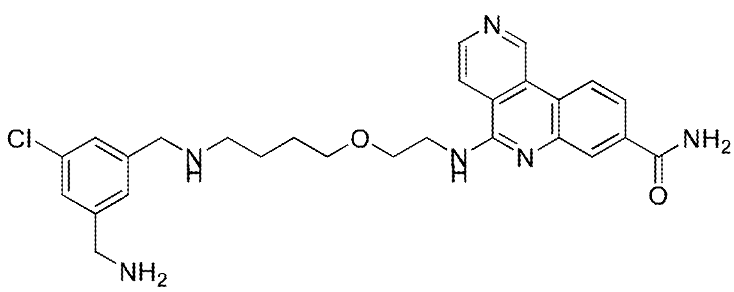
Example 84	5-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Hydroxymethyl)-5-(trifluoromethoxy)benzaldehyde **1.488**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.93 (s, 1H), 8.78 (d, *J* = 5.6 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 8.14 (d, *J* = 5.6 Hz, 1H), 7.83 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.24 (br s, 1H), 7.16 (br s, 1H), 7.12 (br s, 1H), 4.61 (s, 2H), 3.91 (t, *J* = 5.8 Hz, 2H), 3.80 (t, *J* = 5.6 Hz, 2H), 3.69 (s, 2H), 3.56 (t, *J* = 5.8 Hz, 2H), 2.56 (t, *J* = 6.8 Hz, 2H), 1.62–1.58 (m, 4H) ppm LCMS (AM3): rt = 0.705min, (558.3 [M+H]$^+$), 100% purity Purification Method 93
Example 87	5-((2-(4-((3-(cyanomethyl)-5-methoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-methoxyphenyl)acetonitrile **1.491**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.91 (s, 1H), 8.76 (d, *J* = 5.6 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 8.13 (d, *J* = 5.6, 1H), 7.82 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.83–6.81 (d, 2H), 6.79 (d, *J* = 1.6 Hz, 1H), 3.90 (t, *J* = 5.6 Hz, 2H), 3.82–3.78 (m, 4H), 3.77 (s, 3H), 3.65 (s, 2H), 3.57 (t, *J* = 5.6 Hz, 2H), 2.60 (t, *J* = 6.8 Hz, 2H), 1.64–1.61 (m, 4H) ppm LCMS (AM3): rt = 0.710 min, (513.3 [M+H]$^+$), 100% purity Purification Method 90
Example 89	5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile **1.504**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.91 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.59 (d, *J* = 8.8 Hz, 1H), 8.46 (br s, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 7.82 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.45 (s, 1H), 7.37-7.36 (m, 2H), 4.12 (s, 2H), 4.00 (s, 2H), 3.91 (t, *J* = 5.6 Hz, 2H), 3.82 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 1.84-1.76 (m, 2H), 1.72-1.66 (m, 2H) ppm LCMS (AM3): rt = 0.713 min, (567.3 [M+H]$^+$), 99.5% purity Purification Method 88
Example 105	5-((2-(4-((3-chloro-5-(2-cyanopropan-2-yl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Chloro-5-vinylphenyl)-2-methylpropanenitrile **1.632**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.96 (s, 1H), 8.81 (d, *J* = 5.6 Hz, 1H), 8.64 (d, *J* = 8.4 Hz, 1H), 8.44 (br s, 1H), 8.23 (d, *J* = 1.6 Hz, 1H), 8.15 (d, *J* = 4.8 Hz, 1H), 7.84 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.62 (m, 1H), 7.57 (m, 1H), 7.47 (m, 1H), 4.13 (s, 2H), 3.94 (t, *J* = 5.6 Hz, 2H), 3.84 (t, *J* = 5.6 Hz, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.85-1.78 (m, 2H), 1.74 (s, 6H), 1.75-1.68 (m, 2H) ppm LCMS (AM3): rt = 0.742 min, (545.2 [M+H]$^+$), 98.6% purity Purification Method 106

Example 106	5-((2-(4-((3-chloro-5-(1-cyanocyclopropyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 1-(3-Chloro-5-formylphenyl)cyclopropanecarbonitrile **1.630**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.95 (s, 1H), 8.80 (d, *J* = 5.6 Hz, 1H), 8.62 (d, *J* = 8.4 Hz, 1H), 8.48 (br s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 8.14 (d, *J* = 5.6 Hz, 1H), 7.84 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.40-7.37 (m, 3H), 4.08 (s, 2H), 3.94 (t, *J* = 5.6 Hz, 2H), 3.84 (t, *J* = 5.6 Hz, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.05 (t, *J* = 7.2 Hz, 2H), 1.86-1.78 (m, 4H), 1.75-1.68 (m, 2H), 1.55-1.52 (m, 2H) ppm LCMS (AM3): rt = 0.730 min, (543.3 $[M+H]^+$), 99.7% purity Purification Method 107
Example 123	5-((2-(4-((2-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-Chloro-5-(hydroxymethyl)benzaldehyde **1.834**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.07 (s, 1H), 8.87 (d, *J* = 5.6 Hz, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 5.6 Hz, 1H), 8.20 (s, 1H), 8.18 (br s, 1H), 8.15 (d, *J* = 2.0 Hz, 1H), 8.02-7.97 (t, 1H), 7.81 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.44-7.41 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.17 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.47 (s, 2H), 3.79 (t, *J* = 5.2 Hz, 2H), 3.74 (s, 2H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.47 (t, *J* = 6.0 Hz, 2H), 2.56-2.54 (m, 2H), 1.61-1.46 (m, 4H) ppm. LCMS (AM3): rt = 0.701 min, (508.2 $[M+H]^+$), 99.8% purity Purification Method 62
Example 135	5-((2-(4-((3-(cyanomethyl)-5-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Cyclopropyl-5-formylphenyl)acetonitrile **1.747**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.94 (s, 1H), 8.79 (d, *J* = 5.6 Hz, 1H), 8.62 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 5.6 Hz, 1H), 8.15 (d, *J* = 5.2 Hz, 1H), 7.85 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.03 (s, 1H), 6.96 (s, 2H), 3.93 (t, *J* = 5.6 Hz, 2H), 3.84-3.81 (m, 4H), 3.64 (s, 2H), 3.58 (t, *J* = 5.2 Hz, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 1.92-1.85 (m, 1H), 1.64-1.60 (m, 4H), 0.99-0.94 (m, 2H), 0.71-0.67 (m, 2H) ppm LCMS (AM3): rt = 0.762 min, (523.5 $[M+H]^+$), 98.5% purity Purification Method 134
Example 136	5-((2-(4-((3-(cyanomethyl)-5-ethoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Ethoxy-5-formylphenyl)acetonitrile **1.741**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.96 (s, 1H), 8.80 (d, *J* = 5.6 Hz, 1H), 8.64 (d, *J* = 8.4 Hz, 1H), 8.50 (br s, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.15 (d, *J* = 5.6 Hz, 1H), 7.86 (dd, *J* =8.4, 1.6 Hz, 1H), 6.93 (d, *J* = 6.4 Hz, 2H), 6.91 (s, 1H), 4.07-4.02 (m, 4H), 3.94 (t, *J* = 5.6 Hz, 2H), 3.89 (s, 2H), 3.84 (t, *J* = 5.6 Hz, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 7.2 Hz, 2H), 1.86-1.78 (m, 2H), 1.75-1.68 (m, 2H), 1.39 (t, *J* = 7.2 Hz, 3H) ppm LCMS (AM3): rt = 0.708 min, (527.3 $[M+H]^+$), 100% purity Purification Method 135

Example 137	5-((2-(4-((3-cyclopropyl-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Cyclopropyl-5-(hydroxymethyl)benzaldehyde **1.744**	[1]H NMR (400 MHz, MeOH-d_4) δ: 9.96 (d, *J* = 4.4 Hz, 1H), 8.81-8.79 (m, 1H), 8.66-8.61 (m, 1H), 8.52 (br s, 1H), 8.23 (s, 1H), 8.15 (d, *J* = 6.0 Hz, 1H), 7.86-7.84 (m, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 7.02 (s, 1H), 4.59 (s, 2H), 4.02 (s, 2H), 3.94 (t, *J* = 5.6 Hz, 2H), 3.84 (t, *J* = 5.6 Hz, 2H), 3.64 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 1.96-1.89 (m, 1H), 1.84-1.77 (m, 2H), 1.73-1.67 (m, 2H), 1.01-0.96 (m, 2H), 0.73-0.68 (m, 2H) ppm LCMS (AM3): rt = 0.726 min, (514.5 [M+H]$^+$), 100% purity. Purification Method 68
Example 140	5-((2-(4-((3-(cyanomethyl)-5-(2,2,2-trifluoroethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-(2,2,2-trifluoroethoxy)phenyl)acetonitrile **1.754**	[1]H NMR (400 MHz, MeOH-d_4) δ: 9.94 (s, 1H), 8.79 (d, *J* = 5.6 Hz, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.16 (d, *J* = 5.2 Hz, 1H), 7.85 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.97 (s, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 4.54 (q, *J* = 8.4 Hz, 2H), 3.93 (t, *J* = 5.2 Hz, 2H), 3.87-3.81 (m, 4H), 3.66 (s, 2H), 3.59 (t, *J* = 5.6 Hz, 2H), 2.58 (t, *J* = 6.8 Hz, 2H), 1.65-1.61 (m, 4H) ppm LCMS (AM3): rt = 0.737 min, (581.3 [M+H]$^+$), 100% Purification Method 137

Example 43

5-((2-(4-((3-(Aminomethyl)-5-chlorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



[00390] To a mixture of **compound 1.573** (60 mg, 119.29 μmol) and ammonium hydroxide (3.64 g, 25.97 mmol, 25% purity) in MeOH (10 mL) was added Raney-Ni (60.00 mg) under nitrogen protection. The reaction mixture was then hydrogenated under one atmosphere H_2 pressure at 20 °C for 8 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified (PM58) to afford **Example 43** (28.80 mg, 46.37 μmol, 38.9% yield, TFA salt) as a yellow gum.

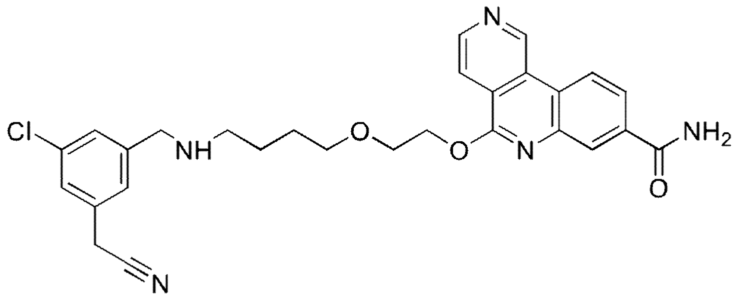
LCMS (AM7): rt = 0.916 min, (507.2 [M+H]$^+$), 98.4% purity.

[1]H NMR (400 MHz, MeOH-d_4) δ: 10.02 (br s, 1H), 8.95 (br s, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 8.41–8.38 (m, 2H), 8.00 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.58 (s, 2H), 7.51 (s, 1H), 4.18 (s, 2H), 4.15

(s, 2H), 4.07 (t, *J* = 5.2 Hz, 2H), 3.88 (t, *J* = 5.2 Hz, 2H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H), 1.87–1.76 (quin, 2H), 1.72–1.63 (m, 2H) ppm.

Example 44

5-(2-(4-((3-Chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6] naphthyridine-8-carboxamide



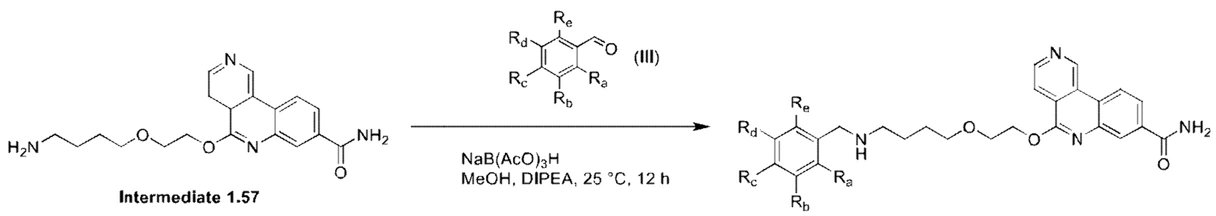
[00391] A mixture of **compound 1.57** (100 mg, 213.48 μmol), **compound 1.366** (38.34 mg, 213.48 μmol) and DIPEA (55.18 mg, 426.96 μmol) in MeOH (10 mL) was stirred at 25 °C for 1 h, then sodium triacetoxyborohydride (226.23 mg, 1.07 mmol) was added. The mixture was stirred at 25 °C for another 11 h. The mixture was concentrated *in vacuo* and the residue was purified (PM59) to afford **Example 44** (43.54 mg, 84.05 μmol, 39.4% yield) as a brown solid.

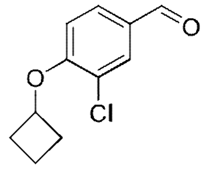
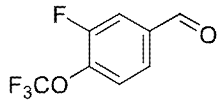
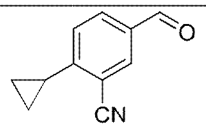
LCMS (AM3): rt = 0.787 min, (518.2 $[M+H]^+$),100% purity.

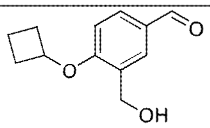
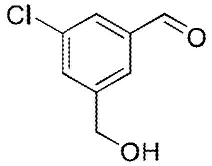
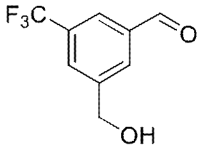
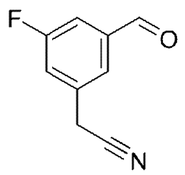
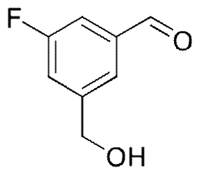
^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.90 (s, 1H), 8.80 (d, *J* = 5.2 Hz, 1H), 8.64 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 2.0 Hz,1H), 8.11 (d, *J* = 5.4 Hz, 1H), 7.99 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.44 (s, 1H), 7.40 (1H, s), 7.37 (s, 1H), 4.77 (t, *J* = 4.8 Hz, 2H), 4.12 (s, 2H), 3.98 (t, *J* = 4.8 Hz, 2H), 3.92 (s, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.07 (t, *J* = 6.0 Hz, 2H), 1.86–1.80 (quin, 2H), 1.76–1.67 (quin, 2H) ppm.

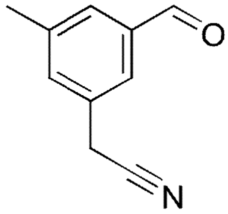
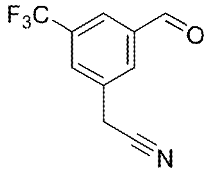
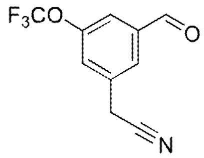
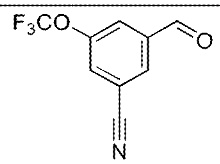
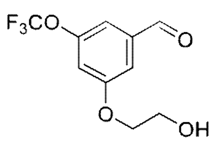
The following examples in Table 6 were made with non-critical changes or substitutions to the exemplified procedure in Example 44, that would be understood by one skilled in the art using intermediate 1.57 and compounds of formula (III).

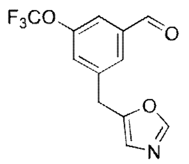
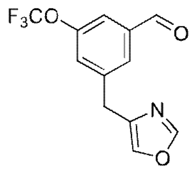
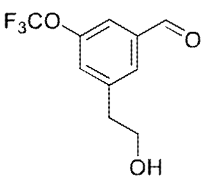
Table 6



Example No.	Chemical IUPAC name	Compound (III)	Analytical
Example 45	5-(2-(4-((3-chloro-4-cyclobutoxybenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-chloro-4-cyclobutoxybenzaldehyde **1.32**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.95 (s, 1H), 8.82 (d, *J* = 5.6 Hz, 1H), 8.69 (d, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 1.6 Hz,1H), 8.15 (d, *J* = 5.2 Hz, 1H), 8.02 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.43 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.79 (t, *J* = 4.8 Hz, 2H), 4.71–4.64 (quin, 1H), 4.03 (s, 2H), 3.98 (t, *J* = 4.8 Hz, 2H), 3.67 (t, *J* = 5.6 Hz, 2H), 3.04 (t, *J* = 5.6 Hz, 2H), 2.47–2.40 (m, 2H), 2.16–2.06 (m, 2H), 1.89–1.66 (m, 6H) ppm. LCMS (AM3): rt = 0.842 min, (549.2 [M+H]$^+$), 99.2% purity. Purification Method 60
Example 50	5-(2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-fluoro-4-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.96 (s, 1H), 8.83 (d, *J* = 5.2 Hz, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 1.6 Hz,1H), 8.16 (d, *J* = 5.2 Hz, 1H), 8.03 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.51-7.46 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 4.81 (t, *J* = 4.8 Hz, 2H), 4.19 (s, 2H), 4.00 (t, *J* = 4.4 Hz, 2H), 3.70 (t, *J* = 5.6 Hz, 2H), 3.11 (t, *J* = 7.2 Hz, 2H), 1.90–1.82 (m, 2H), 1.78–1.71 (m, 2H) ppm. LCMS (AM3): rt = 0.818 min, (547.2 [M+H]$^+$), 99.5% purity. Purification Method 64
Example 51	5-(2-(4-((3-cyano-4-cyclopropylbenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 2-cyclopropyl-5-formylbenzonitrile **1.52**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.89 (s, 1H), 8.80 (d, *J* = 5.6 Hz, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 8.50 (br s, 1H), 8.28 (d, *J* = 1.6 Hz, 1H), 8.10 (d, *J* = 5.2 Hz, 1H), 7.99 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 4.77 (t, *J* = 4.8 Hz, 2H), 4.13 (s, 2H), 3.99 (t, *J* = 4.8 Hz, 2H), 3.69 (t, *J* = 6.0 Hz, 2H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.24–2.17 (m, 1H), 1.89–1.80 (quin, 2H), 1.78–1.70 (quin, 2H) 1.18–1.12 (m, 2H), 0.83–0.77 (m, 2H) ppm. LCMS (AM3): rt = 0.793 min, (510.3 [M+H]$^+$), 100% purity. Purification Method 65

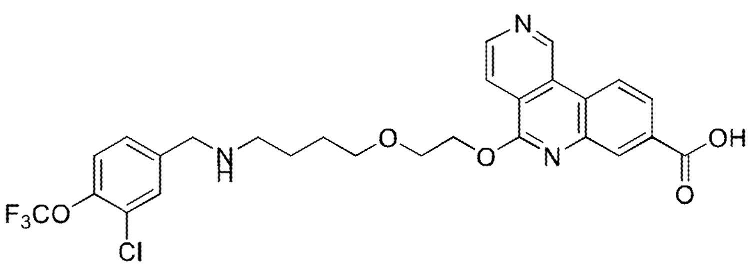
Example 52	5-(2-(4-((4-cyclobutoxy-3-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 (4-cyclobutoxy-3-(hydroxymethyl)benzaldehyde) **1.64**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.90 (s, 1H), 8.80 (d, J = 5.2 Hz, 1H), 8.64 (d, J = 8.4 Hz, 1H), 8.47 (br s, 1H), 8.30 (d, J = 1.6 Hz, 1H), 8.11 (d, J = 5.6 Hz, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.43 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.4 Hz,1H), 4.76 (d, J = 8.4 Hz, 2H), 4.69–4.62 (m, 1H), 4.60 (s, 2H), 4.04 (s, 2H), 3.97 (t, J = 4.4 Hz, 2H), 3.67 (t, J = 5.6 Hz, 2H), 3.04 (t, J = 7.2 Hz, 2H), 2.46–2.38 (m, 2H), 2.13–2.04 (m, 2H), 1.86–1.65 (m, 6H) ppm. LCMS (AM3): rt = 0.800 min, (545.3 [M+H]$^+$), 99.0% purity Purification Method 66
Example 53	5-(2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Chloro-5-(hydroxymethyl)benzaldehyde **1.102**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.69 (s, 1H), 8.69 (d, J = 5.2 Hz, 1H), 8.49 (br s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H), 7.94–7.86 (m, 2H), 7.36–7.30 (m, 3H), 4.66 (t, J = 4.8 Hz, 2H), 4.58 (s, 2H), 4.12 (s, 2H), 3.94 (t, J = 4.8 Hz, 2H), 3.67 (t, J = 5.6 Hz, 2H), 3.08 (t, J = 5.6 Hz, 2H), 1.91–1.80 (m, 2H), 1.77–1.69 (m, 2H) ppm. LCMS (AM3): rt = 0.769 min, (509.2 [M+H]$^+$), 100% purity Purification Method 59
Example 91	5-(2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Hydroxymethyl)-5-(trifluoromethyl)benzaldehyde **1.501**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.18 (s, 1H), 8.93–8.88 (m, 2H), 8.37 (d, J = 1.6 Hz, 1H), 8.28 (br s, 1H), 8.10–8.05 (m, 2H), 7.55 (br s, 1H), 7.50–7.48 (m, 3H), 5.37 (br s, 1H), 4.73 (t, J = 4.4 Hz, 2H), 4.54 (s, 2H), 3.88 (t, J = 4.4 Hz, 2H), 3.68 (s, 2H), 3.53 (t, J = 6.4 Hz, 2H), 2.45 (t, J = 6.8 Hz, 2H), 1.60–1.53 (quin, 2H), 1.50–1.43 (quin, 2H) ppm LCMS (AM7): rt = 0.916 min, (543.3 [M+H]$^+$), 100% purity Purification Method 86
Example 92	5-(2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Fluoro-5-formylphenyl)acetonitrile **1.472**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.15 (s, 1H), 8.90 (d, J = 5.2 Hz, 1H), 8.86 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 1.6 Hz, 1H), 8.28 (br s, 1H), 8.07–8.05 (m, 2H), 7.55 (br s, 1H), 7.12 (s, 1H), 7.06 (d, J = 9.6 Hz, 1H), 6.99 (d, J = 9.6 Hz, 1H), 4.72 (t, J = 4.8 Hz, 2H), 4.01 (s, 2H), 3.88 (t, J = 4.8 Hz, 2H), 3.61 (s, 2H), 3.52 (t, J = 6.4 Hz, 2H), 2.43 (t, J = 6.8 Hz, 2H), 1.59–1.50 (quin, 2H), 1.48–1.41 (quin, 2H) ppm LCMS (AM7): rt = 0.896 min, (502.3 [M+H]$^+$), 100% purity Purification Method 85
Example 94	5-(2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Fluoro-5-(hydroxymethyl)benzaldehyde **1.500**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.70 (br s, 1H), 8.69 (br s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H), 7.96–7.92 (d, 1H), 7.89–7.85 (d, 1H), 7.07 (s, 1H), 6.95 (t, J = 9.2 Hz, 2H), 4.68 (t, J = 4.8 Hz, 2H), 4.55 (s, 2H), 3.92 (t, J = 4.8 Hz, 2H), 3.78 (br s, 2H), 3.62 (t, J = 5.2 Hz, 2H), 2.75–2.64 (m, 2H), 1.68–1.62 (m, 4H) ppm LCMS (AM7): rt = 0.885 min, (493.3 [M+H]$^+$), 98.9% purity Purification Method 95

Example 96	5-(2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-methylphenyl)acetonitrile **1.475**	[1]H NMR (400 MHz, MeOH-d_4) δ: 9.80 (s, 1H), 8.74 (d, *J* = 5.2 Hz, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.04 (d, *J* = 5.2 Hz, 1H), 7.93 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.04–7.00 (m, 3H), 4.72 (t, *J* = 4.8 Hz, 2H), 3.94 (t, *J* = 4.8 Hz, 2H), 3.77 (s, 2H), 3.65–3.61 (m, 4H), 2.65–2.56 (m, 2H), 2.26 (s, 3H), 1.67–1.59 (m, 4H) ppm LCMS (AM7): rt = 0.966 min, (498.3 [M+H]$^+$), 100% purity Purification Method 97
Example 97	5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-(trifluoromethyl)phenyl)acetonitrile **1.469**	[1]H NMR (400 MHz, DMSO-d_6) δ: 10.19 (s, 1H), 8.93-8.87 (m, 2H), 8.38 (d, *J* = 1.6 Hz, 1H), 8.28 (br s, 1H), 8.10–8.06 (m, 2H), 7.63–7.55 (m, 4H), 4.75–4.71 (t, 2H), 4.14 (s, 2H), 3.89 (t, *J* = 4.8 Hz, 2H), 3.74 (s, 2H), 3.52 (t, *J* = 6.0 Hz, 2H), 2.50–2.49 (m, 2H), 1.60–1.52 (m, 2H), 1.52–1.44 (m, 2H) ppm LCMS (AM7): rt = 0.932 min, (552.3 [M+H]$^+$), 98.4% purity Purification Method 98
Example 107	5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile **1.504**	[1]H NMR (400 MHz, DMSO-d_6) δ:10.19 (s, 1H), 8.93–8.87 (m, 2H), 8.38 (s, 1H), 8.28 (br s, 1H), 8.10–8.04 (m, 2H), 7.55 (br s, 1H), 7.31–7.17 (m, 3H), 4.73 (t, *J* = 4.4 Hz, 2H), 4.08 (s, 2H), 3.88 (t, *J* = 4.0 Hz, 2H), 3.67 (s, 2H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.45 (t, *J* = 6.4 Hz, 2H), 1.59–1.52 (m, 2H), 1.50–1.42 (m, 2H) ppm LCMS (AM7): rt = 0.942 min, (568.3 [M+H]$^+$), 99.5% purity Purification Method 108
Example 160	5-(2-(4-((3-cyano-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Formyl-5-(trifluoromethoxy)benzonitrile **1.714**	[1]H NMR (400 MHz, MeOH-d_4) δ: 9.99 (s, 1H), 8.84 (d, *J* = 5.6 Hz, 1H), 8.74 (d, *J* = 8.4 Hz, 1H), 8.38 (d, *J* = 1.6 Hz, 1H), 8.21 (d, *J* = 5.6 Hz, 1H), 8.05 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.65 (s, 1H), 7.56-7.53 (m, 2H), 4.83-4.80 (m, 2H), 3.98 (t, *J* = 4.8 Hz, 2H), 3.75 (s, 2H), 3.64 (t, *J* = 5.6 Hz, 2H), 2.57 (t, *J* = 6.8 Hz, 2H), 1.70-1.57 (m, 4H) ppm LCMS (AM3): rt = 0.802 min, (554.2 [M+H]$^+$), 99.1% purity Purification Method 156
Example 161	5-(2-(4-((3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(2-Hydroxyethoxy)-5-(trifluoromethoxy)benzaldehyde **1.718**	[1]H NMR (400 MHz, MeOH-d_4) δ: 10.02 (s, 1H), 8.85 (d, *J* = 5.6 Hz, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 8.49 (s, 1H), 8.38 (d, *J* = 2.0 Hz, 1H), 8.20 (d, *J* = 5.6 Hz, 1H), 8.05 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.01 (d, *J* = 1.6 Hz, 1H), 6.94 (s, 1H), 6.88 (s, 1H), 4.84-4.82 (m, 2H), 4.08-4.05 (m, 4H), 4.00 (t, *J* = 4.8 Hz, 2H), 3.85 (t, *J* = 4.8 Hz, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 1.86-1.78 (m, 2H), 1.75-1.68 (m, 2H) ppm LCMS (AM3): rt = 0.793 min, (589.2 [M+H]$^+$), 100% purity Purification Method 157

Example 162	5-(2-(4-((3-(oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzaldehyde **1.713**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.04 (s, 1H), 8.86 (d, J = 5.6 Hz, 1H), 8.79 (d, J = 8.4 Hz, 1H), 8.47 (br s, 1H), 8.40 (d, J = 2.0 Hz, 1H), 8.22 (d, J = 5.2 Hz, 1H), 8.10 (s, 1H), 8.07 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.31 (s, 1H), 7.28 (s, 1H), 7.23 (s, 1H), 6.93 (s, 1H), 4.84-4.81 (m, 2H), 4.12 (s, 2H), 4.10 (s, 2H), 4.00 (t, J = 4.8 Hz, 2H), 3.67 (t, J = 5.6 Hz, 2H), 3.02 (t, J = 7.6 Hz, 2H), 1.84-1.76 (quin, 2H), 1.74-1.67 (quin, 2H) ppm LCMS (AM3): rt = 0.812 min, (610.2 [M+H]$^+$), 99.4% purity Purification Method 158
Example 163	5-(2-(4-((3-(oxazol-4-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Oxazol-4-ylmethyl)-5-(trifluoromethoxy)benzaldehyde **1.712**	^{1}H NMR (400 MHz, MeOH-d_4) δ:10.01 (s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.75 (d, J = 8.4 Hz, 1H), 8.50 (s, 1H), 8.38 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 5.6 Hz, 1H), 8.15 (s, 1H), 8.04 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.77 (s, 1H), 7.31 (s, 1H), 7.24-7.18 (m, 2H), 4.82 (t, J =4.8 Hz, 2H), 4.10 (s, 2H), 3.97 (t, J = 4.4 Hz, 2H), 3.93 (s, 2H), 3.67 (t, J = 6.0 Hz, 2H), 3.03 (t, J = 7.2 Hz, 2H), 1.85-1.77 (quin, 2H), 1.74-1.68 (quin, 2H) ppm LCMS (AM3): rt = 0.818 min, (610.2 [M+H]$^+$), 100% purity Purification Method 159
Example 164	5-(2-(4-((3-(2-hydroxyethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(2-Hydroxyethyl)-5-(trifluoromethoxy)benzaldehyde **1.723**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.99 (s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.74 (d, J = 8.4 Hz, 1H), 8.49 (s, 1H), 8.36 (d, J = 2.0 Hz, 1H), 8.19 (d, J = 5.6 Hz, 1H), 8.04 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.30 (s, 1H), 7.22 (s, 2H), 4.83-4.80 (t, 2H), 4.12 (s, 2H), 3.99 (t, J = 5.2 Hz, 2H), 3.78 (t, J = 6.4 Hz, 2H), 3.68 (t, J = 6.0 Hz, 2H), 3.06 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 6.4 Hz, 2H), 1.86-1.78 (quin, 2H), 1.75-1.68 (quin, 2H) ppm LCMS (AM3): rt = 0.794 min, (573.3 [M+H]$^+$), 100% purity Purification Method 160

Example 46

5-(2-(4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6] naphthyridine-8-carboxylic acid



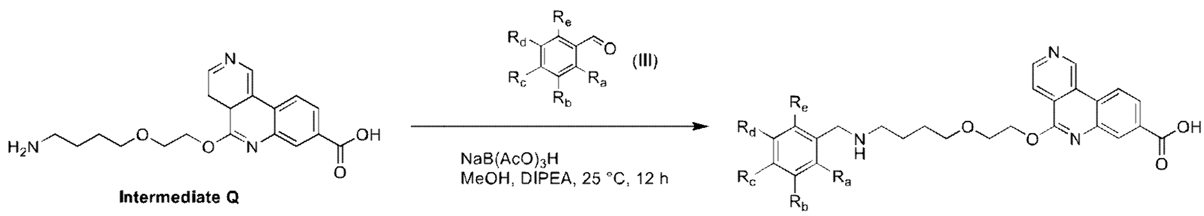
[00392] A mixture of **Intermediate Q** (100 mg, 213.03 µmol), 3-chloro-4-(trifluoromethoxy)benzaldehyde (47.84 mg, 213.03 µmol) and DIPEA (55.06 mg, 426.07 µmol) in MeOH (10 mL) was stirred at 25 °C for 1 h, then sodium triacetoxyborohydride (225.75 mg, 1.07 mmol) was added. The mixture was stirred at 25 °C for another 11 h. The mixture was concentrated *in vacuo* and the residue was purified (PM61) to afford **Example 46** (29.02 mg, 51.46 μmol, 24.2% yield) as a brown solid.

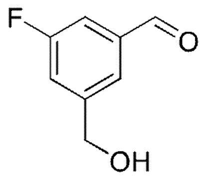
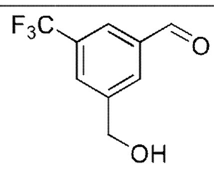
LCMS (AM3): rt = 0.857 min, (564.2 $[M+H]^+$), 100% purity.

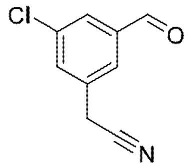
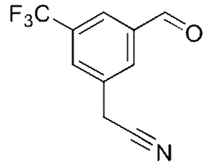
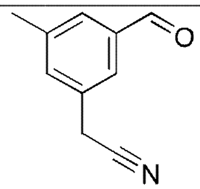
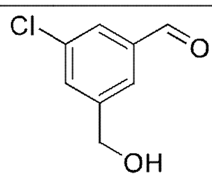
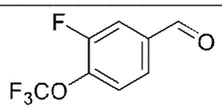
^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.88 (s, 1H), 8.76 (d, *J* = 5.6 Hz, 1H), 8.57 (d, *J* = 8.4 Hz, 1H), 8.37 (s, 1H), 8.11–8.05 (m, 2H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.51–7.45 (m, 2H), 4.76 (t, *J* = 4.8 Hz, 2H), 4.16 (s, 2H), 3.95 (t, *J* = 4.8 Hz, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.08 (t, *J* =7.8 Hz, 2H), 1.89–1.81 (quin, 2H), 1.74–1.67 (quin, 2H) ppm.

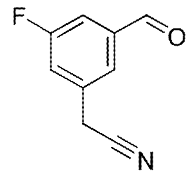
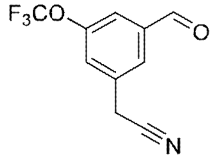
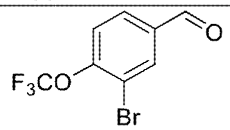
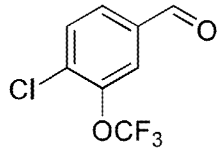
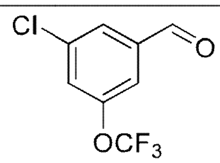
The following examples in Table 7 were made with non-critical changes or substitutions to the exemplified procedure in Example 46, that would be understood by one skilled in the art using intermediate Q and compounds of formula (III).

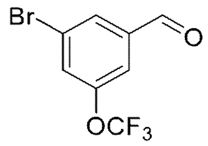
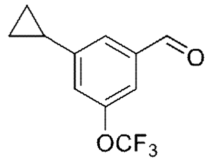
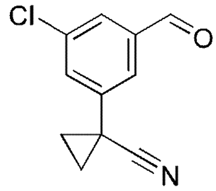
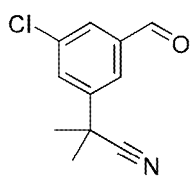
Table 7

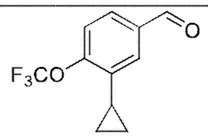
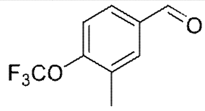
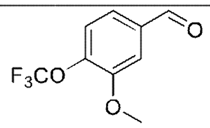
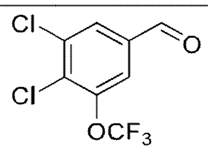


Example No.	Chemical IUPAC name	Compound (III)	Analytical
Example 74	5-(2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Fluoro-5-(hydroxymethyl)benzaldehyde **1.500**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.69 (br s, 1H), 8.66 (d, *J* = 5.2 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 1.6 Hz, 1H), 8.03 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.87 (d, *J* = 5.2 Hz, 1H), 7.27 (s, 1H), 7.15–7.11 (m, 2H), 4.65 (t, *J* = 4.8 Hz, 2H), 4.61 (s, 2H), 4.13 (s, 2H), 3.90 (t, *J* = 4.8 Hz, 2H), 3.66 (t, *J* = 6.0 Hz, 2H), 3.05 (t, *J* = 7.8, 2H), 1.91–1.82 (quin, 2H), 1.75–1.68 (quin, 2H) ppm LCMS (AM7): rt = 0.698 min, (494.3 $[M+H]^+$), 100% purity Purification Method 78
Example 75	5-(2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-(Hydroxymethyl)-5-(trifluoromethyl)benzaldehyde **1.501**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.73 (s, 1H), 8.66 (d, *J* = 5.6 Hz, 1H), 8.41 (d, *J* = 8.8 Hz, 1H), 8.33 (d, *J* = 1.6 Hz, 1H), 8.04 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.91 (d, *J* = 5.2 Hz, 1H), 7.72–7.68 (m, 3H), 4.71–4.66 (m, 4H), 4.21 (s, 2H), 3.91 (t, *J* = 4.8 Hz, 2H), 3.67 (t, *J* =6.0 Hz, 2H), 3.07 (t, *J* = 7.8 Hz, 2H), 1.91–1.84 (quin, 2H), 1.76–1.69 (quin, 2H) ppm LCMS (AM7): rt = 0.708 min, (544.3 $[M+H]^+$), 100% purity Purification Method 79

Example 76	5-(2-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Chloro-5-formylphenyl)acetonitrile **1.366**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.05 (s, 1H), 8.87 (d, *J* = 5.2 Hz, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 8.30 (s, 1H), 8.06–7.98 (m, 2H), 7.43 (s, 1H), 7.32–7.26 (m, 2H), 4.69–4.63 (m, 2H), 4.03 (s, 2H), 3.88–3.80 (m, 4H), 3.57–3.47 (m, 2H), 2.65–2.58 (m, 2H), 1.59–1.51 (m, 4H) ppm LCMS (AM7): rt = 0.704 min, (519.2 [M+H]$^+$), 100% purity Purification Method 79
Example 77	5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Formyl-5-(trifluoromethyl)phenyl)acetonitrile **1.469**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.12 (s, 1H), 8.89 (d, *J* = 5.2 Hz, 1H), 8.81 (d, *J* = 8.4 Hz, 1H), 8.32 (d, *J* = 1.6 Hz, 1H), 8.08–8.04 (m, 2H), 7.68–7.62 (m, 2H), 7.57 (s, 1H), 4.71 (t, *J* = 4.8 Hz, 2H), 4.14 (s, 2H), 3.87 (t, *J* = 4.8 Hz, 2H), 3.82 (s, 2H), 3.53 (t, *J* = 6.0 Hz, 2H), 2.56 (t, *J* = 6.4 Hz, 2H), 1.61–1.49 (m, 4H) ppm LCMS (AM7): rt = 0.720 min, (553.3 [M+H]$^+$), 100% purity Purification Method 80
Example 78	5-(2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Formyl-5-methylphenyl)acetonitrile **1.475**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.63 (s, 1H), 8.59 (d, *J* = 5.6 Hz, 1H), 8.36–8.32 (d, 1H), 8.26 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 5.2 Hz, 1H), 7.20–7.10 (m, 3H), 4.60 (t, *J* = 4.8 Hz, 2H), 4.03 (s, 2H), 3.87 (t, *J* = 4.8 Hz, 2H), 3.81 (s, 2H), 3.63 (t, *J* =6.0 Hz, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 1.88–1.80 (m, 2H), 1.70–1.62 (m, 2H) ppm LCMS (AM7): rt = 0.709 min, (499.3 [M+H]$^+$), 100% purity Purification Method 79
Example 90	5-(2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Chloro-5-(hydroxymethyl)benzaldehyde **1.102**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.82 (s, 1H), 8.72 (d, *J* = 5.6 Hz, 1H), 8.52 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 1.6 Hz, 1H), 8.09–8.05 (d, 1H), 8.04–8.00 (d, 1H), 7.34–7.31 (m, 2H), 7.26–7.24 (m, 1H), 4.73 (t, *J* = 4.8 Hz, 2H), 4.57 (s, 2H), 4.00 (s, 2H), 3.92 (t, *J* = 4.8 Hz, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.95 (t, *J* = 7.8 Hz, 2H), 1.85–1.78 (quin, 2H), 1.72–1.64 (quin, 2H) ppm LCMS (AM3): rt = 0.699 min, (510.2 [M+H]$^+$), 97.7% purity Purification Method 87
Example 93	5-(2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-fluoro-4-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.69 (s, 1H), 8.65 (d, *J* = 5.6 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 1.2 Hz, 1H), 8.02 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.87 (d, *J* = 5.6 Hz, 1H), 7.52 (dd, *J* = 10.8, 2.0 Hz, 1H), 7.46–7.37 (m, 2H), 4.64 (t, *J* = 4.8 Hz, 2H), 4.16 (s, 2H), 3.89 (t, *J* = 4.8 Hz, 2H), 3.66 (t, *J* = 6.0 Hz, 2H), 3.05 (t, *J* = 7.8 Hz, 2H), 1.90–1.83 (quin, 2H), 1.74–1.67 (quin, 2H) ppm LCMS (AM7): rt = 0.753 min, (548.3 [M+H]$^+$), 98.3% purity Purification Method 94

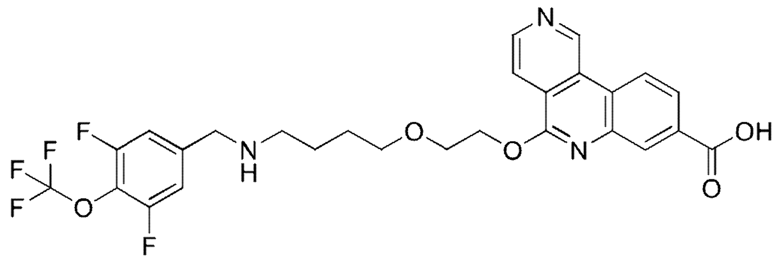
Example 95	5-(2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Fluoro-5-formylphenyl)acetonitrile **1.472**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.82 (s, 1H), 8.75 (d, J = 5.6 Hz, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.35 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 5.2 Hz, 1H), 7.29 (s, 1H), 7.22–7.14 (m, 2H), 4.74 (t, J = 4.8 Hz, 2H), 4.14 (s, 2H), 3.95–3.91 (m, 4H), 3.68 (t, J =6.0 Hz, 2H), 3.07 (t, J = 7.8 Hz, 2H), 1.89–1.82 (quin, 2H), 1.74–1.67 (quin, 2H) ppm LCMS (AM3): rt = 0.593 min, (503.2 [M+H]$^{+}$), 98.0% purity Purification Method 96
Example 111	5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile **1.504**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.11 (s, 1H), 8.89 (d, J = 5.2 Hz, 1H), 8.82 (d, J = 8.4 Hz, 1H), 8.32 (s, 1H), 8.08–8.02 (m, 2H), 7.38–7.33 (m, 2H), 7.21 (s, 1H), 4.70 (t, J = 4.4 Hz, 2H), 4.09 (s, 2H), 3.87 (t, J = 4.0 Hz, 2H), 3.79 (s, 2H), 3.53 (t, J = 6.0 Hz, 2H), 2.56 (t, J = 6.0 Hz, 2H), 1.62–1.48 (m, 4H) ppm LCMS (AM7): rt = 0.751 min, (569.3 [M+H]$^{+}$), 100% purity Purification Method 111
Example 112	5-(2-(4-((3-bromo-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-bromo-4-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.77 (s, 1H), 8.69 (d, J = 5.6 Hz, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 1.6 Hz, 1H), 8.05 (dd, J = 8.4, 1.6 Hz, 1H), 7.95 (d, J = 4.2 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 8.4, 2.0 Hz, 1H), 7.43 (dd, J = 8.4, 1.6 Hz, 1H), 4.70 (t, J = 4.8 Hz, 2H), 4.12 (s, 2H), 3.92 (t, J = 4.8 Hz, 2H), 3.67 (t, J = 6.0 Hz, 2H), 3.04 (t, J = 7.8 Hz, 2H), 1.89–1.81 (quin, 2H), 1.74–1.67 (quin, 2H) ppm LCMS (AM7): rt = 0.777 min, (608.1 [M+H]$^{+}$), 100% purity Purification Method 112
Example 113	5-(2-(4-((4-chloro-3-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 4-chloro-3-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.75 (s, 1H), 8.69 (d, J = 5.6 Hz, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 1.6 Hz, 1H), 8.04 (dd, J = 8.4, 1.6 Hz, 1H), 7.92 (d, J = 5.2 Hz, 1H), 7.60–7.58 (m, 2H), 7.47 (dd, J = 8.4, 2.0 Hz, 1H), 4.68 (t, J = 4.8 Hz, 2H), 4.15 (s, 2H), 3.91 (t, J = 4.8 Hz, 2H), 3.66 (t, J = 6.0 Hz, 2H), 3.04 (t, J = 7.8 Hz, 2H), 1.89–1.82 (quin, 2H), 1.74–1.67 (quin, 2H) ppm LCMS (AM7): rt = 0.768 min, (564.2 [M+H]$^{+}$), 100% purity Purification Method 112
Example 114	5-(2-(4-((3-chloro-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-chloro-5-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.79 (s, 1H), 8.71 (d, J = 5.2 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 4.4 Hz, 1H), 7.54 (s, 1H), 7.40–7.33 (m, 2H), 4.70 (t, J = 4.8 Hz, 2H), 4.14 (s, 2H), 3.92 (t, J = 4.4 Hz, 2H), 3.67 (t, J = 5.6 Hz, 2H), 3.03 (t, J = 7.8 Hz, 2H), 1.88–1.81 (m, 2H), 1.74–1.66 (m, 2H) ppm LCMS (AM7): rt = 0.767 min, (564.2 [M+H]$^{+}$), 100% purity Purification Method 113

Example 115	5-(2-(4-((3-bromo-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-bromo-5-(trifluoromethoxy) benzaldehyde	[1]H NMR (400 MHz, MeOH-d_4) δ: 9.76 (s, 1H), 8.68 (d, *J* = 5.6 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.32 (d, *J* = 1.2 Hz, 1H), 8.05 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.93 (d, *J* = 5.2 Hz, 1H), 7.70 (s, 1H), 7.51 (s, 1H), 7.46 (s, 1H), 4.68 (t, *J* = 4.8 Hz, 2H), 4.17 (s, 2H), 3.92 (t, *J* = 4.8 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.90–1.82 (quin, 2H), 1.74–1.67 (quin, 2H) ppm LCMS (AM7): rt = 0.781 min, (610.2 $[M+H]^+$), 100% purity Purification Method 113
Example 117	5-(2-(4-((3-cyclopropyl-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Cyclopropyl-5-(trifluoromethoxy) benzaldehyde **1.509**	[1]H NMR (400 MHz, MeOH-d_4) δ: 9.82 (s, 1H), 8.71 (d, *J* = 5.2 Hz, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 8.36 (d, *J* = 1.6 Hz, 1H), 8.08 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.00 (d, *J* = 5.2 Hz, 1H), 7.16 (s, 2H), 6.98 (s, 1H), 4.73 (t, *J* = 4.8 Hz, 2H), 4.09 (s, 2H), 3.93 (t, *J* = 4.8 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 7.2 Hz, 2H), 1.96–1.91 (m, 1H), 1.89–1.81 (quin, 2H), 1.74–1.66 (quin, 2H), 1.04–0.98 (m, 2H), 0.74–0.69 (m, 2H) ppm LCMS (AM7): rt = 0.785 min, (570.3 $[M+H]^+$), 98.4% purity Purification Method 113
Example 129	5-(2-(4-((3-chloro-5-(1-cyanocyclopropyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 1-(3-Chloro-5-formylphenyl)cyclopropanecarbonitrile **1.630**	[1]H NMR (400 MHz, MeOH-d_4) δ: 9.91 (s, 1H), 8.76 (d, *J* = 5.6 Hz, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.40 (s, 1H), 8.12-8.09 (m, 2H), 7.36-7.30 (m, 3H), 4.79 (t, *J* = 4.8 Hz, 2H), 3.97-3.95 (t, 4H), 3.67 (t, *J* = 6.0 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 1.81-1.65 (m, 6H), 1.51-1.48 (m, 2H) ppm LCMS (AM7): rt = 0.736 min, (545.3 $[M+H]^+$), 100% purity Purification Method 129
Example 130	5-(2-(4-((3-chloro-5-(2-cyanopropan-2-yl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Chloro-5-vinylphenyl)-2-methylpropanenitrile **1.632**	[1]H NMR (400 MHz, MeOH-d_4) δ: 9.78 (s, 1H), 8.70 (d, *J* = 5.6 Hz, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 8.34 (s, 1H), 8.06 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.97 (d, *J* = 5.2 Hz, 1H), 7.59 (s, 1H), 7.55 (t, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 1.2 Hz, 1H), 4.70 (t, *J* = 4.8 Hz, 2H), 4.12 (s, 2H), 3.92 (t, *J* = 4.8 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 1.89-1.81 (quin, 2H), 1.74-1.71 (m, 2H), 1.70 (s, 6H) ppm LCMS (AM7): rt = 0.745 min, (547.3 $[M+H]^+$), 100% purity Purification Method 130

Example 131	5-(2-(4-((3-cyclopropyl-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Cyclopropyl-4-(trifluoromethoxy)benzaldehyde **1.710**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.82 (s, 1H), 8.71 (d, *J* = 5.6 Hz, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 8.36 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 5.6 Hz, 1H), 7.31-7.24 (m, 2H), 7.12 (s, 1H), 4.73 (t, *J* = 4.8 Hz, 2H), 4.08 (s, 2H), 3.92 (t, *J* = 4.8 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.13-2.06 (m, 1H), 1.87-1.80 (quin, 2H), 1.72-1.65 (quin, 2H), 1.03-0.98 (m, 2H), 0.75-0.71 (m, 2H) ppm. LCMS (AM7): rt = 0.777 min, (570.3 $[M+H]^+$), 100% purity Purification Method 131
Example 132	5-(2-(4-((3-methyl-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Methyl-4-(trifluoromethoxy)benzaldehyde **1.709**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.73 (s, 1H), 8.66 (d, *J* = 5.6 Hz, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 8.30 (br s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 5.6 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.36 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.24 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.66 (t, *J* = 4.8 Hz, 2H), 4.09 (s, 2H), 3.89 (t, *J* = 4.8 Hz, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.27 (s, 3H), 1.89-1.81 (quin, 2H), 1.73-1.64 (quin, 2H) ppm LCMS (AM7): rt = 0.763 min, (544.3 $[M+H]^+$), 100 % purity Purification Method 132
Example 133	5-(2-(4-((3-methoxy-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Methoxy-4-(trifluoromethoxy)benzaldehyde **1.707**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.73 (s, 1H), 8.67 (d, *J* = 5.6 Hz, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 1.6 Hz, 1H), 8.04 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.91 (d, *J* = 5.6 Hz, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.24 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.03 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.67 (t, *J* = 4.8 Hz, 2H), 4.08 (s, 2H), 3.90 (t, *J* = 4.8 Hz, 2H), 3.86 (s, 3H), 3.66 (t, *J* = 6.0 Hz, 2H), 3.01 (t, *J* = 7.6 Hz, 2H), 1.88-1.81 (m, 2H), 1.74-1.67 (m, 2H) ppm LCMS (AM3): rt = 0.829 min, (560.1 $[M+H]^+$), 100% purity. Purification Method 133
Example 134	5-(2-(4-((3,4-dichloro-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3,4-Dichloro-5-(trifluoromethoxy)benzaldehyde **1.704**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.91 (s, 1H), 8.76 (d, *J* = 5.6 Hz, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.41 (s, 1H), 8.13-8.10 (m, 2H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.46 (s, 1H), 4.78 (t, *J* = 4.8 Hz, 2H), 3.95 (t, *J* = 4.8 Hz, 2H), 3.89 (s, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.78 (t, *J* = 7.2 Hz, 2H), 1.76-1.63 (m, 4H) ppm LCMS (AM7): rt = 0.770 min, (598.2 $[M+H]^+$), 99.1% purity Purification Method 133

Example 116

5-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid



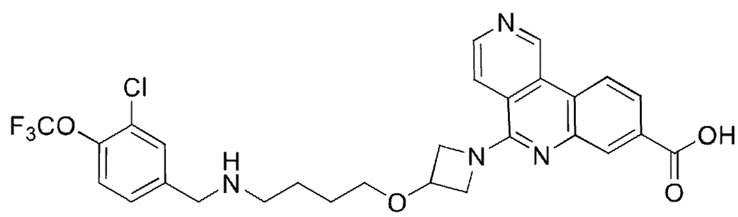
[00393] A mixture of **Intermediate Q** (300 mg, 514.20 μmol), **compound 1.507** (116.26 mg, 514.20 μmol) and DIPEA (199.36 mg, 1.54 mmol) in MeOH (5 mL) was stirred at 25 °C for 1 h, then sodium triacetoxyborohydride (544.90 mg, 2.57 mmol) was added. The mixture was stirred at 25 °C for another 11 h. The mixture was concentrated *in vacuo* and the residue was purified (PM113) to afford **Example 116** (99.09 mg, 175.23 μmol, 34.1% yield) as a yellow solid.

LCMS (Method 7): rt = 0.769 min, (566.3 $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.69 (s, 1H), 8.65 (d, *J* = 5.6 Hz, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 8.27 (d, *J* = 1.6 Hz, 1H), 8.01 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.87 (d, *J* = 5.2 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 4.64 (t, *J* = 4.8 Hz, 2H), 4.16 (s, 2H), 3.90 (t, *J* = 4.8 Hz, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 1.91–1.84 (quin, 2H), 1.76–1.69 (quin, 2H) ppm.

Example 54

5-(3-(4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid



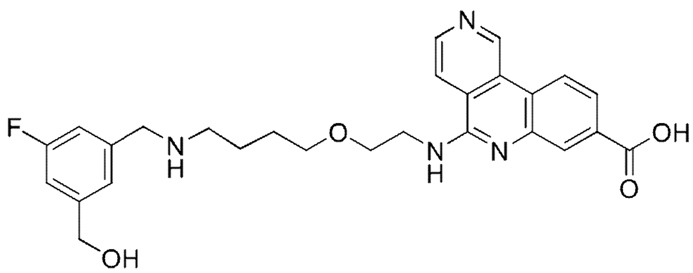
[00394] A mixture of **compound 1.399** (0.17 g, 0.289 mmol) and lithium hydroxide monohydrate (0.1 g, 2.38 mmol) in THF (4 mL) and water (2 mL) was stirred at room temperature for 2 h. The mixture was neutralized with formic acid (0.5 mL) and concentrated *in vacuo*. The residue was purified (PM65) to afford **Example 54** (124.42 mg, 75.0% yield) as a yellow solid.

LCMS (AM3): rt = 0.788 min, (575.2 [M+H]$^+$), 100% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.12 (s, 1H), 8.83 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.8 Hz, 1H), 8.23–8.21 (m, 1H), 7.96 (d, *J* = 5.2 Hz, 1H), 7.91–7.89 (d, 1H), 7.67 (s, 1H), 7.52–7.42 (q, 2H), 4.73–4.69 (t, 2H), 4.49–4.43 (m, 1H), 4.33–4.29 (m, 2H), 3.78 (s, 2H), 3.45 (t, *J* = 6.4 Hz, 2H), 2.58–2.55 (m, 2H), 1.62–1.50 (m, 4H) ppm.

Example 69

5-((2-(4-((3-Fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6] naphthyridine-8-carboxylic acid



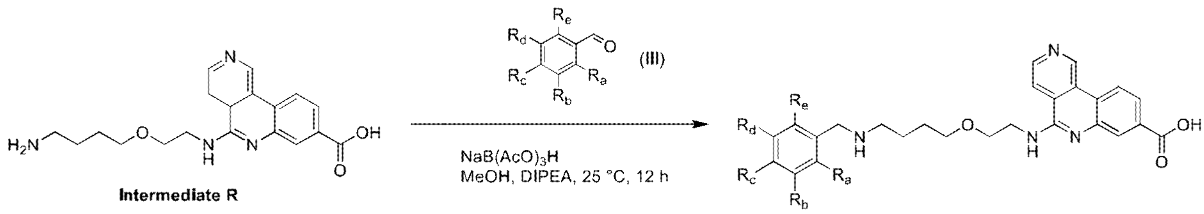
[00395] A mixture of **Intermediate R** (300 mg, 646.85 μmol), **compound 1.500** (99.70 mg, 646.85 μmol) and DIPEA (250.80 mg, 1.94 mmol) in MeOH (3 mL) was stirred at 25 °C for 1 h, then sodium triacetoxyborohydride (411.28 mg, 1.94 mmol) was added. The mixture was stirred at 25 °C for another 11 h. The mixture was filtered and concentrated *in vacuo*. The residue was purified (PM74) to afford **Example 69** (74.49 mg, 151.24 μmol, 23.4% yield) as a yellow solid.

LCMS (AM7): rt = 0.673 min, (493.2 [M+H]$^+$), 100% purity.

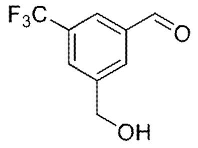
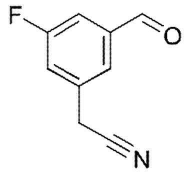
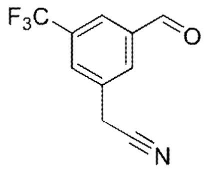
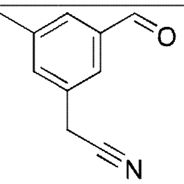
^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.66 (s, 1H), 8.56 (d, *J* = 5.6 Hz, 1H), 8.31 (d, *J* = 8.8 Hz, 1H), 8.16 (d, *J* = 1.6 Hz, 1H), 7.86–7.82 (t, 2H), 7.22 (s, 1H), 7.08 (d, *J* = 9.2 Hz, 2H), 4.58 (s, 2H), 4.05 (s, 2H), 3.78–3.67 (m, 4H), 3.56 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 8.0 Hz, 2H), 1.84–1.76 (quin, 2H), 1.68–1.58 (quin, 2H) ppm.

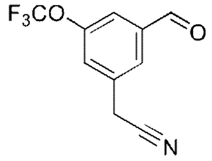
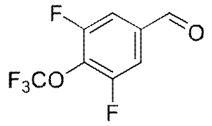
The following examples in Table 8 were made with non-critical changes or substitutions to the exemplified procedure in Example 69, that would be understood by one skilled in the art using intermediate R and compounds of formula (III).

Table 8



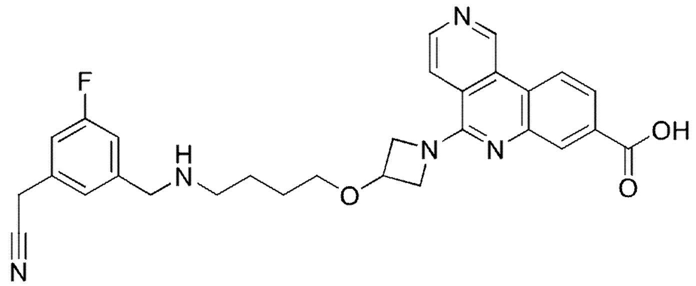
Intermediate R

Example No.	Chemical IUPAC name	Compound (III)	Analytical
Example 70	5-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-(Hydroxymethyl)-5-(trifluoromethyl)benzaldehyde **1.501**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.63 (s, 1H), 8.54 (d, J = 5.6 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.15 (s, 1H), 7.84–7.81 (m, 2H), 7.70–7.63 (m, 3H), 4.66 (s, 2H), 4.15 (s, 2H), 3.74–3.67 (m, 4H), 3.56 (t, J = 6.0 Hz, 2H), 3.01 (t, J = 7.8 Hz, 2H), 1.86–1.78 (m, 2H), 1.70–1.60 (m, 2H) ppm LCMS (AM7): rt = 0.684 min, (543.3 [M+H]$^+$), 100% purity. Purification Method 75
Example 71	5-((2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Fluoro-5-formylphenyl)acetonitrile **1.472**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.66 (s, 1H), 8.56 (d, J = 5.6 Hz, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 1.6 Hz, 1H), 7.86–7.81 (m, 2H), 7.27 (s, 1H), 7.20–7.16 (d, 1H), 7.10–7.06 (d, 1H), 4.06 (s, 2H), 3.89 (s, 2H), 3.78–3.68 (m, 4H), 3.57 (t, J = 6.0 Hz, 2H), 2.99 (t, J = 7.8 Hz, 2H), 1.87–1.77 (quin, 2H), 1.70–1.61 (quin, 2H) ppm LCMS (AM7): rt = 0.675 min, (502.2 [M+H]$^+$), 100% purity Purification Method 74
Example 72	5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Formyl-5-(trifluoromethyl)phenyl)acetonitrile **1.469**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.72 (br s, 1H), 8.61 (d, J = 5.4 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.18 (s, 1H), 7.93–7.87 (m, 2H), 7.76–7.65 (m, 3H), 4.13 (s, 2H), 4.02 (s, 2H), 3.81–3.71 (m, 4H), 3.60 (t, J = 6.0 Hz, 2H), 3.00 (t, J = 7.2 Hz, 2H), 1.85–1.78 (m, 2H), 1.72–1.63 (m, 2H) ppm LCMS (AM7): rt = 0.710 min, (552.3 [M+H]$^+$), 100% purity Purification Method 76
Example 73	5-((2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Formyl-5-methylphenyl)acetonitrile **1.475**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.71 (s, 1H), 8.59 (d, J = 5.6 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 7.92–7.89 (d, 1H), 7.86–7.85 (d, 1H), 7.17–7.12 (m, 3H), 3.97 (s, 2H), 3.81–3.76 (m, 4H), 3.73 (t, J = 5.2 Hz, 2H), 3.60 (t, J = 5.6 Hz, 2H), 2.96 (t, J = 7.6 Hz, 2H), 2.28 (s, 3H), 1.84–1.77 (quin, 2H), 1.68–1.62 (quin, 2H) ppm LCMS (AM7): rt = 0.693 min, (498.3 [M+H]$^+$), 99.7% purity Purification Method 77

Example 108	5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile **1.504**	[1]H NMR (400 MHz, DMSO-d_6) δ: 10.04 (s, 1H), 8.85 (d, J = 5.2 Hz, 1H), 8.68 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 5.6 Hz, 1H), 8.14 (s, 1H), 8.02–7.98 (m, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.34–7.28 (m, 2H), 7.20 (s, 1H), 4.09 (s, 2H), 3.80–3.77 (m, 2H), 3.72–3.67 (m, 6H), 2.50–2.49 (m, 2H), 1.58–1.42 (m, 4H) ppm LCMS (AM7): rt = 0.734 min, (568.3 $[M+H]^+$), 99.2% purity Purification Method 101
Example 178	5-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3,5-Difluoro-4-(trifluoromethoxy)benzaldehyde **1.507**	[1]H NMR (400 MHz, DMSO-d_6) δ: 10.05 (s, 1H), 8.86 (d, J = 5.6 Hz, 1H), 8.70 (d, J = 8.5 Hz, 1H), 8.27 (d, J = 5.6 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 8.01 (t, J = 5.6 Hz, 1H), 7.82 (dd, J = 8.4, 1.6 Hz, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 3.77 (t, J = 5.2 Hz, 2H), 3.69 (t, J = 5.2 Hz, 2H), 3.67 (s, 2H), 3.45 (t, J = 5.6 Hz, 2H), 2.45 (t, J = 6.8 Hz, 2H), 1.57-1.51 (m, 2H), 1.49-1.42 (m, 2H) ppm LCMS (AM7): rt = 0.760 min, (565.2 $[M+H]^+$), 96.9 % purity Purification Method 172

Example 79

5-(3-(4-((3-(Cyanomethyl)-5-fluorobenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid



[00396] To a solution of **compound 1.472** (121.49 mg, 744.65 μmol) and **Intermediate O** (300 mg, 744.65 μmol) in MeOH (10 mL) was added DIPEA (309.89 mg, 2.40 mmol) at 20 °C. The mixture was stirred at 20 °C for 12 h before sodium triacetoxyborohydride (631.28 mg, 2.98 mmol) was added. The reaction mixture was stirred at 20 °C for another 1 h. The mixture was concentrated and purified (PM81) to afford **Example 79** (84.42 mg, 164.38 μmol, 22% yield) as an off-white solid.

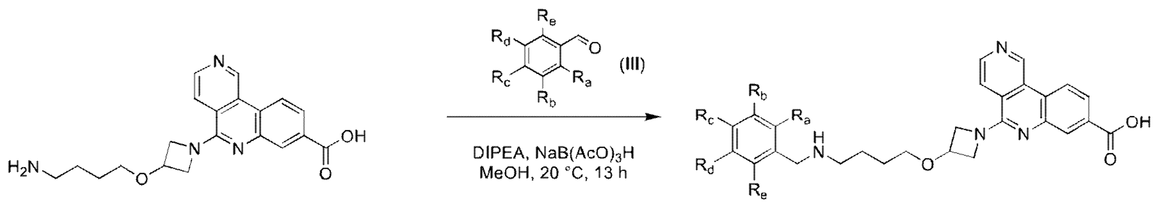
LCMS (AM3): rt = 0.724 min, (514.3 $[M+H]^+$), 100% purity.

[1]H NMR (400 MHz, DMSO-d_6) δ: 10.11 (s, 1H), 8.82 (d, J = 5.6 Hz, 1H), 8.76 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 1.6 Hz, 1H), 7.94 (d, J = 5.6 Hz, 1H), 7.89 (dd, J = 8.4, 1.6 Hz, 1H), 7.19 (s, 1H), 7.16 (d, J = 10 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 4.72–4.68 (m, 2H), 4.48–4.43 (m, 1H),

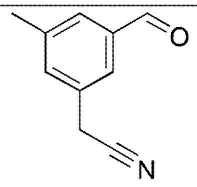
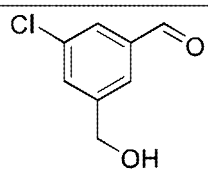
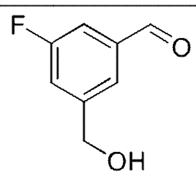
4.32–4.28 (m, 2H), 4.04 (s, 2H), 3.75 (s, 2H), 3.44 (t, J = 6.4 Hz, 2H), 2.56–2.52 (m, 2H), 1.63–1.51 (m, 4H) ppm.

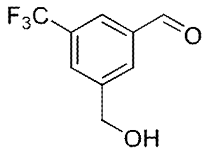
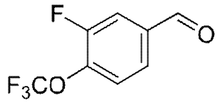
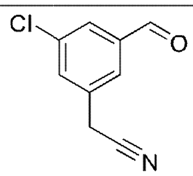
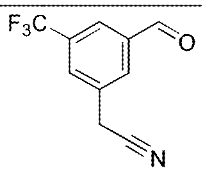
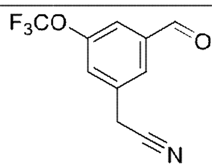
The following examples in Table 9 were made with non-critical changes or substitutions to the exemplified procedure in Example 79, that would be understood by one skilled in the art using intermediate O and compounds of formula (III).

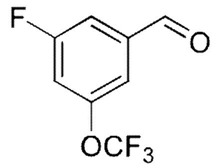
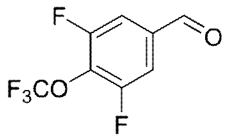
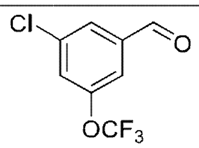
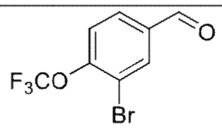
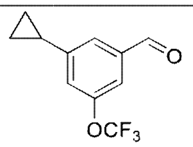
Table 9

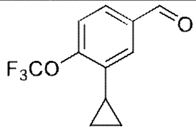
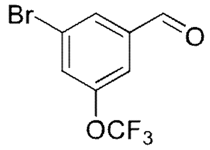
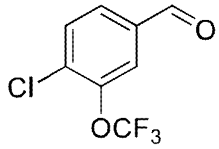
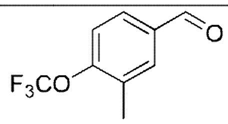
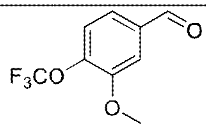


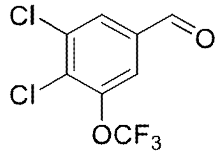
intermediate O

Example No.	Chemical IUPAC name	Compound (III)	Analytical
Example 80	5-(3-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Formyl-5-methylphenyl)acetonitrile **1.475**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.08 (s, 1H), 8.78 (d, J = 5.6 Hz, 1H), 8.68 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 7.93 (d, J = 5.2 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.10 (s, 2H), 6.99 (s, 1H), 4.68 (t, J = 7.6 Hz, 2H), 4.48–4.42 (m, 1H), 4.29–4.24 (m, 2H), 3.95 (s, 2H), 3.67 (s, 2H), 3.45–3.42 (m, 2H), 2.54–2.52 (m, 2H), 2.27 (s, 3H), 1.62–1.49 (m, 4H) ppm LCMS (AM3): rt = 0.737 min, (510.3 [M+H]$^+$), 100% purity Purification Method 78
Example 81	5-(3-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Chloro-5-(hydroxymethyl)benzaldehyde **1.102**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.05 (s, 1H), 8.78 (d, J = 5.2 Hz, 1H), 8.69 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 7.90–7.88 (m, 2H), 7.33 (s, 1H), 7.28 (s, 1H), 7.23 (s, 1H), 4.67–4.63 (m, 2H), 4.47 (s, 2H), 4.45–4.40 (m, 1H), 4.29–4.25 (m, 2H), 3.81 (s, 2H), 3.43 (t, J = 5.6 Hz, 2H), 2.62 (t, J = 6.2 Hz, 2H), 1.61–1.55 (m, 4H) ppm LCMS (AM3): rt = 0.713 min, (521.2 [M+H]$^+$), 98.9% purity Purification Method 82
Example 82	5-(3-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Fluoro-5-(hydroxymethyl)benzaldehyde **1.500**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.06 (s, 1H), 8.78 (d, J = 5.6 Hz, 1H), 8.70 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 1.2 Hz, 1H), 7.90 (s, 1H), 7.89–7.87 (m, 1H), 7.15 (s, 1H), 7.08 (d, J = 9.6 Hz, 1H), 6.98 (d, J = 9.6 Hz, 1H), 4.68–4.64 (t, 2H), 4.48 (s, 2H), 4.45–4.41 (m, 1H), 4.29–4.26 (m, 2H), 3.80 (s, 2H), 3.44 (t, J = 6.0 Hz, 2H), 2.60 (t, J = 6.4 Hz, 2H), 1.62–1.50 (m, 4H) ppm LCMS (AM3): rt = 0.705 min, (505.2 [M+H]$^+$), 100% purity Purification Method 83

Example 100	5-(3-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-(Hydroxymethyl)-5-(trifluoromethyl)benzaldehyde **1.501**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.07 (s, 1H), 8.78 (d, *J* = 5.6 Hz, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 7.91–7.87 (m, 2H), 7.60 (s, 2H), 7.52 (s, 1H), 4.68–4.64 (m, 2H), 4.56 (s, 2H), 4.46–4.41 (m, 1H), 4.29–4.26 (m, 2H), 3.85 (s, 2H), 3.44 (t, *J* = 6.0 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 2H), 1.65–1.50 (m, 4H) ppm LCMS (AM3): rt = 0.748 min, (555.3 $[M+H]^+$), 99.2% purity Purification Method 101
Example 101	5-(3-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-fluoro-4-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.10 (s, 1H), 8.81 (d, *J* = 5.6 Hz, 1H), 8.74 (d, *J* = 8.8 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 7.94 (d, *J* = 5.6 Hz, 1H), 7.89 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.47–7.43 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 4.71–4.67 (m, 2H), 4.48–4.42 (m, 1H), 4.31–4.28 (m, 2H), 3.73 (s, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.53–2.52 (m, 2H), 1.63–1.47 (m, 4H) ppm LCMS (AM3): rt = 0.784 min, (559.3 $[M+H]^+$), 100% purity Purification Method 102
Example 102	5-(3-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Chloro-5-formylphenyl)acetonitrile **1.366**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.09 (s, 1H), 8.80 (d, *J* = 5.6 Hz, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 5.6 Hz, 1H), 7.89 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.40 (s, 1H), 7.31 (s, 1H), 7.27 (s, 1H), 4.70–4.66 (m, 2H), 4.46–4.42 (m, 1H), 4.31–4.27 (m, 2H), 4.04 (s, 2H), 3.76 (s, 2H), 3.44 (t, *J* = 6.0 Hz, 2H), 2.55 (t, *J* = 6.8 Hz, 2H), 1.64–1.49 (m, 4H) ppm LCMS (AM3): rt = 0.728 min, (530.1 $[M+H]^+$), 95.9% purity Purification Method 103
Example 103	5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Formyl-5-(trifluoromethyl)phenyl)acetonitrile **1.469**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.10 (s, 1H), 8.81 (d, *J* = 5.6 Hz, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 7.94 (d, *J* = 5.2 Hz, 1H), 7.89 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.70 (s, 1H), 7.66 (s, 1H), 7.58 (s, 1H), 4.71–4.67 (m, 2H), 4.47–4.43 (m, 1H), 4.31–4.28 (m, 2H), 4.15 (s, 2H), 3.84 (s, 2H), 3.44 (t, *J* = 6.0 Hz, 2H), 2.57 (t, *J* = 6.4 Hz, 2H), 1.64–1.50 (m, 4H) ppm LCMS (AM3): rt = 0.751 min, (564.2 $[M+H]^+$), 99.7% purity Purification Method 104
Example 109	5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile **1.504**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.09 (s, 1H), 8.81 (d, *J* = 5.2 Hz, 1H), 8.74 (d, *J* = 8.8 Hz, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 5.6 Hz, 1H), 7.89 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.39 (s, 1H), 7.34 (s, 1H), 7.21 (s, 1H), 4.71–4.67 (m, 2H), 4.47–4.42 (m, 1H), 4.31–4.27 (m, 2H), 4.10 (s, 2H), 3.79 (s, 2H), 3.44–3.43 (m, 2H), 2.55 (t, *J* = 6.8 Hz, 2H), 1.64–1.49 (m, 4H) ppm LCMS (AM3): rt = 0.758 min, (580.5 $[M+H]^+$), 97.8% purity Purification Method 109

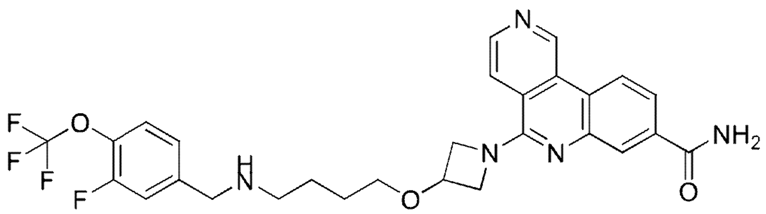
Example 118	5-(3-(4-((3-fluoro-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-fluoro-5-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.11 (s, 1H), 8.82 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 7.95 (d, *J* = 5.2 Hz, 1H), 7.89 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.23 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 4.72–4.68 (m, 2H), 4.47–4.43 (m, 1H), 4.31–4.28 (m, 2H), 3.77 (s, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.53–2.52 (m, 2H), 1.63–1.47 (m, 4H) ppm LCMS (AM3): rt = 0.762 min, (559.3 $[M+H]^+$), 96.1% purity Purification Method 114
Example 119	5-(3-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3,5-Difluoro-4-(trifluoromethoxy)benzaldehyde **1.507**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.11 (s, 1H), 8.82 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 7.95 (d, *J* = 5.2 Hz, 1H), 7.89 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.36 (d, *J* = 9.2 Hz, 2H), 4.72–4.68 (m, 2H), 4.47–4.43 (m, 1H), 4.32–4.29 (m, 2H), 3.74 (s, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.54–2.52 (m, 2H), 1.64–1.49 (m, 4H) ppm LCMS (AM3): rt = 0.777 min, (577.4 $[M+H]^+$), 98.3% purity Purification Method 115
Example 120	5-(3-(4-((3-chloro-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-chloro-5-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.11 (s, 1H), 8.82 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.20 (s, 1H), 7.95 (d, *J* = 5.6 Hz, 1H), 7.89 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.48 (s, 1H), 7.36 (d, *J* = 4.4 Hz, 2H), 4.72–4.68 (m, 2H), 4.47–4.44 (m, 1H), 4.31–4.28 (m, 2H), 3.77 (s, 2H), 3.44 (t, *J* = 5.6 Hz, 2H), 2.53–2.52 (m, 2H), 1.62–1.48 (m, 4H) ppm LCMS (AM3): rt = 0.774 min, (575.4 $[M+H]^+$), 100% purity Purification Method 116
Example 121	5-(3-(4-((3-bromo-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-bromo-4-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.11 (s, 1H), 8.82 (d, *J* = 5.6 Hz, 1H), 8.76 (d, *J* = 8.8 Hz, 1H), 8.20 (d, *J* = 1.6 Hz, 1H), 7.95 (d, *J* = 5.6 Hz, 1H), 7.89 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.78 (s, 1H), 7.46 (s, 2H), 4.72–4.68 (m, 2H), 4.47–4.44 (m, 1H), 4.32–4.28 (m, 2H), 3.74 (s, 2H), 3.45–3.43 (m, 2H), 2.55–2.53 (m, 2H), 1.63–1.48 (m, 4H) ppm LCMS (AM3): rt = 0.785 min, (621.1 $[M+H]^+$), 99.7% purity. Purification Method 117
Example 122	5-(3-(4-((3-cyclopropyl-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Cyclopropyl-5-(trifluoromethoxy)benzaldehyde **1.509**	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.56 (s, 1H), 8.63 (d, *J* = 5.6 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 5.6 Hz, 1H), 8.02 (s, 1H), 7.88 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.07 (br s, 2H), 6.97 (br s, 1H), 4.24-4.18 (m, 3H), 3.89 (s, 2H), 3.85-3.61 (m, 4H), 2.86 (t, *J* = 7.6 Hz, 2H), 1.99-1.82 (m, 1H), 1.74-1.61 (m, 4H), 1.06-1.01 (m, 2H), 0.75-0.71 (m, 2H) ppm LCMS (AM3): rt = 0.764 min, (581.4 $[M+H]^+$), 100% purity Purification Method 118

Example 142	5-(3-(4-((3-cyclopropyl-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Cyclopropyl-4-(trifluoromethoxy)benzaldehyde **1.710**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.07 (s, 1H), 8.79 (d, J = 5.6 Hz, 1H), 8.72 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 7.91-7.88 (m, 2H), 7.23 (s, 2H), 7.03 (s, 1H), 4.69-4.65 (m, 2H), 4.46-4.41 (m, 1H), 4.28-4.24 (m, 2H), 3.74 (s, 2H), 3.45-3.42 (m, 2H), 2.57 (t, J = 6.8 Hz, 2H), 2.06-1.99 (m, 1H), 1.61-1.52 (m, 4H), 0.99-0.95 (m, 2H), 0.72-0.68 (m, 2H) ppm LCMS (AM3): rt = 0.802 min, (581.4 [M+H]$^+$), 100% purity Purification Method 133
Example 143	5-(3-(4-((3-bromo-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-bromo-5-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.11 (s, 1H), 8.82 (d, J = 5.6 Hz, 1H), 8.76 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 5.6 Hz, 1H), 7.88 (dd, J = 8.4, 1.6 Hz, 1H), 7.61 (s, 1H), 7.44 (s, 1H), 7.38 (s, 1H), 4.72-4.68 (m, 2H), 4.48-4.43 (m, 1H), 4.31-4.28 (m, 2H), 3.75 (s, 2H), 3.50-3.43 (m, 2H), 2.50-2.49 (m, 2H), 1.62-1.46 (m, 4H) ppm LCMS (AM3): rt = 0.781 min, (619.4 [M+H]$^+$), 97.0% purity Purification Method 133
Example 144	5-(3-(4-((4-chloro-3-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 4-chloro-3-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.07 (s, 1H), 8.78 (d, J = 5.6 Hz, 1H), 8.71 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 1.2 Hz, 1H), 7.91-7.88 (m, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.56 (s, 1H), 7.41 (dd, J = 8.4, 2.0 Hz, 1H), 4.68-4.64 (m, 2H), 4.46-4.41 (m, 1H), 4.29-4.26 (m, 2H), 3.79 (s, 2H), 3.43 (t, J = 5.2 Hz, 2H), 2.55 (t, J = 6.8 Hz, 2H), 1.62-1.49 (m, 4H) ppm LCMS (AM3): rt = 0.781 min, (575.2 [M+H]$^+$), 96.4% purity. Purification Method 114
Example 145	5-(3-(4-((3-methyl-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Methyl-4-(trifluoromethoxy)benzaldehyde **1.709**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.09 (s, 1H), 8.81 (d, J = 5.6 Hz, 1H), 8.74 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 7.93 (d, J = 5.6 Hz, 1H), 7.89 (dd, J = 8.8, 1.6 Hz, 1H), 7.36 (s, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 4.71-4.67 (m, 2H), 4.46-4.42 (m, 1H), 4.31-4.27 (m, 2H), 3.75 (s, 2H), 2.59 (t, J = 6.4 Hz, 4H), 2.24 (s, 3H), 1.61-1.52 (m, 4H) ppm LCMS (AM3): rt = 0.799 min, (555.3 [M+H]$^+$), 94.2% purity Purification Method 139
Example 146	5-(3-(4-((3-methoxy-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3-Methoxy-4-(trifluoromethoxy)benzaldehyde **1.707**	^{1}H NMR : (400 MHz, DMSO-d_6) δ: 10.08 (s, 1H), 8.80 (d, J = 5.6 Hz, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 1.2 Hz, 1H), 7.92 (d, J = 5.6 Hz, 1H), 7.89 (dd, J = 8.4, 1.2 Hz, 1H), 7.26 (dd, J = 4.4, 3.2 Hz, 2H), 6.99 (d, J = 8.4 Hz, 1H), 4.70-4.66 (m, 2H), 4.47-4.42 (m, 1H), 4.30-4.25 (m, 2H), 3.83 (s, 3H), 3.79 (s, 2H), 2.60 (t, J = 6.4 Hz, 2H), 2.53-2.52 (m, 2H), 1.63-1.52 (m, 4H) ppm LCMS (AM3): rt = 0.783 min, (571.3 [M+H]$^+$), 98.5% purity Purification Method 140

Example 147	5-(3-(4-((3,4-dichloro-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid	 3,4-Dichloro-5-(trifluoromethoxy) benzaldehyde **1.704**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.12 (s, 1H), 8.83 (d, *J* = 5.6 Hz, 1H), 8.78 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 7.96 (d, *J* = 6.0 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.72 (d, *J* = 1.6 Hz, 1H), 7.57 (s, 1H), 4.73-4.69 (m, 2H), 4.48-4.43 (m, 1H), 4.32-4.28 (m, 2H), 3.80 (s, 2H), 2.55-2.50 (m, 4H), 1.62-1.48 (m, 4H) ppm LCMS (AM3): rt = 0.827 min, (609.1 [M+H]$^+$), 100% purity. Purification Method 141

Example 83

5-(3-(4-((3-Fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide



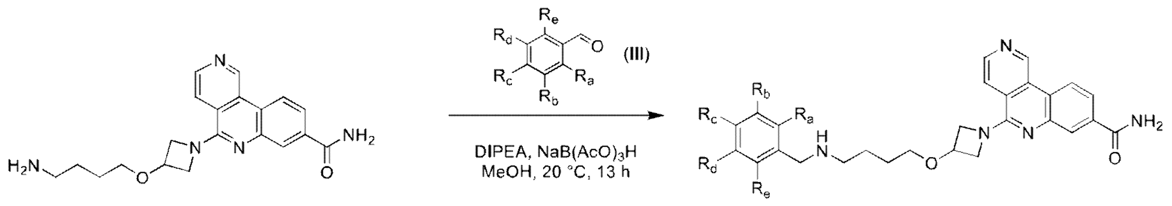
[00397] To a solution of **Intermediate P** (300 mg, 820.96 μmol) and 3-fluoro-4-(trifluoromethoxy)benzaldehyde (170.85 mg, 820.96 μmol) in MeOH (10 mL) was added DIPEA (341.64 mg, 2.64 mmol). The mixture was stirred at 20 °C for 12 h before sodium triacetoxyborohydride (695.97 mg, 3.28 mmol) was added. The mixture was stirred at 20 °C for another 1 h. **LCMS** (AM3) indicated the reaction was complete. The mixture was concentrated *in vacuo* and the residue was purified (PM84) to afford **Example 83** (64.07 mg, 114.46 μmol, 13.9% yield) as yellow solid.

LCMS (AM3): rt = 0.747 min, (558.3 [M+H]$^+$), 99.6% purity.

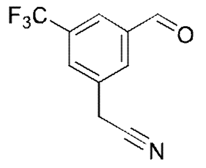
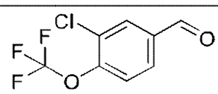
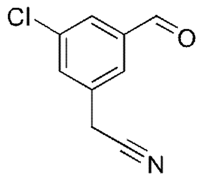
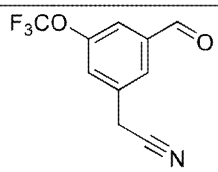
^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.97 (s, 1H), 8.76 (d, *J* = 5.6 Hz, 1H), 8.64 (d, *J* = 8.8 Hz, 1H), 8.24 (s, 1H), 7.99 (d, *J* = 5.6 Hz, 1H), 7.87 (dd, *J* = 8.4,1.6, Hz, 1H), 7.36–7.31 (m, 2H), 7.21 (d, *J* = 8.8 Hz, 1H), 4.78–4.74 (m, 2H), 4.54–4.49 (m, 1H), 4.40–4.37 (m, 2H), 3.77 (s, 2H), 3.54 (t, *J* = 5.8 Hz, 2H), 2.63 (t, *J* = 7.0 Hz, 2H), 1.68–1.62 (m, 4H) ppm.

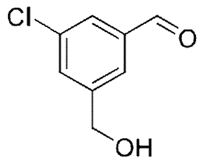
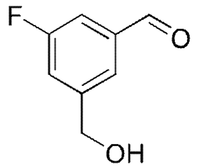
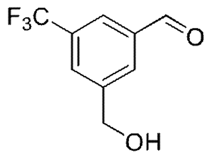
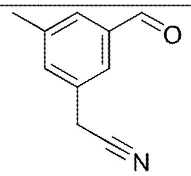
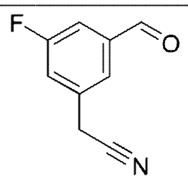
The following examples in Table 10 were made with non-critical changes or substitutions to the exemplified procedure in Example 83, that would be understood by one skilled in the art using intermediate P and compounds of formula (III).

Table 10



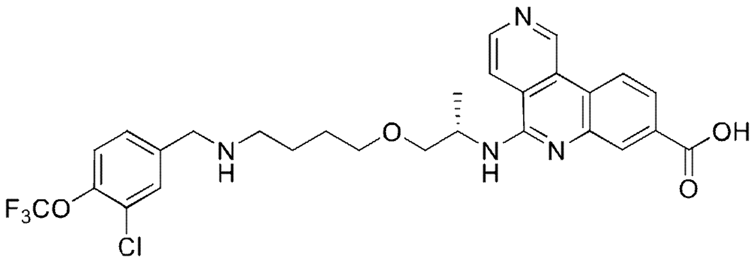
intermediate P

Example No.	Chemical IUPAC name	Compound (III)	Analytical
Example 98	5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-(trifluoromethyl)phenyl)acetonitrile **1.469**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.13 (s, 1H), 8.82 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 8.20 (s, 1H), 7.96 (d, *J* = 5.6 Hz, 1H), 7.88 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 4.73–4.69 (m, 2H), 4.48–4.44 (m, 1H), 4.32–4.29 (m, 2H), 4.15 (s, 2H), 3.78 (s, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.53–2.52 (m, 2H), 1.64–1.47 (m, 4H) ppm LCMS (AM3): rt = 0.729 min, (563.3 [M+H]$^+$), 100% purity Purification Method 99
Example 99	5-(3-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide	 3-chloro-4-(trifluoromethoxy)benzaldehyde	^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.96 (s, 1H), 8.75 (d, *J* = 5.6 Hz, 1H), 8.63 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 1.6 Hz, 1H), 7.98 (d, *J* = 5.6 Hz, 1H), 7.87 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.56 (s, 1H), 7.35 (s, 2H), 4.77–4.73 (m, 2H), 4.54–4.48 (m, 1H), 4.40–4.37 (m, 2H), 3.76 (s, 2H), 3.53 (t, *J* = 5.6 Hz, 2H), 2.62 (t, *J* = 6.8 Hz, 2H), 1.68–1.62 (m, 4H) ppm LCMS (AM3): rt = 0.765 min, (574.1 [M+H]$^+$), 96.2% purity Purification Method 100
Example 104	5-(3-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Chloro-5-formylphenyl)acetonitrile **1.366**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.13 (s, 1H), 8.82 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.20 (s, 1H), 7.96 (d, *J* = 5.6 Hz, 1H), 7.88 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.46 (s, 1H), 7.36 (s, 1H), 7.28 (s, 1H), 7.25 (s,1H), 4.73–4.69 (m, 2H), 4.48–4.44 (m, 1H), 4.32–4.29 (m, 2H), 4.04 (s, 2H), 3.68 (s, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.52–2.46 (m, 2H), 1.63–1.56 (quin, 2H), 1.53–1.45 (quin, 2H) ppm LCMS (AM3): rt = 0.730 min, (529.4 [M+H]$^+$), 100% purity Purification Method 105
Example 110	5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile **1.504**	^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.13 (s, 1H), 8.81 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.20 (s, 1H), 7.96 (d, *J* = 5.6 Hz, 1H), 7.88 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.46 (s, 1H), 7.36 (s, 1H), 7.29 (s, 1H), 7.18 (s, 1H), 4.73–4.69 (m, 2H), 4.48–4.44 (m, 1H), 4.32–4.29 (m, 2H), 4.10 (s, 2H), 3.73 (s, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.54–2.52 (m, 2H), 1.63–1.56 (quin, 2H), 1.53–1.46 (quin, 2H) ppm LCMS (AM3): rt = 0.744 min, (579.3 [M+H]$^+$), 98.1% purity Purification Method 110

Example 124	5-(3-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Chloro-5-(hydroxymethyl)benzaldehyde **1.102**	^1H NMR (400 MHz, MeOH-d_4) δ: 9.87 (s, 1H), 8.71 (d, *J* = 5.2 Hz, 1H), 8.54 (d, *J* = 8.8 Hz, 1H), 8.17 (d, *J* = 1.6 Hz, 1H), 7.89 (d, *J* = 5.6 Hz, 1H), 7.83 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.29 (s, 1H), 7.28 (s, 1H), 7.26 (s, 1H), 4.72-4.68 (m, 2H), 4.57 (s, 2H), 4.52-4.46 (m, 1H), 4.35-4.31 (m, 2H), 3.87 (s, 2H), 3.53 (t, *J* = 5.6 Hz, 2H), 2.77 (t, *J* = 6.8 Hz, 2H), 1.74-1.67 (m, 4H) ppm LCMS (AM3): rt = 0.692 min, (520.2 $[M+H]^+$), 98.6% purity Purification Method 124
Example 125	5-(3-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide	 3-Fluoro-5-(hydroxymethyl)benzaldehyde **1.500**	^1H NMR (400 MHz, MeOH-d_4) δ : 9.87 (s, 1H), 8.71 (d, *J* = 5.6 Hz, 1H), 8.55 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 1.6 Hz, 1H), 7.90 (d, *J* = 5.6 Hz, 1H), 7.83 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.12 (s, 1H), 7.00-6.96 (m, 2H), 4.72-4.68 (m, 2H), 4.58 (s, 2H), 4.52-4.46 (m, 1H), 4.36-4.32 (m, 2H), 3.79 (s, 2H), 3.53 (t, *J* = 5.6 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.69-1.66 (m, 4H) ppm LCMS (AM3): rt = 0.655 min, (504.3 $[M+H]^+$), 98.5% purity Purification Method 125
Example 126	5-(3-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Hydroxymethyl)-5-(trifluoromethyl)benzaldehyde **1.501**	^1H NMR (400 MHz, MeOH-d_4) δ: 9.98 (s, 1H), 8.76 (d, *J* = 5.6 Hz, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 1.6 Hz, 1H), 8.00 (d, *J* = 5.6 Hz, 1H), 7.88 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.58-7.55 (m, 3H), 4.78-4.74 (m, 2H), 4.67 (s, 2H), 4.54-4.49 (m, 1H), 4.40-4.36 (m, 2H), 3.83 (s, 2H), 3.53 (t, *J* = 5.6 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 1.69-1.65 (m, 4H) ppm LCMS (AM3): rt = 0.715 min, (554.3 $[M+H]^+$), 96.7% purity Purification Method 126
Example 127	5-(3-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Formyl-5-methylphenyl)acetonitrile **1.475**	^1H NMR (400 MHz, MeOH-d_4) δ: 9.93 (s, 1H), 8.75 (d, *J* = 5.6 Hz, 1H), 8.61 (d, *J* = 8.8 Hz, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 7.94 (d, *J* = 5.6 Hz, 1H), 7.86 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.17 (s, 2H), 7.12 (s, 1H), 4.75-4.71 (m, 2H), 4.54-4.48 (m, 1H), 4.36-4.33 (m, 2H), 3.93 (s, 2H), 3.84 (s, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 2H), 2.32 (s, 3H), 1.80-1.68 (m, 4H) ppm LCMS (AM3): rt = 0.660 min, (509.2 $[M+H]^+$), 100% purity Purification Method 127
Example 128	5-(3-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide	 2-(3-Fluoro-5-formylphenyl)acetonitrile **1.472**	^1H NMR (400 MHz, DMSO-d_6) δ: 10.13 (s, 1H), 8.82 (d, *J* = 5.6 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.22-8.20 (m, 2H), 7.96 (d, *J* = 5.6 Hz, 1H), 7.88 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.46 (s, 1H), 7.18-7.12 (m, 2H), 7.02 (d, *J* = 9.2 Hz, 1H), 4.73-4.69 (m, 2H), 4.48-4.44 (m, 1H), 4.32-4.29 (m, 2H), 4.04 (s, 2H), 3.70 (s, 2H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.53-2.51 (m, 2H), 1.62-1.56 (m, 2H), 1.55-1.47 (m, 2H) ppm LCMS (AM3): rt = 0.687 min, (513.3 $[M+H]^+$), 97.2% purity Purification Method 128

Example 86

(*S*)-5-((1-(4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid



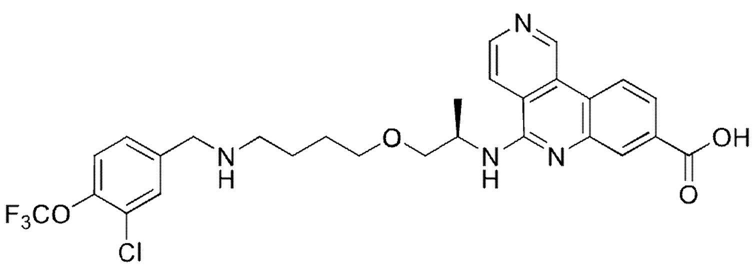
[00398] A mixture of **compound 1.625** (40 mg, 67.68 μmol) and lithium hydroxide monohydrate (8.52 mg, 203.04 μmol) in MeOH (0.5 mL), THF (1 mL) and H_2O (1 mL) was stirred at 15 °C for 12 h. The mixture was concentrated *in vacuo* and the residue was purified (PM121) to afford **Example 86** (16.58 mg, 42.2% yield, FA salt) as a yellow solid.

LCMS (AM3): rt = 0.688 min, (577.1 $[M+H]^+$), 99.25% purity.

^{1}H NMR (400 MHz, MeOH-*d*$_4$) δ : 9.93 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.55 (d, *J* = 8.4 Hz, 1H), 8.48 (br s, 1H), 8.28 (d, *J* =1.2 Hz, 1H), 8.21 (d, *J* = 5.6 Hz, 1H), 7.95 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.67 (s, 1H), 7.48 (s, 2H), 4.91–4.89 (m, 1H), 4.07 (s, 2H), 3.82–3.76 (m, 2H), 3.64–3.59 (m, 1H), 3.55–3.51 (m, 1H), 3.02 (t, *J* =7.2 Hz, 2H), 1.86–1.78 (m, 2H), 1.71–1.63 (m, 2H), 1.40 (d, *J* = 6.8 Hz, 3H) ppm.

Example 88

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid



[00399] A mixture of **compound 1.609** (0.15 g, 0.161 mmol) and lithium monohydrate (0.07 g, 1.67 mmol) in THF (3 mL) and H_2O (1.5 mL) was stirred at 35 °C for 20 h. The mixture was neutralized with TFA to pH 6 and the resulting mixture was then concentrated *in vacuo.* The residue was purified (PM194) and then basified with aqueous NaOH solution (1 N) to pH 8. The mixture was concentrated and re-purified (PM89) afford **Example 88** (35.73 mg, 61.92 μmol, 38.6% yield) as a yellow solid.

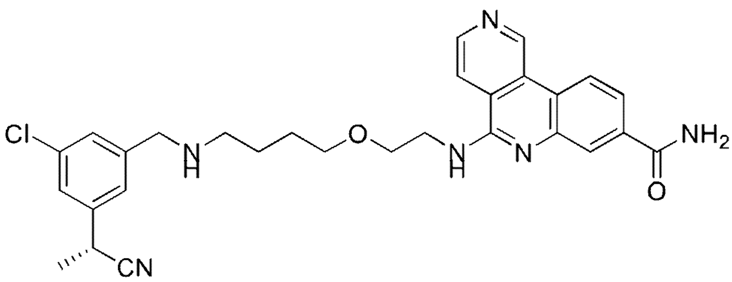
LCMS (AM3): rt = 0.800 min, (577.2 [M+H]$^+$), 99.1% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ : 9.84 (s, 1H), 8.69 (d, *J* = 5.6 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.12 (d, *J* = 6.0 Hz, 1 H), 7.89 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.46–7.38 (m, 2H), 4.83–4.76 (m, 1H), 3.99 (s, 2H), 3.74–3.66 (m, 2H), 3.58–3.53 (m, 1H), 3.50–3.46 (m, 1H), 2.96–2.89 (m, 2H), 1.81–1.74 (m, 2H), 1.67–1.59 (m, 2H), 1.35 (d, *J* = 6.8 Hz, 3H) ppm.

Examples 138 and 139 have been assigned the following stereochemical nomenclature but could be defined as either enantiomer as definitive stereochemistry has not been fully elucidated by analytical techniques.

Example 138

(R)-5-((2-(4-((3-chloro-5-(1-cyanoethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



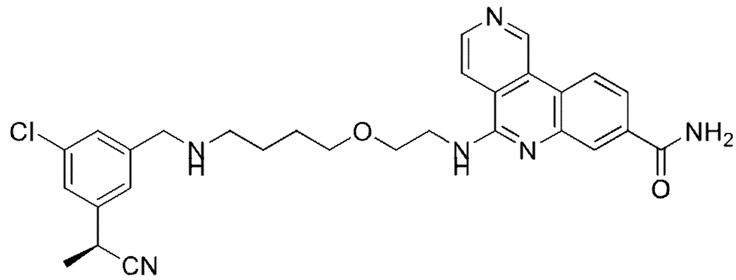
A mixture of **Intermediate E** (108.42 mg, 278.09 μmol), NaOAc (68.43 mg, 834.27 μmol) and **compound 1.837** (70 mg, 361.52 μmol) in MeOH (3 mL) was stirred at 25 °C for 12 h, then sodium cyanoborohydride (174.75 mg, 2.78 mmol) was added. The mixture was stirred at 25 °C for 2 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified (PM136) to afford **Example 138** (57.40 mg, 99.47 μmol, 35.8% yield, FA salt, 55% ee) as a yellow gum.

LCMS (AM3): rt = 0.755 min, (531.4 [M+H]$^+$), 96.9% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.91 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.59 (d, *J* = 8.8 Hz, 1H), 8.43 (br s, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 8.11 (d, *J* = 5.6 Hz, 1H), 7.81 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.48 (d, *J* = 1.6 Hz, 1H), 7.44 (s, 1H), 7.43 (s, 1H), 4.17 (q, *J* = 7.6 Hz, 1H), 4.10 (s, 2H), 3.91 (t, *J* = 5.6 Hz, 2H), 3.83 (t, *J* = 5.6 Hz, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.05 (t, *J* = 7.6 Hz, 2H), 1.84-1.77 (m, 2H), 1.75-1.66 (m, 2H), 1.60 (d, *J* = 7.2 Hz, 3H) ppm.

Example 139

(S)-5-((2-(4-((3-chloro-5-(1-cyanoethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



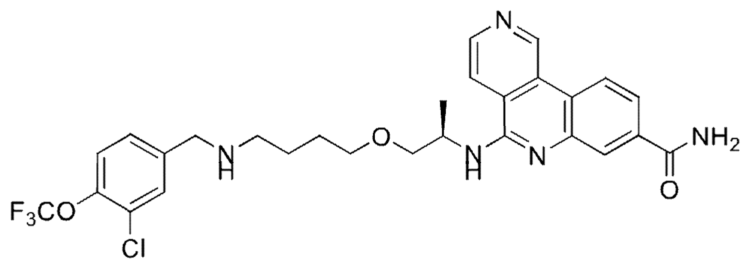
A mixture of **Intermediate E** (123.91mg, 317.82 µmol), NaOAc (78.21 mg, 953.45 µmol) and **compound 1.838** (80 mg, 413.16 µmol) in MeOH (3 mL) was stirred at 25 °C for 12 h, then sodium cyanoborohydride (199.72 mg, 3.18 mmol) was added. The mixture was stirred at 25 °C for 2 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified (PM136) to afford **Example 139** (57.27 mg, 99.24 µmol, 31.2% yield, FA salt, 69% ee) as a yellow solid.

LCMS (AM3): rt = 0.749 min, (531.4 $[M+H]^+$), 97.7% purity.

^1H NMR (400 MHz, MeOH-d_4) δ: 9.91 (s, 1H), 8.77 (d, *J* = 5.6 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.41 (br s, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 7.81 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.48 (d, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 7.43 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 1H), 4.10 (s, 2H), 3.91 (t, *J* = 5.6 Hz, 2H), 3.82 (t, *J* = 5.6 Hz, 2H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H), 1.85-1.77 (m, 2H), 1.73-1.66 (m, 2H), 1.60 (d, *J* = 7.2 Hz, 3H) ppm.

Example 141

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



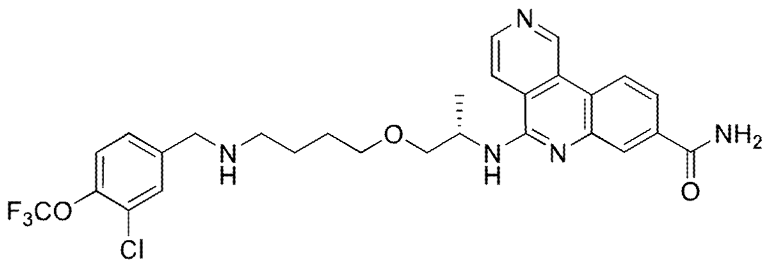
Compound 1.609 (90 mg, 152.28 μmol) in a solution of NH_3 in MeOH (10 mL, 7 M) was stirred at 90 °C in a 30 mL sealed tube for 12 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified (PM138) to afford **Example 141** (34.29 mg, 55.13 μmol, 36.2% yield, FA salt) as a yellow solid.

LCMS (AM3): rt = 0.762 min, (576.3 $[M+H]^+$), 100% purity.

^1H NMR (400 MHz, MeOH-d_4) δ: 9.92 (br s, 1H), 8.78 (d, *J* = 5.2 Hz, 1H), 8.60 (d, *J* = 8.4 Hz, 1H), 8.45 (br s, 1H), 8.21 (d, *J* = 5.6 Hz, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 7.81 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64 (d, *J* = 1.6 Hz, 1H), 7.47-7.40 (m, 2H), 4.85-4.83 (m, 1H), 4.07 (s, 2H), 3.77-3.73 (m, 1H), 3.70-3.53 (m, 3H), 3.02 (t, *J* = 7.6, 2H), 1.82-1.73 (quin, 2H), 1.72-1.63 (quin, 2H), 1.38 (d, *J* = 6.8 Hz, 3H) ppm.

Example 148

(S)-5-((1-(4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



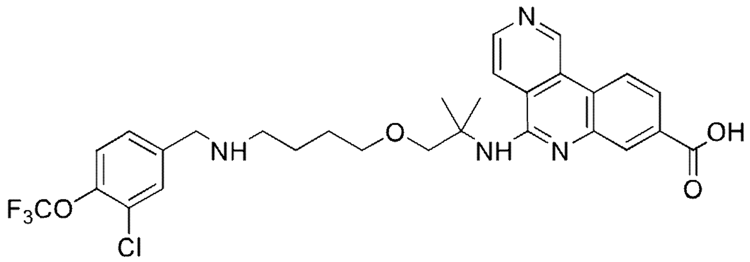
Compound 1.625 (300 mg, 0.47 mmol, FA salt) in a solution of NH_3 in MeOH (10 mL, 7 M) was stirred in a sealed tube at 100 °C for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM142) to afford **Example 148** (34.24 mg, 11.4% yield, FA salt) as a yellow gum.

LCMS (AM3): rt = 0.798 min, (576.2 $[M+H]^+$), 100% purity.

^1H NMR (400 MHz, MeOH-d_4) δ: 9.88 (s, 1H), 8.76 (d, *J* = 5.6 Hz, 1H), 8.55 (d, *J* = 8.4 Hz, 1H), 8.47 (br s, 1H), 8.19-8.16 (m, 2H), 7.79 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.65 (s, 1H), 7.47-7.43 (m, 2H), 4.85-4.80 (m, 1H), 4.08 (s, 2H), 3.77-3.73 (m, 1H), 3.68-3.54 (m, 3H), 3.03 (t, *J* = 7.6 Hz, 2H), 1.83-1.76 (quin, 2H), 1.73-1.67 (quin, 2H), 1.38 (d, *J* = 6.8 Hz, 3H) ppm.

Example 149

5-((1-(4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)-2-methylpropan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid



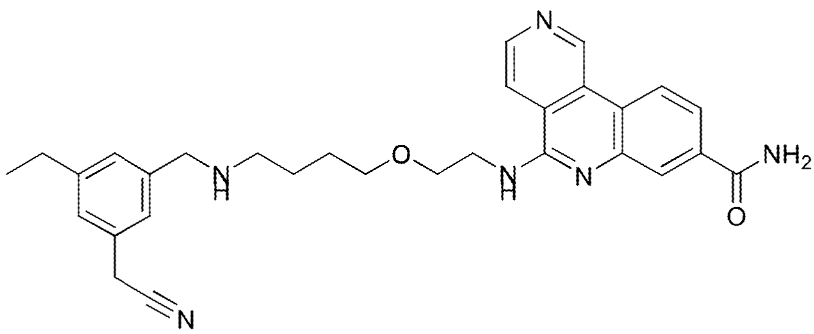
A mixture of **compound 1.734** (25 mg, 0.04 mmol, FA salt) and LiOH.H$_2$0 (17 mg, 0.41 mmol) in THF (2 mL) and H_2O (0.5 mL) was stirred at room temperature for 15 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM145) to afford **Example 149** (14.67 mg, 64.6% yield) as a white solid.

LCMS (AM3): rt = 0.824 min, (591.2 $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz, MeOH-*d$_4$*) δ: 9.86 (s, 1H), 8.72 (d, *J* = 6.0 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 8.26 (s, 1H), 8.08 (d, *J* = 5.6 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.48-7.46 (m, 1H), 7.44-7.41 (m, 1H), 4.01 (s, 2H), 3.97 (s, 2H), 3.54 (t, *J* = 5.6 Hz, 2H), 2.89 (t, *J* = 6.8 Hz, 2H), 1.72-1.60 (m, 4H), 1.60 (s, 6H) ppm.

Example 150

5-((2-(4-((3-(Cyanomethyl)-5-ethylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



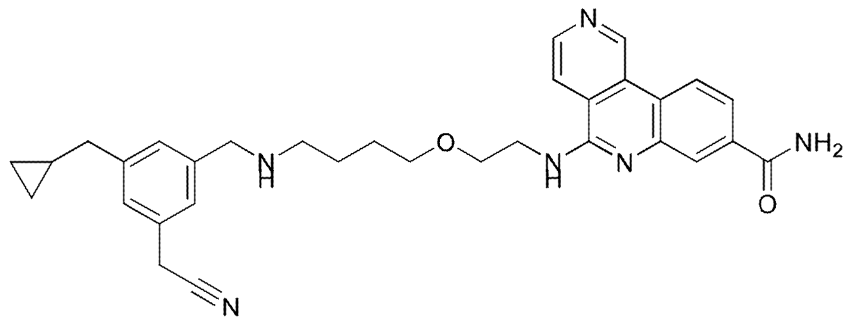
A mixture of **Intermediate E** (100 mg, 256.49 μmol, HCl salt), sodium acetate (63.12 mg, 769.47 μmol) and **compound 1.689** (44.43 mg, 256.49 μmol) in MeOH (3 mL) was stirred at 20 °C for 12 h, then sodium triacetoxyborohydride (163.08 mg, 769.47 μmol) was added. The reaction mixture was stirred at 20 °C for another 3 h. The reaction mixture was filtered and concentrated and the crude product was purified (PM146) to afford **Example 150** (36.44 mg, 71.36 µmol, 27.8% yield) as a yellow gum.

LCMS (AM3): rt = 0.666 min, (511.2 [M+H]$^+$), 96.6 % purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 10.06 (s, 1H), 8.85 (d, *J* = 5.6 Hz, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 5.6 Hz, 2H), 8.18 (br s, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 8.00 (t, *J* = 5.2 Hz, 1H), 7.81 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.42 (br s, 1H), 7.14 (br s, 2H), 7.08 (s, 1H), 3.97 (s, 2H), 3.79 (t, *J* = 5.6 Hz, 2H), 3.75 (s, 2H), 3.70 (t, *J* = 5.6 Hz, 2H), 3.46 (t, *J* = 5.6 Hz, 2H), 2.63-2.58 (m, 2H), 2.57-2.55 (m, 2H), 1.57-1.51 (br m, 4H), 1.15 (t, *J* = 7.6 Hz, 3H) ppm.

Example 151

5-((2-(4-((3-(Cyanomethyl)-5-(cyclopropylmethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



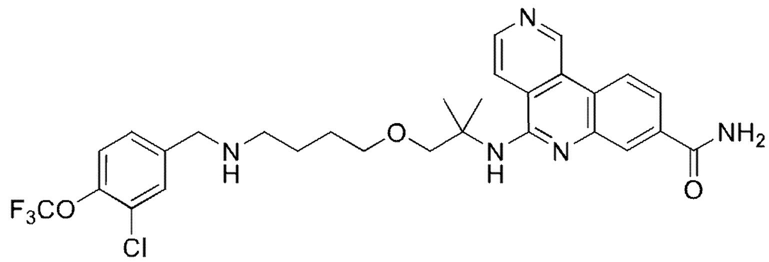
A mixture of **Intermediate E** (100 mg, 256.49 µmol, HCl salt), sodium acetate (63.12 mg, 769.47 µmol) and **compound 1.697** (51.11 mg, 256.49 µmol) was stirred at 20 °C for 5 h, then sodium triacetoxyborohydride (163.08 mg, 769.47 µmol) was added. The reaction mixture was stirred at 20 °C for another 0.4 h. The reaction mixture was filtered and concentrated *in vacuo* to give the crude product that was purified (PM147) to afford **Example 151** (54.59 mg, 93.69 µmol, 36.5% yield, FA salt) as a yellow oil.

LCMS (AM3): rt = 0.748 min, (537.1 [M+H]$^+$), 98.9 % purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.06 (s, 1H), 8.85 (d, *J* = 5.6 Hz, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.28-8.26 (m, 2H), 8.19 (br s, 1H), 8.14 (d, *J* = 1.6 Hz, 1H), 8.00 (t, *J* = 4.8 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.43 (br s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.09 (s, 1H), 3.99 (s, 2H), 3.78 (t, *J* = 5.2 Hz, 2H), 3.75 (s, 2H), 3.70 (t, *J* = 5.2 Hz, 2H), 3.46 (t, *J* = 5.2 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 2H), 2.50-2.46 (m, 2H), 1.55-1.50 (m, 4H), 0.96-0.88 (m, 1H), 0.47-0.42 (q, 2H), 0.18-0.14 (q, 2H) ppm.

Example 152

5-((1-(4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)-2-methylpropan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



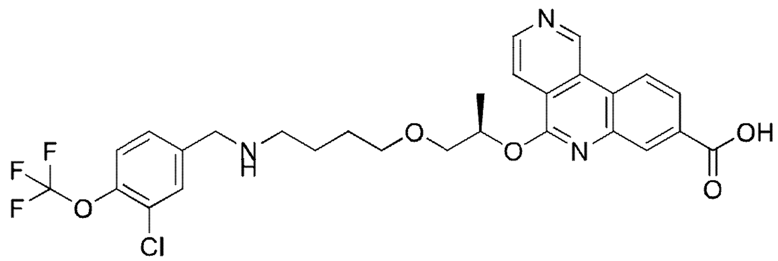
Compound 1.734 (10 mg, 0.017 mmol, FA salt) in a solution of NH_3 in MeOH (10 mL, 7 M) was stirred in a sealed tube at 90 °C for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM148) to afford **Example 152** (4.12 mg, 39.2% yield, FA salt) as an off-white solid.

LCMS (AM3): rt = 0.804 min, (590.2 $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz, MeOH-*d₄*) δ: 9.92 (s, 1H), 8.76 (d, *J* = 6.0 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.52 (br s, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.14 (d, *J* = 5.6 Hz, 1H), 7.84 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.43-7.40 (m, 1H), 7.35-7.32 (m, 1H), 3.99 (s, 2H), 3.79 (s, 2H), 3.52 (t, *J* = 5.6 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 1.63 (s, 6H), 1.60-1.55 (m, 4H) ppm.

Example 154

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid



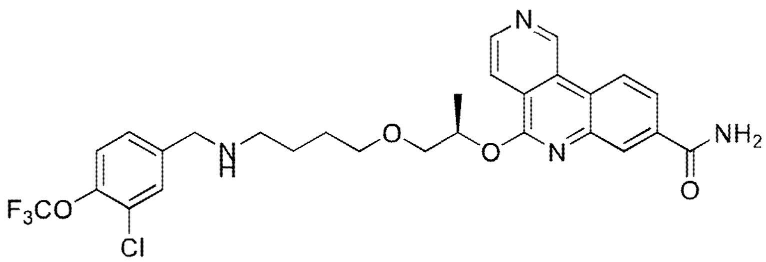
A mixture of **compound 1.782** (67 mg, 0.1 mmol) in a solution of HCl in 1,4-dioxane (10 mL, 2 M) was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by (PM151) to afford **Example 154** (21.5 mg, 37.7% yield) as a white solid.

LCMS (AM3): rt = 0.883 min, (578.2 $[M+H]^+$), 100% purity.

[1]H NMR (400 MHz, MeOH-d_4) δ: 9.96 (s, 1H), 8.79 (d, *J* = 5.6 Hz, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 8.39 (d, *J* = 1.6 Hz, 1 H), 8.16 (d, *J* = 5.6 Hz, 1 H), 8.11 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.65 (s, 1H), 7.47-7.42 (m, 2H), 5.96-5.88 (m, 1H), 4.02 (s, 2H), 3.87-3.83 (m, 1H), 3.76-3.67 (m, 2H), 3.61-3.55 (m, 1H), 2.94 (t, *J* = 7.6 Hz, 2H), 1.79-1.72 (m, 2H), 1.69-1.53 (m, 2H), 1.48 (d, *J* = 6.4 Hz, 3H) ppm.

Example 155

(R)-5-((1-(4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxamide



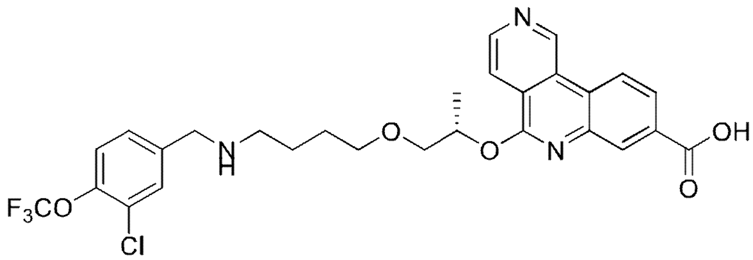
A mixture of 3-chloro-4-(trifluoromethoxy)benzaldehyde (140 mg, 0.62 mmol), **compound 1.729** (250 mg, 0.62 mmol, HCl salt) and DIPEA (0.5 mL, 2.87 mmol) in MeOH (10 mL) was stirred at room temperature for 16 h, then sodium triacetoxyborohydride (522 mg, 2.46 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM152) to afford **Example 155** (36.72 mg, 10.2% yield) as a white solid.

LCMS (AM3): rt = 0.846 min, (577.2 $[M+H]^+$), 98.9% purity.

[1]H NMR (400 MHz, MeOH-d_4) δ: 9.94 (s, 1H), 8.81 (d, *J* = 5.6 Hz, 1H), 8.68 (d, *J* = 8.4 Hz, 1H), 8.33 (d, *J* = 1.6 Hz, 1 H), 8.16 (d, *J* = 5.6 Hz, 1 H), 8.00 (dd, *J* = 8.4 Hz, 2.0 Hz, 1 H), 7.45 (d, *J* = 2.0 Hz, 1 H), 7.31-7.22 (m, 2H), 5.88-5.81 (m, 1H), 3.86-3.82 (m, 1H), 3.77-3.73 (m, 1H), 3.66-3.54 (m, 4H), 2.53 (t, *J* = 7.2 Hz, 2H), 1.62-1.54 (m, 4 H), 1.50 (d, *J* = 6.4 Hz, 3H) ppm.

Example 166

(S)-5-((1-(4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid



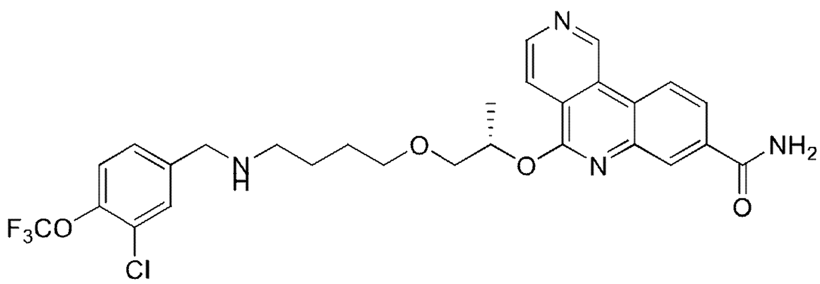
To a solution of **compound 1.681** (50 mg, 84.46 μmol) in H_2O (1 mL) and THF (1 mL) was added LiOH.H_2O (14.18 mg, 337.84 μmol) at 20 °C. The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was neutralized with formic acid and concentrated *in vacuo.* The crude product was purified (PM161) to afford **Example 166** (19.83 mg, 34.31 μmol, 40.6% yield) as a yellow gum.

LCMS (AM3): rt = 0.851 min, (578.0 $[M+H]^+$), 95.4% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.94 (s, 1H), 8.78 (d, *J* = 5.6 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.39 (d, *J* = 1.2 Hz, 1H), 8.14 (d, *J* = 5.6 Hz, 1H), 8.10 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.63 (s, 1H), 7.43 (s, 2H), 5.93-5.85 (m, 1H), 3.99 (s, 2H), 3.86-3.80 (m, 1H), 3.75-3.67 (m, 2H), 3.60-3.55 (m, 1H), 2.90 (t, *J* = 7.6 Hz, 2H), 1.78-1.70 (quin, 2H), 1.68-1.52 (m, 2H), 1.47 (d, *J* = 6.4 Hz, 3H) ppm.

Example 167

(S)-5-((1-(4-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxamide



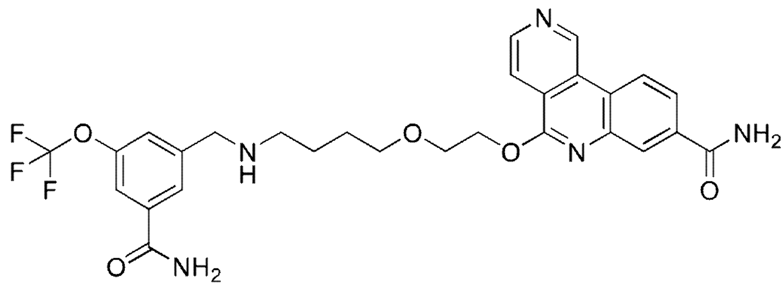
Compound 1.681 (100 mg, 168.92 μmol) in a solution of NH_3 in MeOH (10 mL, 7 M) was stirred in a 30 mL sealed tube at 80 °C for 12 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified (PM162) to afford **Example 167** (28.11 mg, 45.12 μmol, 26.7% yield, FA salt) as a yellow solid.

LCMS (AM3): rt = 0.826 min, (577.0 [M+H]$^+$), 100% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.03 (s, 1H), 8.86 (d, J = 5.6 Hz, 1H), 8.77 (d, J = 8.4 Hz, 1H), 8.48 (br s, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.22 (d, J = 5.2 Hz, 1H), 8.05 (dd, J = 8.4, 1.6 Hz, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.47-7.40 (m, 2H), 5.95-5.86 (m, 1H), 4.04 (s, 2H), 3.89-3.84 (m, 1H), 3.81-3.74 (m, 1H), 3.71-3.66 (m, 1H), 3.63-3.58 (m, 1H), 2.96 (t, J = 7.6 Hz, 2H), 1.78-1.70 (m, 2H), 1.70-1.61 (m, 2H), 1.51 (d, J = 6.4 Hz, 3H) ppm.

Example 169

5-(2-(4-((3-Carbamoyl-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide



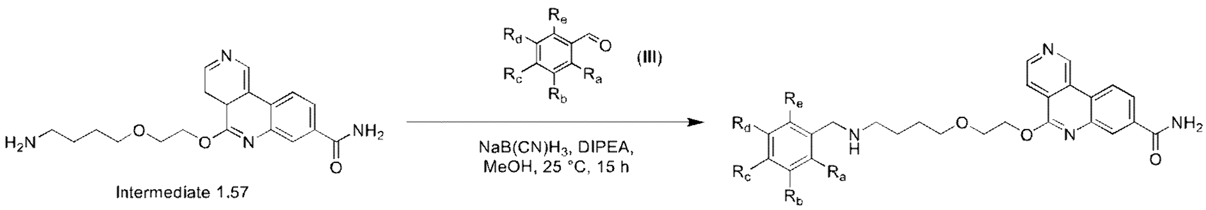
A mixture of **compound 1.57** (223.28 mg, 557.60 μmol, FA salt), DIPEA (216.20 mg, 1.67 mmol) and **compound 1.675** (130 mg, 557.60 μmol) in MeOH (3 mL) was stirred at 20 °C for 12 h, then sodium cyanoborohydride (105.12 mg, 1.67 mmol) was added. The reaction mixture was stirred at 20 °C for 0.5 h. The reaction mixture was filtered and concentrated to give the crude product that was purified (PM163) to afford **Example 169** (123.81 mg, 216.62 μmol, 38.9% yield) as a white solid.

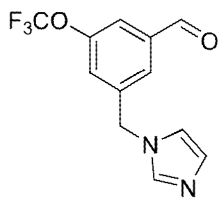
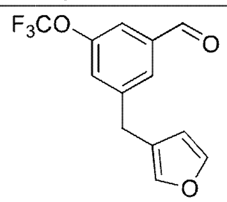
LCMS (AM3): rt = 0.872 min, (572.2 [M+H]$^+$), 100 % purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.93 (s, 1H), 8.81 (d, J = 5.6 Hz, 1H), 8.67 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 1.6 Hz, 1H), 8.15 (dd, J = 5.6, 0.8 Hz, 1H), 8.00 (dd, J = 8.4, 1.6 Hz, 1H), 7.79 (s, 1H), 7.63 (br s, 1H), 7.41 (br s, 1H), 4.78 (t, J = 4.4 Hz, 2H), 3.96 (t, J = 4.8 Hz, 2H), 3.76 (s, 2H), 3.63 (t, J = 5.6 Hz, 2H), 2.59 (t, J = 7.2 Hz, 2H), 1.68-1.58 (m, 4H) ppm.

The following examples in Table 11 were made with non-critical changes or substitutions to the exemplified procedure in Example 169, that would be understood by one skilled in the art using intermediate 1.57 and compounds of formula (III).

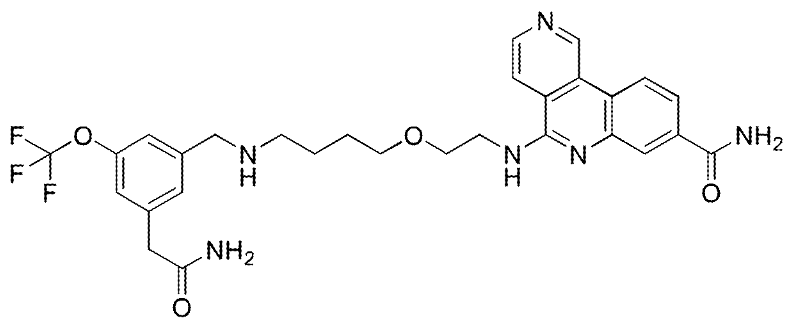
Table 11



Example No.	Chemical IUPAC name	Compound (III)	Analytical
Example 174	5-(2-(4-((3-((1H-imidazol-1-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-((1H-imidazol-1-yl)methyl)-5-(trifluoromethoxy)benzaldehyde **1.825**	[1]H NMR (400 MHz, MeOH-d_4) δ: 9.79 (s, 1H), 8.73 (d, *J* = 5.6 Hz, 1H), 8.53 (d, *J* = 8.8 Hz, 1H), 8.21 (d, *J* = 1.6 Hz, 1H), 8.04 (d, *J* = 5.6 Hz, 1H), 7.92 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.76 (s, 1H), 7.16 (d, *J* = 5.6 Hz, 2H), 7.11 (t, *J* = 1.6 Hz, 1H), 6.98 (s, 2H), 5.22 (s, 2H), 4.71 (t, *J* = 4.8 Hz, 2H), 3.94 (t, *J* = 4.8 Hz, 2H), 3.67 (s, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 2.55 (t, *J* = 6.8 Hz, 2H), 1.65-1.57 (m, 4H) ppm LCMS (AM7): rt = 0.980 min, (609.3 $[M+H]^+$), 99.6% purity Purification Method 153
Example 176	5-(2-(4-((3-(furan-3-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide	 3-(Furan-3-ylmethyl)-5-(trifluoromethoxy)benzaldehyde **1.826**	[1]H NMR (400 MHz, MeOH-d_4) δ: 9.92 (s, 1H), 8.80 (d, *J* = 5.6 Hz, 1H), 8.65 (d, *J* = 8.8 Hz, 1H), 8.43 (s, 1H), 8.32 (d, *J* = 1.6 Hz, 1H), 8.12 (dd, *J* = 5.2, 0.4 Hz, 1H), 8.00 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.41 (t, *J* = 1.6 Hz, 1H), 7.33 (s, 1H), 7.30 (s, 1H), 7.24 (s, 1H), 7.17 (s, 1H), 6.24 (d, *J* = 0.8 Hz, 1H), 4.78-4.76 (m, 2H), 4.13 (s, 2H), 3.98 (t, *J* = 4.8 Hz, 2H), 3.81 (s, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H), 1.88-1.79 (m, 2H), 1.75-1.66 (m, 2H) ppm LCMS (AM3): rt = 0.859 min, (609.3 [M+H] +), 99.3% purity Purification Method 170

Example 170

5-((2-(4-((3-(2-Amino-2-oxoethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



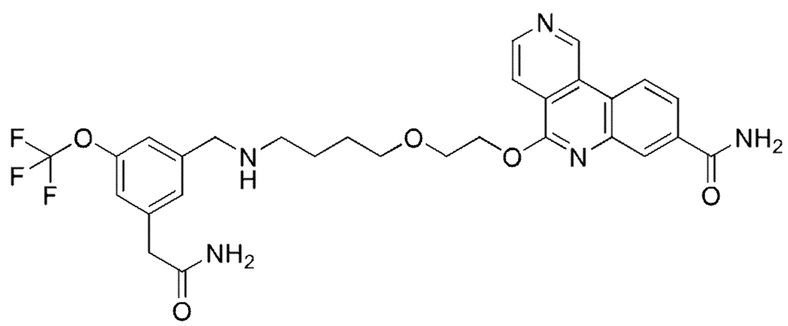
To a mixture of **Example 89** (160 mg, 282.40 μmol) and K_2CO_3 (19.51 mg, 141.20 μmol) in MeOH (1 mL) was added H_2O_2 (0.108 g, 1.11 mmol, 35% wt.) slowly at 20 °C. The reaction mixture was stirred at 20 °C for 2 h. The reaction was quenched with sat. aq. Na_2SO_3 solution (0.5 mL), then the mixture was filtered and the filtrate was purified (PM164); and then re-purified (PM117) to afford **Example 170** (34.19 mg, 58.49 μmol, 20.7% yield) as a white solid.

LCMS (AM7): rt = 0.855 min, (585.3 $[M+H]^+$), 96.9% purity.

^1H NMR (400 MHz, MeOH-d_4) δ: 9.89 (d, *J* = 8.0 Hz, 1H), 8.76-8.74 (m, 1H), 8.57 (t, *J* = 7.6 Hz, 1H), 8.20-8.18 (m, 1H), 8.11 (t, *J* = 5.6 Hz, 1H), 7.83-7.80 (m, 1H), 7.22 (s, 1H), 7.13 (s, 2H), 3.91-3.87 (m, 2H), 3.88 (t, *J* = 5.6 Hz, 2H), 3.70 (s, 2H), 3.56 (t, *J* = 5.6 Hz, 2H), 3.53 (s, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 1.63-1.57 (m, 4H) ppm.

Example 171

5-(2-(4-((3-(2-Amino-2-oxoethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide



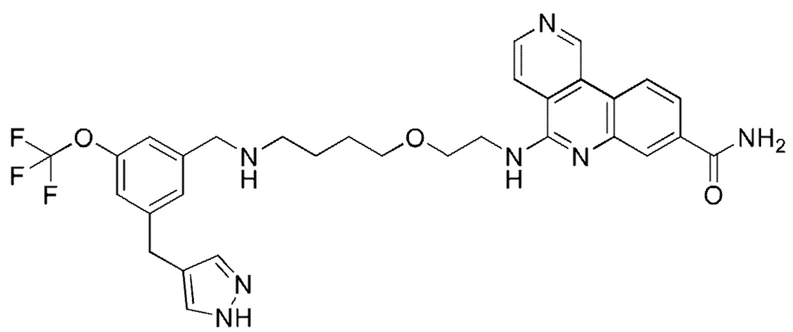
To a mixture of **Example 107** (130 mg, 229.05 μmol) and K_2CO_3 (15.83 mg, 114.53 μmol) in MeOH (2 mL) was added H_2O_2 (0.050 g, 440.99 μmol, 30% wt.) slowly at 20 °C. The reaction mixture was stirred at 20 °C for 2 h. The reaction was quenched with sat. aq. Na_2SO_3 solution (1 mL) slowly and then the mixture was concentrated *in vacuo*. The crude product was purified (PM165) and re-purified (PM166) to afford **Example 171** (16.06 mg, 25.21 μmol, 11.0% yield, FA salt) as an off-white gum.

LCMS (AM3): rt = 0.758 min, (586.1 $[M+H]^+$), 99.1 % purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.05 (s, 1H), 8.87 (d, *J* = 5.2 Hz, 1H), 8.80 (d, *J* = 8.4 Hz, 1H), 8.49 (s, 1H), 8.43 (d, *J* = 1.6 Hz, 1H), 8.24 (dd, *J* = 5.6, 0.8 Hz, 1H), 8.07 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.34 (s, 1H), 7.27 (s, 2H), 4.85-4.84 (m, 2H), 4.10 (s, 2H), 4.00 (t, *J* = 4.8 Hz, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.58 (s, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 1.86-1.77 (m, 2H), 1.76-1.67 (m, 2H) ppm.

Example 175

5-((2-(4-((3-((1H-pyrazol-4-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide



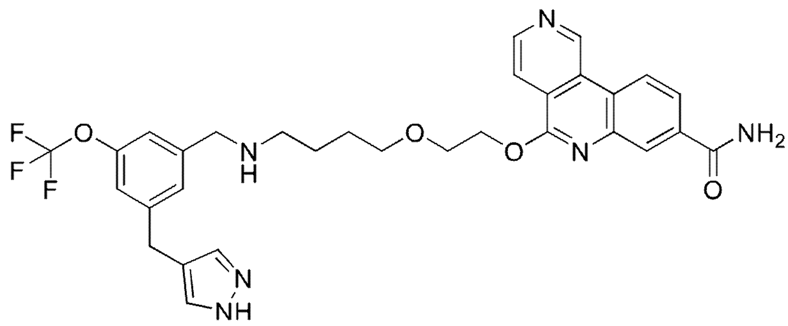
To a solution of **compound 1.828** (100 mg, 141.29 μmol) in DCM (2 mL) was added TFA (1.54 g, 13.51 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 0.5 h. The mixture was concentrated *in vacuo* and purified (PM169) to afford **Example 175** (73.97 mg, 113.16 μmol, 80.1% yield, FA salt) as a yellow solid.

LCMS (AM3): rt = 0.748 min, (608.1 $[M+H]^+$), 98.9% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.92 (s, 1H), 8.77 (d, *J* = 6.0 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.35 (br s, 1H), 8.20 (d, *J* = 2.0 Hz, 1H), 8.12 (d, *J* = 5.6 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.44 (s, 2H), 7.27 (s, 1H), 7.20 (d, *J* = 2.4 Hz, 2H), 4.09 (s, 2H), 3.93-3.90 (m, 4H), 3.81 (t, *J* = 5.2 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.8 Hz, 2H), 1.85-1.76 (m, 2H), 1.73-1.64 (m, 2H) ppm.

Example 177

5-(2-(4-((3-((1H-pyrazol-4-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide



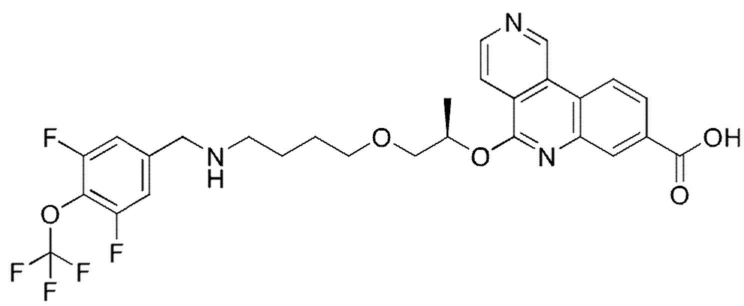
To a solution of **compound 1.829** (130 mg, 183.43 μmol) in MeOH (1.5 mL) was added K_2CO_3 (76.05 mg, 550.28 μmol) at 20 °C. The reaction mixture was stirred at 20 °C for 1 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified (PM166) to afford **Example 177** (69.34 mg, 103.92 μmol, 56.7% yield, FA salt) as a white solid.

LCMS (AM3): rt = 0.816 min, (609.3 $[M+H]^+$), 95.7% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.03 (s, 1H), 8.85 (d, *J* = 5.6 Hz, 1H), 8.78 (d, *J* = 8.4 Hz, 1H), 8.50 (s, 1H), 8.40 (d, *J* = 1.6 Hz, 1H), 8.22 (d, *J* = 5.6 Hz, 1H), 8.06 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.43 (s, 2H), 7.27 (s, 1H), 7.20 (s, 1H), 7.17 (s, 1H), 4.84-4.82 (m, 2H), 4.07 (s, 2H), 3.99 (t, *J* = 4.8 Hz, 2H), 3.90 (s, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 1.84-1.76 (m, 2H), 1.74-1.66 (m, 2H) ppm.

Example 179

(R)-5-((1-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid



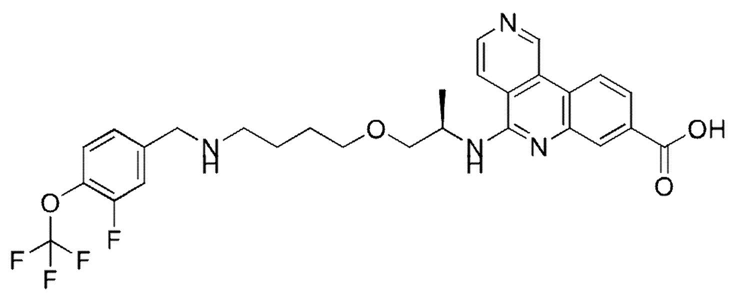
A mixture of **compound 1.507** (120 mg, 0.53 mmol), **compound 1.832** (220 mg, 0.53 mmol, FA salt) and DIPEA (0.19 mL, 1.06 mmol) in MeOH (10 mL) was stirred at room temperature for 16 h, then sodium triacetoxyborohydride (450 mg, 2.12 mmol) was added. The reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM173) to afford **Example 179** (138.28 mg, 41.7% yield, FA salt) as a white solid.

LCMS (AM3): rt = 0.861 min, (580.2 $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.91 (d, *J* = 2.4 Hz, 1H), 8.77 (dd, *J* = 5.6 Hz, 1.6 Hz, 1H), 8.59 (dd, *J* = 8.4 Hz, 3.6 Hz, 1H), 8.45 (s, 1H), 8.37 (s, 1H), 8.12-8.07 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.89-5.81 (m, 1H), 4.07 (s, 2H), 3.85-3.81 (m, 1H), 3.74-3.68 (m, 2H), 3.62-3.56 (m, 1H), 2.96 (t, *J* = 7.6 Hz, 2H), 1.82-1.73 (quin, 2H), 1.70-1.58 (m, 2H), 1.47 (d, *J* = 6.4 Hz, 3H) ppm.

Example 180

(R)-5-((1-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid



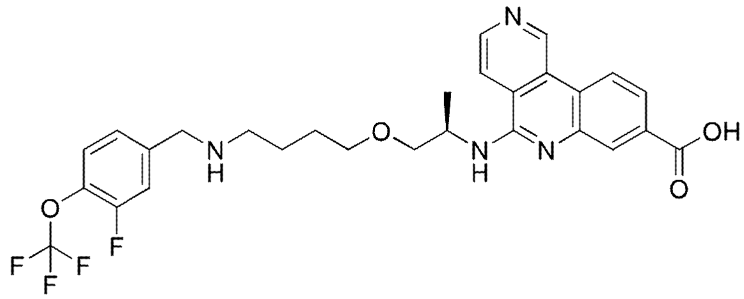
A mixture of 3-fluoro-4-(trifluoromethoxy)benzaldehyde (115 mg, 0.55 mmol), **compound 1.832** (230 mg, 0.55 mmol, TFA salt) and DIPEA (0.19 mL, 1.11 mmol) in MeOH (10 mL) was stirred at room temperature for 16 h, then sodium triacetoxyborohydride (469 mg, 2.21 mmol) was added. The reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM174) to afford **Example 180** (150.91 mg, 44.9% yield, FA salt) as an off-white solid.

LCMS (AM3): rt = 0.858 min, (562.2 $[M+H]^+$), 99.8% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.89 (s, 1H), 8.76 (d, *J* = 5.6 Hz, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 8.47 (s, 1H), 8.35 (d, *J* = 1.2 Hz, 1H), 8.09-8.06 (m, 2H), 7.48-7.43 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1 H), 5.87-5.80 (m, 1H), 4.10 (s, 2H), 3.84-3.80 (m, 1H), 3.74-3.66 (m, 2H), 3.61-3.55 (m, 1H), 3.00 (t, *J* = 7.6 Hz, 2H), 1.83-1.76 (m, 2H), 1.70-1.56 (m, 2H), 1.46 (d, *J* = 6.4 Hz, 3H) ppm.

Example 181

(R)-5-((1-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid



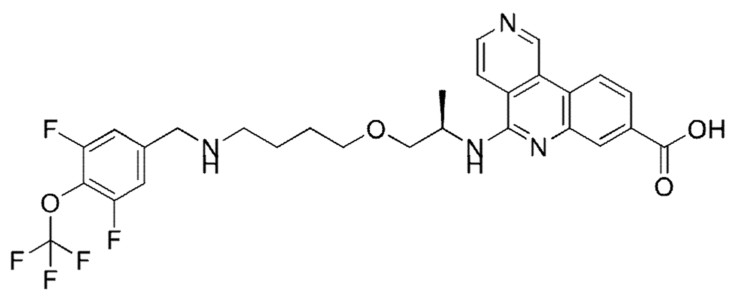
A mixture of **compound 1.831** (130 mg, 0.21 mmol, FA salt) and lithium hydroxide monohydrate (53 mg, 1.26 mmol) in THF (4 mL) and H_2O (1 mL) was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified (PM166) to afford **Example 181** (89.54 mg, 70.5% yield, FA salt) as a yellow solid.

LCMS (AM3): rt = 0.781 min, (561.5 $[M+H]^+$), 100% purity.

^1H NMR (400 MHz, MeOH-d_4) δ: 9.90 (s, 1H), 8.74 (d, J = 5.6 Hz, 1H), 8.53 (d, J = 8.4 Hz, 1 H), 8.43 (s, 1H), 8.26 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 6.0 Hz, 1H), 7.92 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.48-7.42 (m, 2H), 7.32 (d, J = 8.4 Hz, 1H), 4.86-4.85 (m, 1H), 4.08 (s, 2H), 3.78-3.71 (m, 2H), 3.63-3.56 (m, 1H), 3.53-3.47 (m, 1H), 3.01 (t, J = 7.6 Hz, 2H), 1.85-1.76 (m, 2H), 1.70-1.61 (m, 2H), 1.37 (d, J = 6.4 Hz, 3H) ppm.

Example 182

(R)-5-((1-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid



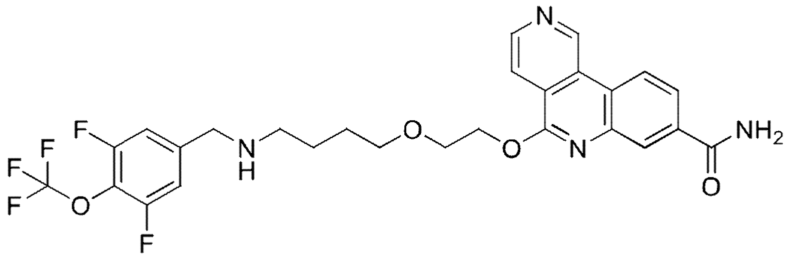
To a solution of **compound 1.830** (100 mg, 168.76 µmol) in THF (2 mL) and H_2O (1.5 mL) was added $LiOH.H_2O$ (35.41 mg, 843.80 µmol) at 20 °C. The reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was neutralized with formic acid to pH = 6, then the mixture was concentrated *in vacuo* and the crude product was purified (PM172) to afford **Example 182** (42.30 mg, 73.12 μmol, 43.3% yield) as a yellow solid.

LCMS (AM3): rt = 0.792 min, (579.1 $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.03 (s, 1H), 8.85 (d, *J* = 6.0 Hz, 1H), 8.66 (d, *J* = 8.8 Hz, 1H), 8.35 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 1.2 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 4.74-4.67 (m, 1H), 3.66-3.62 (m, 3H), 3.47 (t, *J* = 6.4 Hz, 2H), 3.44-3.39 (m, 1H), 2.42 (t, *J* = 6.8 Hz, 2H), 1.56-1.49 (m, 2H), 1.49-1.41 (m, 2H), 1.30 (d, *J* = 6.4 Hz, 3H) ppm.

Example 183

5-(2-(4-((3,5-Difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide



To a solution of **compound 1.840** (80.00 mg, 120.37 μmol) in DCM (1 mL) was added TFA (770.00 mg, 6.75 mmol) at 20 °C. The resulting mixture was stirred at 20 °C for 2 h. The mixture was concentrated *in vacuo* to give a residue. The crude product was purified (PM158) to afford **Example 183** (43.31 mg, 74.80 μmol, 62.2% yield) as white solid.

LCMS (AM3): rt = 0.819 min, (565.2 $[M+H]^+$), 97.6% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 10.04 (s, 1H), 8.87 (d, *J* = 5.2 Hz, 1H), 8.79 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 8.23 (d, *J* = 5.2 Hz, 1H), 8.08 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.87 - 4.85 (m, 2H), 4.17 (s, 2H), 4.02 (t, *J* = 4.8 Hz, 2H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.09 (t, *J* = 8.0 Hz, 2H), 1.88 - 1.81 (m, 2H), 1.77 - 1.71 (m, 2H) ppm.

Biological assays

Assay 1: Biochemical assay for inhibitors of CK2α kinase activity

[00400] The inhibitory activity of putative kinase inhibitors and the potency of selected compounds were determined using ADP-Glo™ assay. The kinase reaction was performed in the presence of excess peptide substrate and ATP at a concentration equivalent to K_m. Upon termination of the kinase reaction, remaining ATP was depleted leaving only ADP reaction product, which was converted back to ATP with a coupled luciferin/luciferase reaction. The luminescent output from the coupled reaction was quantified and correlated with the kinase activity.

[00401] CK2α (residues 2-329) was produced in Escherichia coli BL21 (DE3) for kinase activity screening. Single colonies of the cells were grown in 6x1 L of 2xTY with 100 µg/mL ampicillin at 37 °C. Isopropyl thio-β-D-galactopyranoside (IPTG) was added to a final concentration of 0.4 mM to induce expression when the optical density at 600 nm reached 0.6. The cells were incubated overnight at 25 °C then harvested by centrifugation at 4,000 g for 20 minutes. The cell pellets were suspended in 20 mM Tris, 500 mM NaCl, pH 8.0 and lysed using a high pressure homogenizer. Protease inhibitor cocktail tablets (one tablet per 50 mL extract; Roche Diagnostics) and DNase I were then added. The crude cell extract was then centrifuged at 10,000 g for 45 minutes, the supernatant was filtered with a 0.22 µm filter. The soluble supernatant was applied on a Ni Sepharose Fast Flow6 column at pH 8.0, washed and eluted in 20 mM Tris pH 8.0, 500 mM NaCl, 200 mM imidazole. After overnight dialysis into 20 mM Tris, pH 8.0, 500 mM NaCl the N-terminal His6-tag was cleaved overnight by TEV protease and passed through a second metal affinity column to remove uncleaved protein and the protease. The cleaved protein was further purified on a Sepharose Q HP anion-exchange column and the main peak fraction from this column was further purified by gel filtration on a Superdex 75 16/60 HiPrep column equilibrated with Tris 20 mM, pH 8.0, 500 mM NaCl. Pure protein was concentrated to 15 mg/mL and flash frozen in liquid nitrogen.

[00402] Final assay conditions comprised 0.2 nM CK2α, 50 µM peptide substrate (RRRADDSDDDDD), 15 µM ATP in 1x reaction buffer (40 mM Tris pH7.5, 200 mM NaCl, 20 mM $MgCl_2$, 0.1 mg/mL BSA, 1% DMSO). The assay was conducted as follows:

1. Appropriate serial dilutions of test compound were prepared using Echo (Labcyte) and 50 nL of 100x compound in 100% DMSO transferred to the assay plate (white opaque OptiPlate-384, Perkin-Elmer).
2. Enzyme and peptide substrate were prepared in fresh reaction buffer and added to the assay plate in a total volume of 3 µl and incubated at room temperature for 15 minutes.
3. 2 µL of ATP solution freshly prepared in reaction buffer was added to start the reaction.
4. After 120 minutes, the reaction was stopped by addition of 5 µl ADP-Glo reagent (Promega V9102) and the plate incubated at room temperature for a further 60 minutes.
5. 10 µL of Kinase Detection reagent (Promega V9102) was added to assay plate and incubated for a further 30 minutes prior to reading luminescence on an Envision (Perkin-Elmer).

Data was analysed to calculate compound IC_{50} and K_i as follows:

1. All assay plates contained 32 wells designated as 0% inhibition control wells, which were treated with vehicle only (1% DMSO) and 32 wells designated as 100% inhibition control wells, which were treated with a high concentration of non-specific kinase inhibitor in 1% DMSO.
2. Percent inhibition in each test well was calculated using the formula ($MEAN_{0\%inhibition\ control\ wells}$ – test well reading) / ($MEAN_{0\%inhibition\ control\ wells}$ – $MEAN_{100\%inhibition\ control\ wells}$) X 100%.
3. IC_{50} was determined using a standard 4-parameter fit method (Model 205, XL-fit).
4. Percent activity was calculated for each well using: (Test well reading – $MEAN_{100\%inhibition\ control\ wells}$) / ($MEAN_{0\%inhibition\ control\ wells}$ – $MEAN_{100\%inhibition\ control\ wells}$).
5. Morrison K_i was determined using Morrison K_i equation (XL-fit).

Assay 2: Biochemical assay for inhibitors of CLK2 kinase activity

[00403] The assay was conducted in the same way as described for CK2α, with final assay conditions comprising 20 nM CLK2 (Carna Biosciences-04-127), 50 µM peptide substrate (KRRRLASLR), 100 µM ATP in 1x reaction buffer (40 mM Tris pH7.5, 200 mM NaCl, 20 mM MgCl2, 0.1 mg/mL BSA, 1% DMSO).

Assay 3: Cell-based NanoBRET™ assay for inhibitor binding to intracellular CK2α

[00404] This assay used the NanoBRET™ System (Promega), an energy transfer technique designed to measure molecular proximity in living cells. The assay measured the apparent affinity of test compounds by competitive displacement of a NanoBRET™ tracer reversibly bound to a NanoLucR luciferase CK2α fusion protein in cells. A fixed concentration of tracer was added to cells expressing the desired NanoLucR-CK2α fusion protein to generate a BRET reporter complex. Introduction of competing compounds resulted in a dose-dependent decrease in NanoBRET™ energy transfer, which allowed quantitation of the apparent intracellular affinity of the target protein for the test compound.

[00405] The assay was conducted as follows using HCT116 cell line (ATCC CCL-247™) transiently transfected with CSNK2A2-NanoLuc® Fusion Vector (Promega NV1191):

1. Cells were resuspended to $2x10^5$ cells/mL in Opti-MEM (Invitrogen 11058021).
2. DNA complex was prepared in a final volume of 1.4 ml Opti-MEM containing 15 µg DNA and 42 µl FuGENE HD Transfection reagent (Promega E2311).

3. 20 ml cell suspension was combined with 1 ml DNA complex, added to T75 flask and incubated overnight at 37°C in 5% CO_2 incubator.
4. Appropriate serial dilutions of test compound were prepared and 5 µl/well transferred to the assay plate (white opaque CulturPlate-384, Perkin-Elmer) using Bravo (Agilent) with 5 µl NanoBRET Tracer K-5 (Promega N2501) diluted to the recommended concentration in assay buffer (Invitrogen 11058021) and 30 µl cell suspension. The plate was incubated for 2 hours at 37°C in 5% CO_2 incubator.
5. 20 µl 3X complete substrate plus inhibitor solution (containing NanoBRET Nano-Glo substrate and extracellular NanoLuc inhibitor diluted to manufacturer's recommendations in assay medium) was added to each well.
6. Donor emission wavelength (450nm) and acceptor emission wavelength (610nm or 630nm) were measured on the Envision (Perkin-Elmer) and BRET ratio calculated for data analysis: BRET Ratio = $(Acceptor_{sample} / Donor_{sample}) \times 1{,}000$.
7. All assay plates contained 32 wells designated as 0% inhibition control wells, which were treated with vehicle only (1% DMSO) and 32 wells designated as 100% inhibition control wells, which were treated with a high concentration of non-specific kinase inhibitor in 1% DMSO. Percent inhibition in each test well was calculated using the formula $(MEAN_{0\%inhibition\ control\ wells} - \text{test well reading}) / (MEAN_{0\%inhibition\ control\ wells} - MEAN_{100\%inhibition\ control\ wells}) \times 100\%$.
8. IC_{50} was determined using a standard 4-parameter fit method (Model 205, XL-fit).

Biological data:

Example No	Assay 1: CK2α Enzyme IC_{50} (nM)	Assay 2: CLK2 Enzyme IC_{50} (nM)	Assay 3: NanoBRET™ IC_{50} for binding to intracellular CK2α (nM)
1	0.4249	1448	204
2	0.3062	943.3	35
3	0.2984	931.4	26
4	1.158	492.6	57
5	1.72	1785	136
6	0.378	725.8	70
7	0.5857	896.7	42

8	0.8619	565.6	72
9	0.5678	422.6	42
10	0.372	408.2	32
11	0.2438	748.6	37
12	0.4807	590.4	32
13	0.6347	476.3	183
14	9.929	1069	799
15	0.3817	451.2	32
16	0.8056	1356	215
17	2.939	792.5	139
18	1.007	743.7	83
19	6.25	1586	1490
20	0.2783	608.9	41
21	1.743	801.5	372
22	15.62	1241	5532
23	1.183	1319	229
24	10	1537	2174
25	0.3664	506.6	129
26	0.5535	687.5	19500
27	0.4588	562.3	5323
28	0.3459	366.1	47
29	7.203	1604	1155
30	0.5182	175.9	339
31	0.6764	356.7	6184
32	0.9202	776.1	38500
33	0.2208	364.7	101
34	0.2482	587.6	343

35	3.025	1983	399
36	0.8204	2898	712
37	0.436	358.3	26470
38	9.455	2094	995
39	0.197	311.6	255
40	0.4033	507.1	21
41	0.1446	408.7	489
42	0.2029	255.2	1093
43	5.706	305.3	1599
44	0.8334	451.1	34
45	0.76	383.4	80
46	0.4041	131.8	12
47	3.077	694.5	103
48	0.7044	796.1	53
49	7.873	622.2	174
50	1.309	1195	130
51	2.39	708.7	77
52	1.278	1392	264
53	1.164	637.7	136
54	0.6876	142.4	73
55	1.669	493.8	316
56	0.4267	826.6	25
57	0.665	748	51
58	0.6385	603.1	88
59	8.92	1554	654
60	2.543	503.5	180
61	0.8546	294.1	51

62	4.476	1072	795
63	4.835	1914	988
64	0.5868	2364	252
65	4.934	362	175
66	5.745	695.9	188
67	11.84	804.9	634
68	27.48	1953	3833
69	0.633	331.9	4881
70	0.517	211.5	1196
71	0.6912	227.8	1693
72	0.6553	260.7	862
73	0.713	482	2656
74	0.7866	119	1455
75	0.773	81.65	335
76	0.7778	58.47	99
77	0.67	125.3	140
78	0.7253	147.3	734
79	1.439	78.4	6092
80	1.666	536.3	>10000
81	1.378	49.8	17690
82	2.106	61.32	1149
83	11.82	558.4	2789
84	0.6122	815.1	17
85	4.828	878.5	350
86	0.3606	153.1	18
87	2.499	1152	82
88	0.3593	324.8	31

89	0.4689	918.8	4
90	0.5731	46.88	682
91	2.066	1013	111
92	1.606	670.9	57
93	0.3539	161.4	14
94	7.051	743.7	711
95	0.4176	169.8	323
96	2.931	508.8	179
97	1.137	518	61
98	22.29	989.9	2500
99	14.71	311.3	4331
100	1.074	394	16170
101	0.2578	201.2	368
102	0.3244	69.55	4547
103	0.4534	232.5	3137
104	13.27	185.9	1115
105	0.4756	302.6	59
106	0.2626	340.3	26
107	0.4369	2653	6
108	0.3036	513.3	302
109	0.4756	718.3	373
110	6.214	1348	>50000
111	0.3538	201.7	71
112	0.4107	171.8	8
113	0.4089	123.8	6
114	0.3419	82.35	9
115	0.2477	87.98	10

116	0.3181	326.6	6
117	0.3655	284.3	9
118	0.747	187.7	87
119	0.516	291.9	46
120	0.4926	28.58	40
121	0.505	71.42	58
122	1.262	3850	1245
123	71.65	1006	166
124	75.33	173.9	6068
125	189.4	273	8824
126	88.34	844.7	6727
127	43.01	345.9	5565
128	61.01	324.3	2919
129	0.3328	113.8	96
130	1.399	484.9	158
131	0.4319	288.4	15
132	0.3702	190.4	15
133	0.403	282.6	164
134	0.5324	85.98	8
135	0.9302	812.5	50
136	0.7361	1674	57
137	1.97	1105	673
138	0.6573	768	50
139	0.6001	629.7	33
140	0.3487	1356	18
141	3.443	809	274
142	0.4573	948.7	479

143	0.8568	49.01	50
144	0.7964	76.53	126
145	1.039	146	319
146	0.9338	102.4	3167
147	0.6963	24.14	77
148	0.559	550.5	39
149	0.4945	113.9	4
150	0.8103	1460	27
151	0.9836	1725	12
152	0.5555	400.4	55
153	4.204	629.8	418
154	0.7486	488.8	26
155	17.81	2890	2702
156	0.8404	1392	22
157	0.553	3848	18
158	0.5929	2454	15
159	0.2166	1881	9
160	1.034	720.6	66
161	0.6615	2978	14
162	0.6015	1999	22
163	0.5238	1618	54
164	1.055	1858	26
165	0.3902	1294	17
166	0.4852	124.4	12
167	0.8467	1534	131
168	0.4794	1175	42
169	1.13	1497	41

170	0.5495	1081	165
171	1.17	1818	108
172	0.265	1156	47
173	0.223	2054	19
174	0.5733	992.3	39
175	0.2014	850.3	16
176	0.4917	3591	116
177	0.5928	1731	51
178	0.2361	244.8	30
179	0.4939	558.3	31
180	0.1801	611.7	48
181	0.4278	383.6	78
182	0.5692	353.1	28
183	1.765	2613	133

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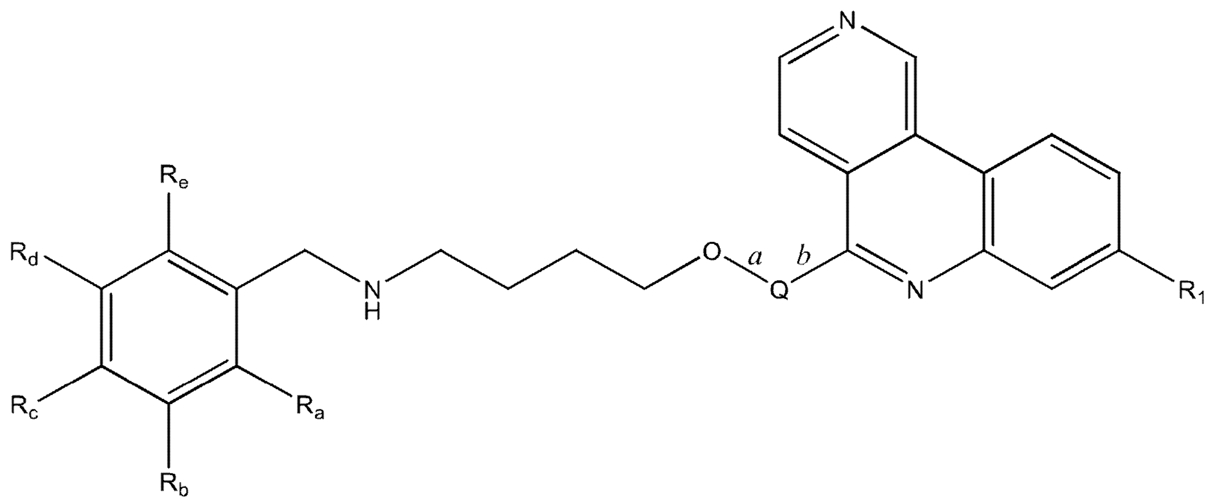
CLAIMS

1. A compound of formula I, or a salt, hydrate or solvate thereof:

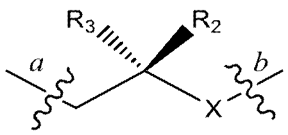


I

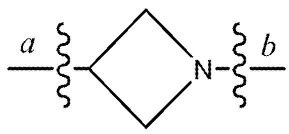
wherein:

R_1 is selected from -C(O)OH or -C(O)NH_2;

Q is selected from formula Ia or Ib:



Ia



Ib

wherein:

bond *a* in formulae Ia and Ib corresponds with bond *a* in formula I and bond *b* in formulae Ia and Ib corresponds with bond *b* in formula I;

R_2 and R_3 are each independently selected from hydrogen or methyl; and

X is NH or O;

R_a and R_e are both independently selected from hydrogen, methyl or halo;

R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

-$[CH_2]_{0-3}$-(1-4C)alkoxy,

-$[CH_2]_{0-3}$-C(O)NH_2,

$-[CH_2]_{0\text{-}3}$-C(O)NH(1-4C)alkyl,

$-[CH_2]_{0\text{-}3}$-C(O)N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0\text{-}3}$-NH(1-4C)alkyl,

$-[CH_2]_{0\text{-}3}$-N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0\text{-}3}$-S(O)$_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

$-[CH_2]_{0\text{-}3}$-C(O)(1-4C)alkyl,

$-[CH_2]_{0\text{-}3}$-C(O)O-(1-4C)alkyl,

$-[CH_2]_{0\text{-}3}$-N(R_f)C(O)-(1-4C)alkyl (wherein R_f is hydrogen or methyl),

$-[CH_2]_{0\text{-}3}$-S(O)$_2$NH(1-4C)alkyl,

$-[CH_2]_{0\text{-}3}$-S(O)$_2$N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0\text{-}3}$-N(R_g)SO$_2$-(1-4C)alkyl (wherein R_g is hydrogen or methyl),

a group of the formula:

$$-Y_1-[CH_2]_{0\text{-}3}-Z_1$$

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -S(O)$_2$-; and

Z_1 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH$_2$, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH$_2$, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -S(O)$_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -S(O)$_2$NH(1-2C)alkyl, -S(O)$_2$N[(1-2C)alkyl]$_2$, or -NHSO$_2$-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl;

R_c is selected from hydrogen, halo, cyano, -C(O)NH$_2$, (1-4C)alkyl,

$-[CH_2]_{0\text{-}3}$-(1-4C)alkoxy,

-$[CH_2]_{0-3}$-(3-6C)cycloalkoxy,

-$[CH_2]_{0-3}$-C(O)NH_2,

-$[CH_2]_{0-3}$-C(O)NH(1-4C)alkyl,

-$[CH_2]_{0-3}$-C(O)N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-3}$-NH(1-4C)alkyl,

-$[CH_2]_{0-3}$-N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-3}$-$S(O)_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

-$[CH_2]_{0-3}$-C(O)(1-4C)alkyl,

-$[CH_2]_{0-3}$-C(O)O-(1-4C)alkyl,

-$[CH_2]_{0-3}$-N(R_h)C(O)-(1-4C)alkyl (wherein R_h is hydrogen or methyl),

-$[CH_2]_{0-3}$-$S(O)_2$NH(1-4C)alkyl,

-$[CH_2]_{0-3}$-$S(O)_2$N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-3}$-N(R_i)SO_2-(1-4C)alkyl (wherein R_i is hydrogen or methyl),

a group of the formula:

-Y_2-$[CH_2]_{0-3}$-Z_2

wherein Y_2 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -$S(O)_2$-; and

Z_2 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

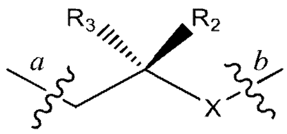
any alkyl, alkoxy or any alkyl moiety within a R_c substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -$S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -$S(O)_2$NH(1-2C)alkyl, -$S(O)_2$N[(1-2C)alkyl]$_2$, or -$NHSO_2$-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl.

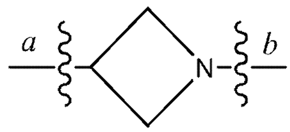
2. A compound according to claim 1, or a salt, hydrate or solvate thereof, wherein R_1 is -C(O)OH.

3. A compound according to claim 1, or a salt, hydrate or solvate thereof, wherein R_1 is C(O)NH_2.

4. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein Q is selected from formula Ia or Ib:



Ia



Ib

wherein:

bond *a* in formulae Ia and Ib corresponds with bond *a* in formula I and bond *b* in formulae Ia and Ib corresponds with bond *b* in formula I;

R_2 and R_3 are both hydrogen or one of R_2 and R_3 is hydrogen and the other is methyl;

X is O or NH.

5. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_a and R_e are each independently selected from hydrogen, methyl, fluoro, chloro or bromo.

6. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein one of R_a and R_e is hydrogen and the other is hydrogen, methyl or halo.

7. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein one of R_a and R_e is hydrogen and the other is hydrogen or chloro.

8. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

-$[CH_2]_{0-1}$-(1-4C)alkoxy,
-$[CH_2]_{0-1}$-C(O)NH_2,
-$[CH_2]_{0-1}$-C(O)NH(1-4C)alkyl,
-$[CH_2]_{0-1}$-C(O)N[(1-4C)alkyl]$_2$,
-$[CH_2]_{0-1}$-NH(1-4C)alkyl,
-$[CH_2]_{0-1}$-N[(1-4C)alkyl]$_2$,
-$[CH_2]_{0-1}$-S(O)$_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

-$[CH_2]_{0-1}$-C(O)(1-4C)alkyl,

-$[CH_2]_{0-1}$-C(O)O-(1-4C)alkyl,

-$[CH_2]_{0-1}$-NHC(O)-(1-4C)alkyl,

-$[CH_2]_{0-1}$-$S(O)_2$NH(1-4C)alkyl,

-$[CH_2]_{0-1}$-$S(O)_2$N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-1}$-$NHSO_2$-(1-4C)alkyl,

a group of the formula:

-Y_1-$[CH_2]_{0-1}$-Z_1

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or -$S(O)_2$-; and Z_1 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, -C(O)N[(1-2C)alkyl]$_2$, -NH(1-2C)alkyl, -N[(1-2C)alkyl]$_2$, -$S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl, -$S(O)_2$NH(1-2C)alkyl, -$S(O)_2$N[(1-2C)alkyl]$_2$, or -$NHSO_2$-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl.

9. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl,

-$[CH_2]_{0-1}$-(1-4C)alkoxy,

-$[CH_2]_{0-1}$-C(O)NH_2,

-$[CH_2]_{0-1}$-C(O)NH(1-4C)alkyl,

-$[CH_2]_{0-1}$-C(O)N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-1}$-NH(1-4C)alkyl,

-$[CH_2]_{0-1}$-N[(1-4C)alkyl]$_2$,

-$[CH_2]_{0-1}$-$S(O)_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

-$[CH_2]_{0-1}$-C(O)(1-4C)alkyl,

-$[CH_2]_{0-1}$-C(O)O-(1-4C)alkyl,

a group of the formula:

$-Y_1-[CH_2]_{0-1}-Z_1$

wherein Y_1 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or $-S(O)_2-$; and

Z_1 is (3-6C)cycloalkyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, $-C(O)NH_2$ or (1-2C)alkoxy; and

Z_1 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, (1-2C)alkoxy, (1-2C)alkyl or (1-2C)haloalkyl.

10. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, halo(1-4C)alkyl, hydroxy(1-4C)alkyl, cyano(1-4C)alkyl, amino(1-4C)alkyl, (1-2C)alkoxy(1-4C)alkyl, (1-4C)alkoxy, halo(1-4C)alkoxy, hydroxy(1-4C)alkoxy, $-[CH_2]_{0-3}-C(O)NH_2$, or a group of the formula:

$[CH_2]_{0-1}-Z_1$

wherein Z_1 is (3-6C)cycloalkyl or a 5-membered heteroaryl;

and wherein Z_1 is optionally substituted by one or more cyano.

11. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_b and R_d are each independently selected from hydrogen, halo, (1-2C)alkyl, (1-2C)alkoxy,

a group of the formula:

$[CH_2]_{0-1}-Z_1$

wherein Z_1 is (3-4C)cycloalkyl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_b and R_d substituent group is optionally substituted by one or more substituents selected from halo.

12. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_b and R_d are each independently selected from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, methoxy, ethoxy, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, $-CH_2CN$, $-CH_2CH_2OH$, $-CF_3$, $-OCF_3$, $-O-CH_2CH_2OH$, $-O-CH_2CF_3$, $-C(O)NH_2$, $-CH_2-C(O)NH_2$, $-CH(CH_3)CN$, $-C(CH_3)_2CN$, cyclopropyl, 1-cyanocyclopropyl, cyclopropylmethyl, furanylmethyl (e.g. furan-3-ylmethyl), imidazolylmethyl (e.g. imidazo-1-ylmethyl), pyrazolylmethyl (e.g. pyrazol-4-ylmethyl), oxazolylmethyl (e.g. oxazo-4-ylmethyl).

13. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein one of R_b and R_d is hydrogen or halogen or $-OCF_3$ and the other is selected from are each independently selected from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, methoxy, ethoxy, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, $-CH_2CN$, $-CH_2CH_2OH$, $-CF_3$, $-OCF_3$, $-O-CH_2CH_2OH$, $-O-CH_2CF_3$, $-C(O)NH_2$, $-CH_2-C(O)NH_2$, $-CH(CH_3)CN$, $-C(CH_3)_2CN$, cyclopropyl, 1-cyanocyclopropyl, cyclopropylmethyl, furanylmethyl (e.g. furan-3-ylmethyl), imidazolylmethyl (e.g. imidazo-1-ylmethyl), pyrazolylmethyl (e.g. pyrazol-4-ylmethyl), oxazolylmethyl (e.g. oxazo-4-ylmethyl).

14. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein one of R_b and R_d is hydrogen or halogen or $-OCF_3$ and the other is selected from are each independently selected from hydrogen, fluoro, chloro, bromo, methyl, $-OCF_3$ or cyclopropyl.

15. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_c is selected from hydrogen, halo, cyano, $-C(O)NH_2$, (1-4C)alkyl,

$-[CH_2]_{0\text{-}1}$-(1-4C)alkoxy,

$-[CH_2]_{0\text{-}1}$-(3-6C)cycloalkoxy,

$-[CH_2]_{0\text{-}1}-C(O)NH_2$,

$-[CH_2]_{0\text{-}1}$-C(O)NH(1-4C)alkyl,

$-[CH_2]_{0\text{-}1}$-C(O)N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0\text{-}1}$-NH(1-4C)alkyl,

$-[CH_2]_{0\text{-}1}$-N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0\text{-}1}$-S(O)$_q$-(1-4C)alkyl (wherein q is 0, 1 or 2),

$-[CH_2]_{0\text{-}1}$-C(O)(1-4C)alkyl,

$-[CH_2]_{0\text{-}1}$-C(O)O-(1-4C)alkyl,

$-[CH_2]_{0\text{-}1}$-N(H)C(O)-(1-4C)alkyl,

$-[CH_2]_{0\text{-}1}$-S(O)$_2$NH(1-4C)alkyl,

$-[CH_2]_{0\text{-}1}$-S(O)$_2$N[(1-4C)alkyl]$_2$,

$-[CH_2]_{0\text{-}1}$-N(H)SO$_2$-(1-4C)alkyl,

a group of the formula:

$-Y_2-[CH_2]_{0-1}-Z_2$

wherein Y_2 is absent, -O-, -NH-, -NMe-, -S-, -S(O)- or $-S(O)_2-$; and

Z_2 is (3-6C)cycloalkyl, phenyl, a 4- to 6-membered heterocyclyl or 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy or any alkyl moiety within a R_c substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, $-C(O)NH_2$, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, -C(O)OH, $-C(O)NH_2$, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(1-2C)alkyl, $-C(O)N[(1-2C)alkyl]_2$, -NH(1-2C)alkyl, $-N[(1-2C)alkyl]_2$, $-S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl, $-N(R_f)C(O)$-(1-2C)alkyl, $-S(O)_2NH$(1-2C)alkyl, $-S(O)_2N[(1-2C)alkyl]_2$, or $-NHSO_2$-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl or (1-2C)alkoxy;

16. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_c is selected from hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)alkoxy, a group of the formula:

$-Y_2-[CH_2]_{0-1}-Z_2$

wherein Y_2 is absent or -O-; and

Z_2 is (3-6C)cycloalkyl or phenyl;

and wherein:

any alkyl or alkoxy substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, $-C(O)NH_2$, or (1-2C)alkoxy; and

Z_2 is optionally substituted by one or more substituents selected from: halo, hydroxy, cyano, amino, (1-2C)alkoxy, (1-2C)alkyl, -C(O)NH(1-2C)alkyl, $-C(O)N[(1-2C)alkyl]_2$, -NH(1-2C)alkyl, $-N[(1-2C)alkyl]_2$, $-S(O)_q$-(1-2C)alkyl (wherein q is 0, 1 or 2), -C(O)(1-2C)alkyl, or -C(O)O-(1-2C)alkyl, and wherein any (1-2C)alkoxy or (1-2C)alkyl group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy or (1-2C)alkoxy.

17. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_c is selected from hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)alkoxy,

a group of the formula:

$$-Y_2-[CH_2]_{0-1}-Z_2$$

wherein Y_2 is absent or -O-; and

Z_2 is (3-6C)cycloalkyl or phenyl;

and wherein:

any alkyl or alkoxy substituent group is optionally substituted by one or more substituents selected from halo or cyano; and

Z_2 is optionally substituted by one or more (1-2C)alkyl substituents, and wherein a (1-2C)alkyl group is optionally substituted by one or more hydroxy substituents.

18. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_c is selected from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, methoxy, ethoxy, $-O-CH(CH_3)_2$, $-CH_2CN$, $-CF_3$, $-OCF_3$, $-O-CH_2CF_3$, cyclopropyl, cyclopropoxy, cyclobutoxy, cyclopentoxy, phenyl or 2-hydroxymethylphenyl.

19. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_c is selected from hydrogen, halo or halo(1-2C)alkoxy.

20. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein R_c is selected from hydrogen, chloro or $-OCF_3$.

21. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein either:

(i) at least one of R_a, R_b, R_c, R_d or R_e is a non-hydrogen substituent;

(ii) one to four of R_a, R_b, R_c, R_d or R_e is/are a non-hydrogen substituent(s);

(iii) one to three of R_a, R_b, R_c, R_d or R_e is/are a non-hydrogen substituent(s);

(iv) two to four of R_a, R_b, R_c, R_d or R_e are hydrogen and the remainder are non-hydrogen substituents.

22. A compound according to any one of claims 1, 8, 9, 15, 16 or 17, or a salt, hydrate or solvate thereof, wherein if R_c is a group of the formula $-Y_2-[CH_2]_{0-3}-Z_2$ then R_b and R_d cannot be a group of the formula $-Y_1-[CH_2]_{0-3}-Z_1$; and if one of R_b and R_d is a group of the formula $-Y_1-[CH_2]_{0-3}-Z_1$ as defined herein, then the other cannot be a group of the formula $-Y_1-[CH_2]_{0-3}-Z_1$ and R_c cannot be a group of the formula $-Y_2-[CH_2]_{0-3}-Z_2$.

23. A compound according to any one of the preceding claims, or a salt, hydrate or solvate thereof, wherein the compound is selected from any one of the following:

5-((2-(4-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chlorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-(((2-chloro-2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)methyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-(cyclopentyloxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-cyclopropoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(2-hydroxyethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chlorobenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-cyclobutoxy-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-chloro-3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((4-cyclopropyl-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chlorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(2-hydroxyethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-chloro-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-chloro-4-cyclopropoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(2-hydroxyethoxy)-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-cyclobutoxy-3-(2-hydroxyethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide

5-((2-(4-((3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(2-hydroxyethoxy)-4-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-4-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-4-cyclobutoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(aminomethyl)-5-chlorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chloro-4-cyclobutoxybenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(hydroxymethyl)-5-methylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((2-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-chloro-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-cyano-4-cyclopropylbenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((4-cyclobutoxy-3-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((2-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-cyano-3-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-4-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-4-(2,2,2-trifluoroethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-4-isopropoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-(cyclopentyloxy)-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-chloro-3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((2-chloro-3-(cyanomethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((2-chloro-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((4-ethoxy-3-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(hydroxymethyl)-4-(trifluoromethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(S)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-methoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-chloro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-fluoro-5-(hydroxymethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-(cyanomethyl)-5-methylbenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-(cyanomethyl)-5-fluorobenzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-(hydroxymethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-chloro-5-(cyanomethyl)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-5-(2-cyanopropan-2-yl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-chloro-5-(1-cyanocyclopropyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(cyanomethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-bromo-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((4-chloro-3-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-chloro-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-bromo-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-cyclopropyl-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-fluoro-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-chloro-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-bromo-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-cyclopropyl-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-chloro-5-(1-cyanocyclopropyl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-chloro-5-(2-cyanopropan-2-yl)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-cyclopropyl-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-methyl-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3-methoxy-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(2-(4-((3,4-dichloro-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-cyclopropylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-ethoxybenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyclopropyl-5-(hydroxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(R)-5-((2-(4-((3-chloro-5-(1-cyanoethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(S)-5-((2-(4-((3-chloro-5-(1-cyanoethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-(2,2,2-trifluoroethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(3-(4-((3-cyclopropyl-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-bromo-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((4-chloro-3-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-methyl-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3-methoxy-4-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-(3-(4-((3,4-dichloro-5-(trifluoromethoxy)benzyl)amino)butoxy)azetidin-1-yl)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(S)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)-2-methylpropan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

5-((2-(4-((3-(cyanomethyl)-5-ethylbenzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-(cyclopropylmethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)-2-methylpropan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(cyanomethyl)-5-(methoxymethyl)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(R)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-cyano-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(oxazol-4-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-cyano-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(oxazol-4-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(2-hydroxyethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(2-hydroxyethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

(S)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(S)-5-((1-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-carbamoyl-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-carbamoyl-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(2-amino-2-oxoethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(2-amino-2-oxoethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-((1H-imidazol-1-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-(furan-3-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-((1H-imidazol-1-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3-((1H-pyrazol-4-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-(furan-3-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-(2-(4-((3-((1H-pyrazol-4-yl)methyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide;

5-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(R)-5-((1-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(R)-5-((1-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)oxy)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(R)-5-((1-(4-((3-fluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid;

(R)-5-((1-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)propan-2-yl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid; or

5-(2-(4-((3,5-Difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethoxy)benzo[c][2,6]naphthyridine-8-carboxamide.

24. A pharmaceutical composition comprising a compound according to any one of claims 1 to 23, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and a pharmaceutically acceptable excipient.

25. A compound according to any one of claims 1 to 23, or a pharmaceutically acceptable salt of solvate thereof, or a pharmaceutical composition according to claim 24 for use in:

(i) therapy:

(ii) the treatment of a disease or condition in which CK2α activity is implicated;

(iii) the treatment of a disease or condition associated with aberrant activity of CK2α;

(iv) the treatment of proliferative disorders (e.g. cancer or benign neoplasms), viral infections, an inflammatory disease or condition, diabetes, vascular and ischemic disorders, neurodegenerative disorders and/or the regulation of circadian rhythm;

(v) the treatment of a cancer; and/or

(vi) the treatment of a viral infection.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2022/050536

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/4375 A61P3/00 A61P25/00 A61P29/00
A61P31/12 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/041785 A1 (CYLENE PHARMACEUTICALS INC [US]; DRYGIN DENIS [US] ET AL.) 7 April 2011 (2011-04-07) page 62 - page 64; claims 1-30; figure 2 -----	1-25
A	VAHTER JÜRGEN ET AL: "Oligo-aspartic acid conjugates with benzo[c][2,6]naphthyridine-8-carboxylic acid scaffold as picomolar inhibitors of CK2", BIOORGANIC, ELSEVIER, AMSTERDAM, NL, vol. 25, no. 7, 28 February 2017 (2017-02-28), pages 2277-2284, XP029948113, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2017.02.055 Abstract; table 1 -----	1-25

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2022	16/05/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rufet, Jacques

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/108912 A1 (CYLENE PHARMACEUTICALS INC [US]; CHUA PETER C [CA] ET AL.) 3 September 2009 (2009-09-03) page 384 - page 389; claims 1-30; tables 19A, 21, 29, 44, 45 -----	1-25

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2022/050536

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		CA 2776278 A1	07-04-2011
		EP 2483686 A1	08-08-2012
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		US 2009239859 A1	24-09-2009
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		WO 2009108912 A1	03-09-2009