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(54) Title: NOVEL COMPOUNDS AS CK2 INHIBITORS

R_L-L-R_R

I

(57) Abstract: Provided are compounds of the Formula I, and salts, hydrates and solvates thereof: wherein R_L, L and R_R, and any groups associated therewith, 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 and to their use for the treatment of diseases and/or conditions in which CK2α activity is implicated.

NOVEL COMPOUNDS AS CK2 INHIBITORS

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 a*l, 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 cholangiocarcinoma (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 upregulation of wnt signaling to restore the 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 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 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 encompass 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 or cyclohexyl.

[0041] “(3-6C)cycloalkoxy” refers to cycloalkoxy groups (i.e. O-cycloalkyl group) wherein the cycloalkyl group means a hydrocarbon ring containing from 3 to 6 carbon atoms, for example, -O-cyclopropyl, -O-cyclobutyl, -O-cyclopentyl or -O-cyclohexyl.

[0042] The term “halo”, “halogen” or “halogeno” refers to fluoro, chloro, bromo and iodo.

[0043] 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 $–CF_3$.

[0044] 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 haloalkoxy group is selected from $-OCHF_2$ and $-OCF_3$, suitably $-OCF_3$.

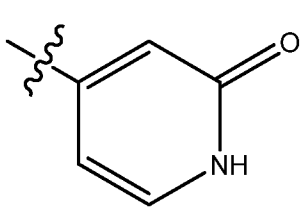
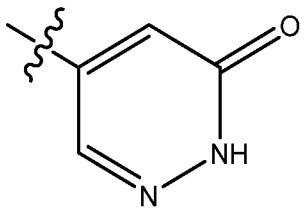
[0045] The term "heterocyclyl", "heterocyclic" or "heterocycle" means a non-aromatic saturated or partially saturated monocyclic, fused, bridged, or spiro bicyclic heterocyclic ring system(s). Monocyclic heterocyclic rings contain from about 3 to 12 (suitably from 3 to 7) ring atoms, with from 1 to 5 (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 a 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.

[0046] 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.

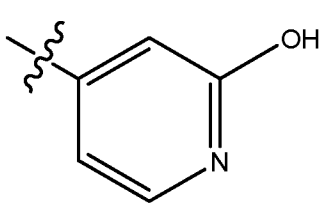
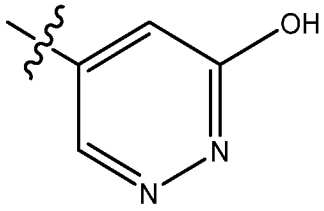
[0047] By "spiro bicyclic ring systems" we mean that the two ring systems share one common spiro carbon atom, i.e. the heterocyclic ring is linked to a further carbocyclic or heterocyclic ring through a single common spiro carbon atom. Examples of spiro ring systems include 6-azaspiro[3.4]octane, 2-oxa-6-azaspiro[3.4]octane, 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.

[0048] 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. The nitrogen atom of a heteroaryl may occasionally be in the form of a N-oxide (N^+-O^-).

[0049] 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. The term heteroaryl also covers exemplified groups such as those depicted below:

as these groups tautomerise to the following:

Occasionally, a N atom present in a heteroaryl ring may be present N^+-O^-.

[0050] "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.

[0051] 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.

[0052] Examples of six membered heteroaryl groups include but are not limited to pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl and triazinyl.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] “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.

[0060] “Heterocyclyl(1-2C)alkyl” means a heterocyclyl group covalently attached to a (1-2C)alkylene group, both of which are defined herein.

[0061] “(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.

[0062] 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.

[0063] 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.

[0064] A wavy bond ( ) is used herein to show a point of attachment.

[0065] The phrase “compound of the invention” means those compounds which are disclosed herein, both generically and specifically.

[0066] 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.

[0067] 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

[0068] 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:

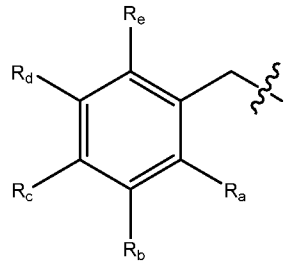
$$R_L\text{-}L\text{-}R_R$$

I

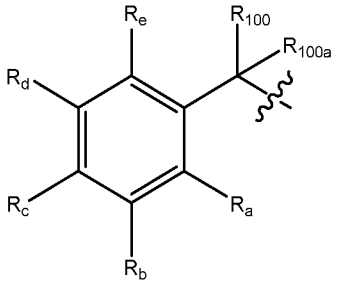
wherein:

L is linker that separates R_L from R_R by 7 to 13 bond lengths;

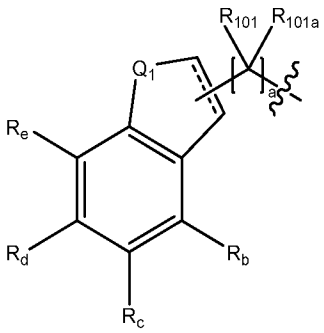
R_L is selected from one of formulae Ic, Id, Ie, If, Ig, Ih, Ii, Ij or Ik shown below:



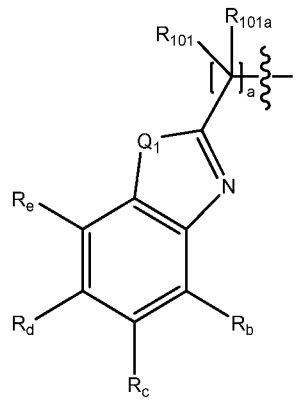
Ic



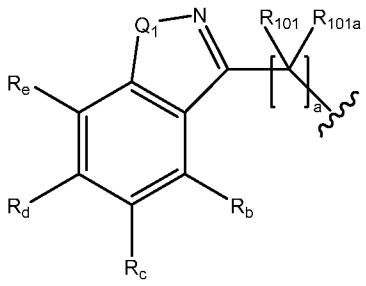
Id



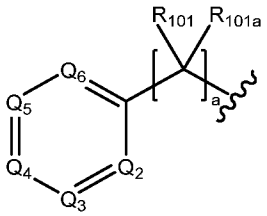
Ie



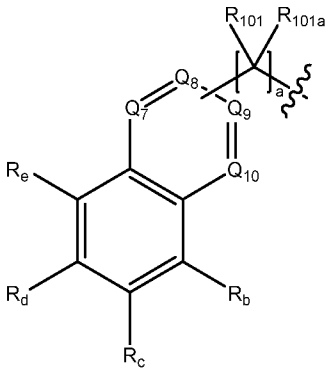
If



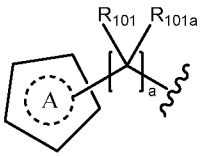
Ig



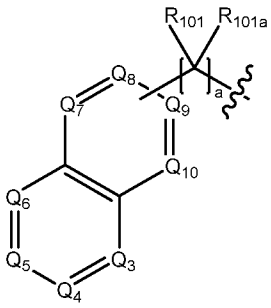
Ih



Ii



Ij



(Ik)

wherein:

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

R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, (3-6C)cycloalkyl,

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

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

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

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

$-[CH_2]_{0-3}-NH_2$,

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

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

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

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

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

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

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

$-[CH_2]_{0-3}-S(O)_2NH$(1-4C)alkyl,

$-[CH_2]_{0-3}-S(O)_2N[(1\text{-}4C)alkyl]_2$,

$-[CH_2]_{0-3}-N(R_g)SO_2$-(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, cycloalkyl or $-[CH_2]$- 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, (3-6C)cycloalkyl

-[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_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)OH,

-[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, cycloalkyl or -[CH_2]- 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;

R_{100} is (1-2C)alkyl optionally substituted by hydroxy or halo;

R_{100a} is selected from hydrogen or methyl;

or R_{100} and R_{100a} are linked to form a cyclopropyl or cyclobutyl ring;

R_{101} is hydrogen or (1-2C)alkyl optionally substituted by hydroxy or halo;

R_{101a} is selected from hydrogen or methyl;

or R_{101} and R_{101a} are linked to form a cyclopropyl or cyclobutyl ring;

integer a is 0, 1 or 2;

Q_1 is selected from -NR_{102}-, -O-, -S- or -CH-;

R_{102} is hydrogen or (1-2C)alkyl;

------ represents a single or double bond;

Q_2 is N or CR_a;

Q_3 is N or CR_b;

Q_4 is N or CR_c;

Q_5 is N or CR_d;

Q_6 is N or CR_e;

R_a, R_b, R_c, R_d and R_e are each as defined above;

with the proviso that one to three of Q_2, Q_3, Q_4, Q_5 or Q_6 is/are N;

Q_7 is N or CR_f;

Q_8 is N or CR_f;

Q_9 is N or CR_f;

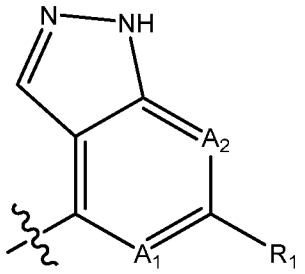
Q_{10} is N or CR_f;

with the proviso that one or two of Q_7, Q_8, Q_9 or Q_{10} is/are N;

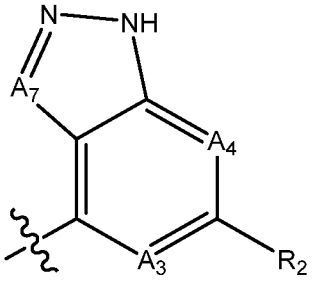
each R_f present is independently selected from hydrogen, methyl or halo;

Ring A is a five-membered heteroaryl ring optionally substituted by one R_b and/or one or two R_c substituents;

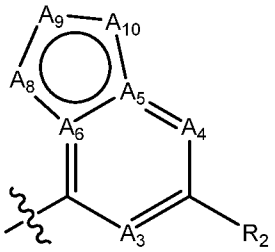
R_R is selected from one of formulae Im, In or Io shown below:



Im



In



Io

wherein:

~~~ denotes the point of attachment;

A_1 and A_2 are both CH; or one of A_1 and A_2 is N and the other is CH;

R_1 is a 5- or 6-membered heteroaryl ring which is optionally substituted on any available carbon atom by one or more R_{1A} substituent groups and on any available nitrogen atom by one or more R_{1B} substituent groups; and wherein:

each R_{1A} group present is selected from hydroxy, cyano, amino, halo, -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 (wherein R_f is hydrogen or methyl), -$S(O)_2$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];

and R_{1B} is (1-2C)alkyl or (3-4C)cycloalkyl;

A_3 is selected from CH, CR_3 or N;

A_4 is selected from CH, CR_4 or N;

A_5 and A_6 are both C, or one of A_5 and A_6 is N and the other is C;

A_7 is selected from CH, CR_7 or N;

R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)cyanoalkyl, (1-4C)hydroxyalkyl, (1-4C)haloalkyl, (1-4C)aminoalkyl,
-$[CH_2]_{0-3}$-(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)OH,
-$[CH_2]_{0-3}$-C(O)O-(1-4C)alkyl,
~~~

-$[CH_2]_{0-3}$-N(R_{2a})C(O)-(1-4C)alkyl (wherein R_{2a} 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_{2b})SO_2-(1-4C)alkyl (wherein R_{2b} is hydrogen or methyl),
a 4- to 7-membered heterocyclyl,
(3-6C)cycloalkyl,
(3-6C)cycloalkyl(1-2C)alkyl,
phenyl, or
phenyl(1-2C)alkyl;
and wherein any cycloalkyl, heterocyclyl or phenyl group present is optionally substituted by one or more hydroxy, cyano, amino, halo, -C(O)OH, -C(O)NH_2, (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, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl (wherein R_f is hydrogen or methyl), -$S(O)_2$NH(1-2C)alkyl, -$S(O)_2$N[(1-2C)alkyl]$_2$, or -$NHSO_2$-(1-2C)alkyl;

R_3 is selected from fluoro, chloro, methyl, methoxy or cyano;

R_4 is selected from fluoro, chloro, methyl, methoxy or cyano;

R_7 is selected from methyl, -NH(1-2C)alkyl or -NH(3-4C)cycloalkyl;

and wherein R_2 is not a group R_1 when A_3, A_4 and A_7 are all CH and A_5 and A_6 are C;

A_8 is selected from CH, CR_8, O, S, NH or N;

A_9 is selected from CH, CR_9, O, S, NH or N;

A_{10} is selected from CH, CR_{10}, O, S, NH or N;

R_8, R_9 and R_{10} are selected from methyl, amino, -NH(1-2C)alkyl or -NH(3-4C)cycloalkyl;

and wherein:

(i) only one of A_8, A_9 and A_{10} can be NH;
(ii) one to four of A_5, A_8, A_9 and A_{10} or A_6, A_8, A_9 and A_{10} can be N
(iii) only one of A_8, A_9 or A_{10} can be O or S;
(iv) when one of A_8, A_9 or A_{10} are O or S, A_5 and/or A_6 cannot be N.

[0069] 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_L, L and R_R, and any groups associated therewith, each have any of the meanings defined hereinbefore or are as defined in any one of paragraphs (1) to (163) hereinafter:-

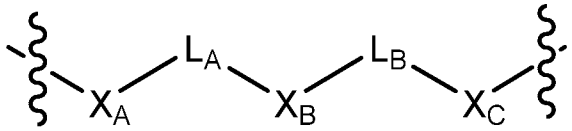
(1) L is linker that separates R_L from R_R by 8 to 12 bond lengths;

(2) L is linker that separates R_L from R_R by 9 to 11 bond lengths;

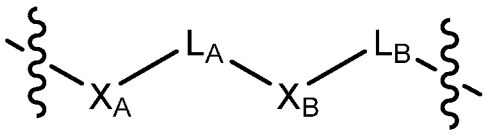
(3) L is linker that separates R_L from R_R by 10 bond lengths;

(4) L is a linker selected from:

(i) a group of the formula:



(II)



(III)

wherein:

X_A is selected from: -O-, -S-, -SO-, $-SO_2$-, $-N(R_{xa})$-, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_{xa})$-, $-N(R_{xa})C(O)$-, $-N(R_{xa1})C(O)N(R_{xa})$-, $-S(O)_2N(R_{xa})$- or $-N(R_{xa})SO_2$-, wherein R_{xa} and R_{xa1} are selected from hydrogen or methyl;

L_A is a (1-6C)alkylene optionally substituted by one or more R_{LA} substituent groups, or a –[(0-3C)alkylene-(3-6C)cycloalkylene-(0-3C)alkylene]- group optionally substituted by one or more R_{LA} substituent groups;

each R_{LA} group present is selected from hydroxy, halo, (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

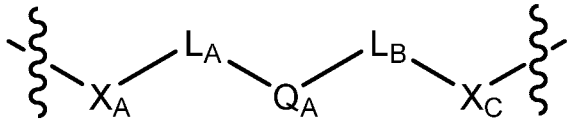
X_B is selected from: -O-, -S-, -SO-, $-SO_2$-, $-N(R_{xb})$-, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R_{xb})$-, $-N(R_{xb1})C(O)$-, $-N(R_{xb1})C(O)N(R_{xb})$-, $-S(O)_2N(R_{xb})$- or $-N(R_{xb})SO_2$-, wherein R_{xb} and R_{xb1} are selected from hydrogen or methyl;

L_B is a (1-6C)alkylene optionally substituted by one or more R_{LB} substituent groups, or a –[(0-3C)alkylene-(3-6C)cycloalkylene-(0-3C)alkylene]- group optionally substituted by one or more R_{LB} substituent groups;

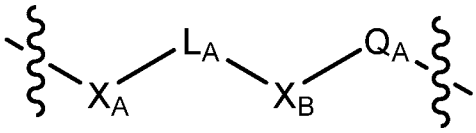
each R_{LB} group present is selected from hydroxy, halo, (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

X_c is selected from: -O-, -S-, -SO-, -SO_2-, -N(R_{xc})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{xc})-, -N(R_{xc1})C(O)-, -N(R_{xc1})C(O)N(R_{xc})-, -$S(O)_2$N(R_{xc})- or -N(R_{xc})SO_2-, wherein R_{xc} and R_{xc1} are selected from hydrogen or methyl;

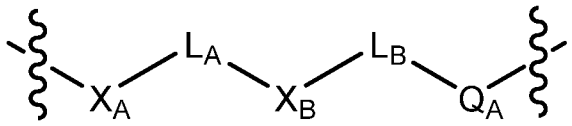
(ii) a group of the formula:



(IV)



(V)



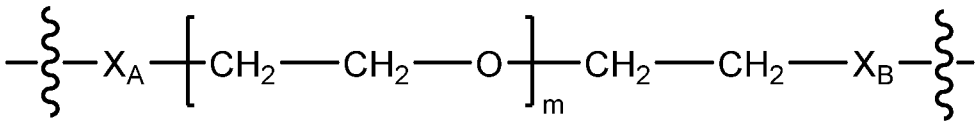
(VI)

wherein:

X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from a 5 or 6-membered heteroaryl ring, a 9 or 10-membered bicyclic heteroaryl ring, (3-6C)cycloalkyl, a phenyl, or a 4 to 6 membered heterocyclic ring;

(iii) a group of the formula:



(VII)

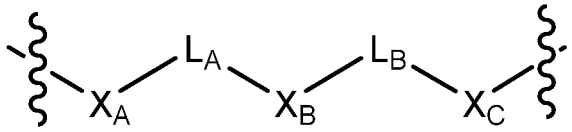
wherein:

X_A and X_B are each as defined above;

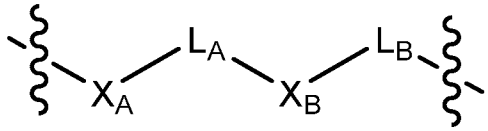
integer m is 1 or 2.

(5) L is a linker selected from:

(i) a group of the formula:



(II)



(III)

wherein:

X_A is selected from: -O-, -S-, -SO-, -SO_2-, -N(R_{xa})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{xa})-, -N(R_{xa})C(O)-, -N(R_{xa1})C(O)N(R_{xa})-, -$S(O)_2$N(R_{xa})- or -N(R_{xa})SO_2-, wherein R_{xa} and R_{xa1} are selected from hydrogen or methyl;

L_A is a (1-5C)alkylene optionally substituted by one or more R_{LA} substituent groups, or a –[(0-2C)alkylene-(3-6C)cycloalkylene-(0-2C)alkylene]- group optionally substituted by one or more R_{LA} substituent groups;

each R_{LA} group present is selected from hydroxy, halo, (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

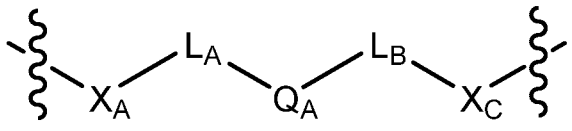
X_B is selected from: -O-, -S-, -SO-, -SO_2-, -N(R_{xb})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{xb})-, -N(R_{xb1})C(O)-, -N(R_{xb1})C(O)N(R_{xb})-, -$S(O)_2$N(R_{xb})- or -N(R_{xb})SO_2-, wherein R_{xb} and R_{xb1} are selected from hydrogen or methyl;

L_B is a (1-5C)alkylene optionally substituted by one or more R_{LB} substituent groups, or a –[(0-2C)alkylene-(3-6C)cycloalkylene-(0-2C)alkylene]- group optionally substituted by one or more R_{LB} substituent groups;

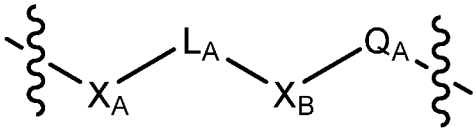
each R_{LB} group present is selected from hydroxy, halo, (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

X_c is selected from: -O-, -S-, -SO-, -SO_2-, -N(R_{xc})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{xc})-, -N(R_{xc1})C(O)-, -N(R_{xc1})C(O)N(R_{xc})-, -$S(O)_2$N(R_{xc})- or -N(R_{xc})SO_2-, wherein R_{xc} and R_{xc1} are selected from hydrogen or methyl;

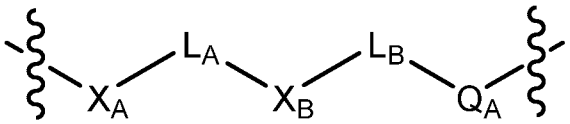
(ii) a group of the formula:



(IV)



(V)



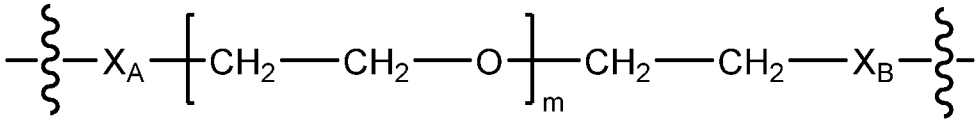
(VI)

wherein:

X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from a 5 or 6-membered heteroaryl ring, a 9 or 10-membered bicyclic heteroaryl ring, or a 4 to 6 membered heterocyclic ring;

(iii) a group of the formula:



(VII)

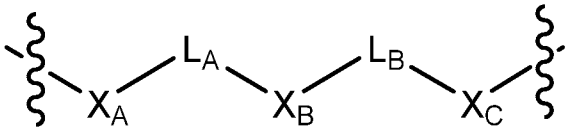
wherein:

X_A and X_B are each as defined above;

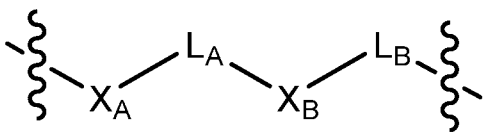
integer m is 1.

(6) L is a linker selected from:

(i) a group of the formula:



(II)



(III)

wherein:

X_A is selected from: -O-, -SO_2-, -N(R_{xa})-, -C(O)-, -C(O)N(R_{xa})-, -N(R_{xa})C(O)-, -$S(O)_2$N(R_{xa})- or -N(R_{xa})SO_2-, wherein R_{xa} is selected from hydrogen or methyl;

L_A is a (1-5C)alkylene optionally substituted by one or more R_{LA} substituent groups, or a –[(0-2C)alkylene-(3-6C)cycloalkylene-(0-2C)alkylene]- group optionally substituted by one or more R_{LA} substituent groups;

each R_{LA} group present is selected from (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

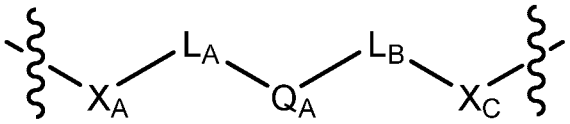
X_B is selected from: -O-, -SO_2-, -N(R_{xb})-, -C(O)-, -C(O)N(R_{xb})-, -N(R_{xb1})C(O)-, -$S(O)_2$N(R_{xb})- or -N(R_{xb})SO_2-, wherein R_{xb} and R_{xb1} are selected from hydrogen or methyl;

L_B is a (1-4C)alkylene optionally substituted by one or more R_{LB} substituent groups, or a –[(0-2C)alkylene-(3-6C)cycloalkylene-(0-2C)alkylene]- group optionally substituted by one or more R_{LB} substituent groups;

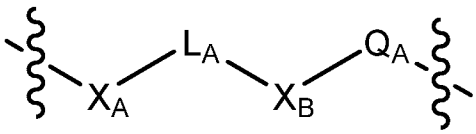
each R_{LB} group present is selected from (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

X_c is selected from: -O-, -SO_2-, -N(R_{xc})-, -C(O)-, -C(O)N(R_{xc})-, -N(R_{xc1})C(O)-, -$S(O)_2$N(R_{xc})- or -N(R_{xc})SO_2-, wherein R_{xc} and R_{xc1} are selected from hydrogen or methyl;

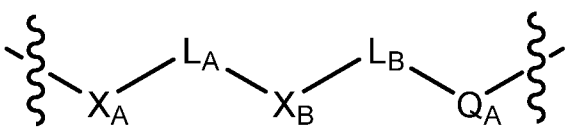
(ii) a group of the formula:



(IV)



(V)



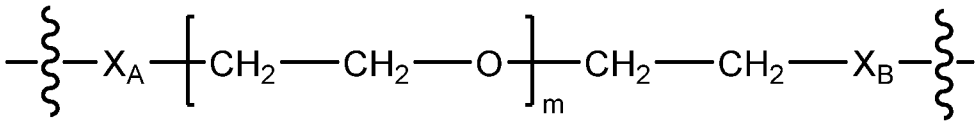
(VI)

wherein:

X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from a 5 or 6-membered heteroaryl ring, or a 4 to 6 membered heterocyclic ring;

(iii) a group of the formula:



(VII)

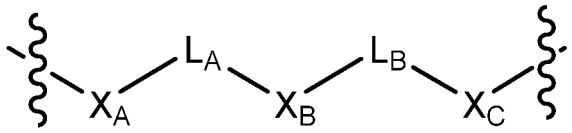
wherein:

X_A and X_B are each as defined above;

integer m is 1.

(7) L is a linker selected from:

(i) a group of the formula:



(II)

wherein:

X_A is selected from: -O-, -SO_2-, -N(R_{xa})-, -C(O)-, -C(O)N(R_{xa})-, -N(R_{xa})C(O)-, -$S(O)_2$N(R_{xa})- or -N(R_{xa})SO_2-, wherein R_{xa} is selected from hydrogen or methyl;

L_A is a (1-5C)alkylene optionally substituted by one or more R_{LA} substituent groups, or a –[(0-2C)alkylene-(3-6C)cycloalkylene-(0-2C)alkylene]- group optionally substituted by one or more R_{LA} substituent groups;

each R_{LA} group present is selected from (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

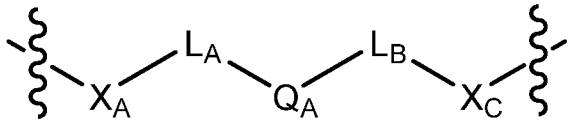
X_B is selected from: -O-, -SO_2-, -N(R_{xb})-, -C(O)-, -C(O)N(R_{xb})-, -N(R_{xb1})C(O)-, -$S(O)_2$N(R_{xb})- or -N(R_{xb})SO_2-, wherein R_{xb} and R_{xb1} are selected from hydrogen or methyl;

L_B is a (1-4C)alkylene optionally substituted by one or more R_{LB} substituent groups, or a –[(0-2C)alkylene-(3-6C)cycloalkylene-(0-2C)alkylene]- group optionally substituted by one or more R_{LB} substituent groups;

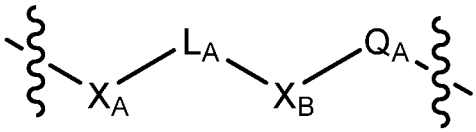
each R_{LB} group present is selected from (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

X_c is selected from: -O-, -SO_2-, -N(R_{xc})-, -C(O)-, -C(O)N(R_{xc})-, -N(R_{xc1})C(O)-, -$S(O)_2$N(R_{xc})- or -N(R_{xc})SO_2-, wherein R_{xc} and R_{xc1} are selected from hydrogen or methyl;

(ii) a group of the formula:



(IV)



(V)

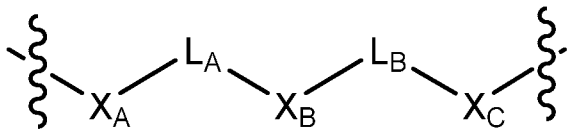
wherein:

X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from a 5 or 6-membered heteroaryl ring, or a 4 to 6 membered heterocyclic ring;

(8) L is a linker selected from:

(i) a group of the formula:



(II)

wherein:

X_A is selected from: -O-, -SO_2-, -N(R_{xa})-, -C(O)N(R_{xa})-, -N(R_{xa})C(O)-, -$S(O)_2$N(R_{xa})- or -N(R_{xa})SO_2-, wherein R_{xa} is selected from hydrogen or methyl;

L_A is a (1-5C)alkylene optionally substituted by one or more R_{LA} substituent groups, or a –[(0-1C)alkylene-(4-6C)cycloalkylene-(0-1C)alkylene]- group,

each R_{LA} group present is selected from (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

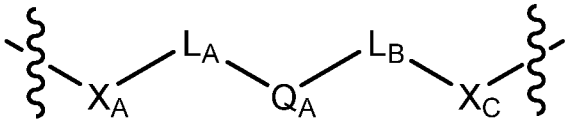
X_B is selected from: -O-, -SO_2-, -N(R_{xb})-, -C(O)N(R_{xb})-, -N(R_{xb1})C(O)-, -$S(O)_2$N(R_{xb})- or -N(R_{xb})SO_2-, wherein R_{xb} and R_{xb1} are selected from hydrogen or methyl;

L_B is a (1-4C)alkylene optionally substituted by one or more R_{LB} substituent groups,

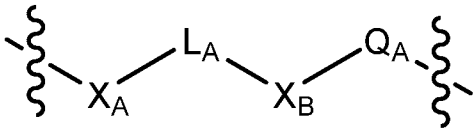
each R_{LB} group present is selected from (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

X_c is selected from: -O-, -SO_2-, -N(R_{xc})-, -C(O)N(R_{xc})-, -N(R_{xc1})C(O)-,-$S(O)_2$N(R_{xc})- or -N(R_{xc})SO_2-, wherein R_{xc} and R_{xc1} are selected from hydrogen or methyl;

(ii) a group of the formula:



(IV)



(V)

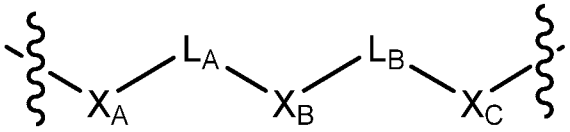
wherein:

X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from a 5 or 6-membered heteroaryl ring, or a 4 to 6 membered heterocyclic ring;

(9) L is a linker selected from:

(i) a group of the formula:



(II)

wherein:

X_A is selected from: -O-, -N(R_{xa})-, -C(O)N(R_{xa})-, or -N(R_{xa})C(O)-, wherein R_{xa} is selected from hydrogen or methyl;

L_A is a (2-5C)alkylene optionally substituted by one or more R_{LA} substituent groups, or a –[(4-6C)cycloalkylene-(0-1C)alkylene]- group,

each R_{LA} group present is (1-2C)alkyl;

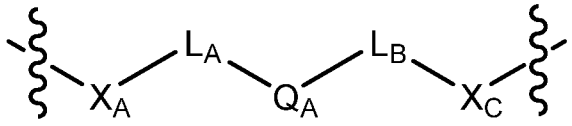
X_B is selected from: -O-, -N(R_{xb})-, -C(O)N(R_{xb})-, or -N(R_{xb1})C(O)-, wherein R_{xb} and R_{xb1} are selected from hydrogen or methyl;

L_B is a (1-4C)alkylene optionally substituted by one or more R_{LB} substituent groups,

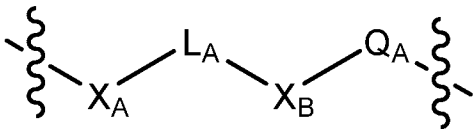
each R_{LB} group present is (1-2C)alkyl;

X_c is selected from: -O-, -N(R_{xc})-, -C(O)N(R_{xc})- or -N(R_{xc1})C(O)-, wherein R_{xc} and R_{xc1} are selected from hydrogen or methyl;

(ii) a group of the formula:



(IV)



(V)

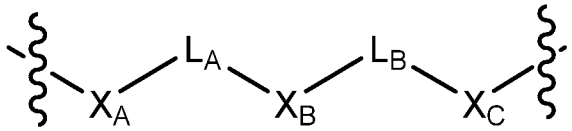
wherein:

X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from a 5 or 6-membered heteroaryl ring, or a 4 to 6 membered heterocyclic ring;

(10) L is a linker selected from:

(i) a group of the formula:



(II)

wherein:

X_A is selected from: -O-, -N(H)-, or -N(Me)-;

L_A is a (2-4C)alkylene optionally substituted by one or more R_{LA} substituent groups, or a –[(4-5C)cycloalkylene-(0-1C)alkylene]- group,

each R_{LA} group present is (1-2C)alkyl;

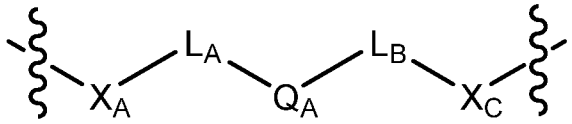
X_B is selected from: -O-, -N(H)-, -N(Me)-, -C(O)N(H)-, -C(O)N(Me)-, -N(H)C(O)- or -N(Me)C(O)-;

L_B is a (1-4C)alkylene optionally substituted by one or more R_{LB} substituent groups,

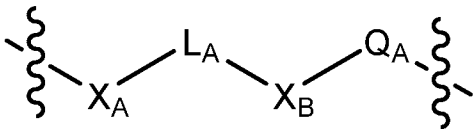
each R_{LB} group present is (1-2C)alkyl;

X_c is selected from: -O-, -N(H)-, -N(Me)-, -C(O)N(H)-, -C(O)N(Me)-, -N(H)C(O)- or -N(Me)C(O)-;

(ii) a group of the formula:



(IV)



(V)

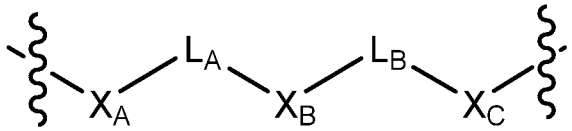
wherein:

X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from a 5-membered heteroaryl ring, or a 4-membered heterocyclic ring;

(11) L is a linker selected from:

(i) a group of the formula:



(II)

wherein:

X_A is selected from: -N(H)-, or -N(Me)-;

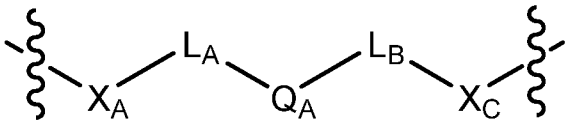
L_A is a (2-4C)alkylene optionally substituted by a methyl group, or L_A is a –[cyclobutylene-(0-1C)alkylene]- group;

X_B is selected from: -O-, -N(H)-, -N(Me)-, -C(O)N(H)-, or -C(O)N(Me)-;

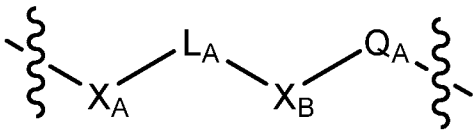
L_B is a (1-4C)alkylene optionally substituted by a methyl group;

X_c is selected from: -O-, -N(H)-, -N(Me)-, -C(O)N(H)- or -C(O)N(Me)- ;

(ii) a group of the formula:



(IV)



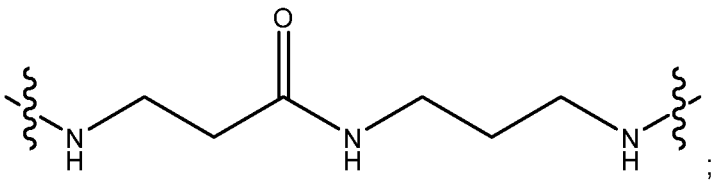
(V)

wherein:

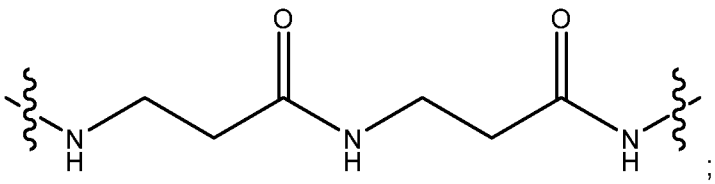
X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from an oxazole group, triazole group or a azetidine group;

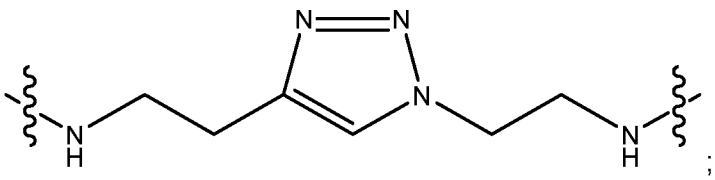
(12) L is a linker selected from:



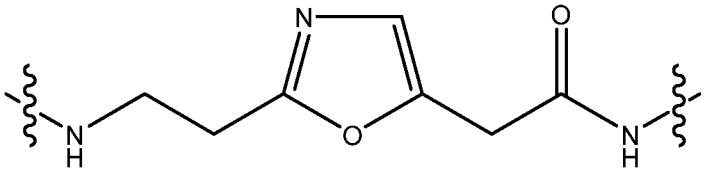
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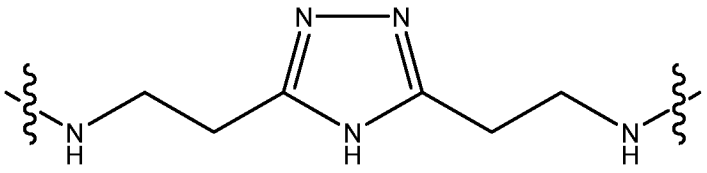


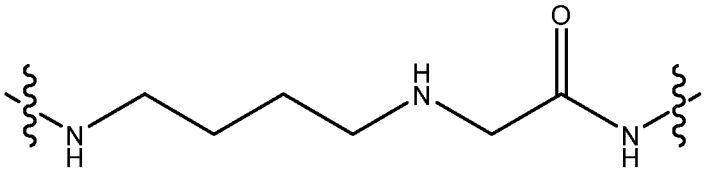
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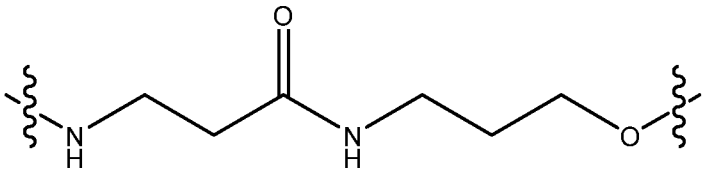


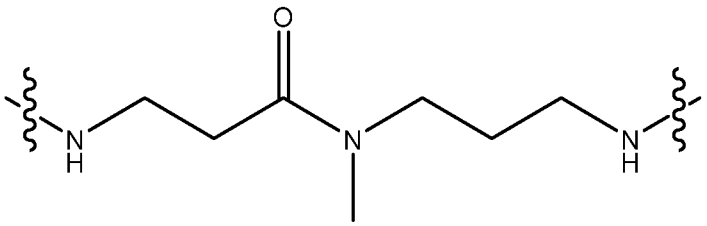
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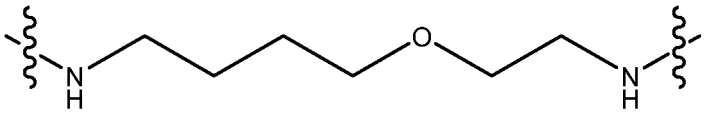

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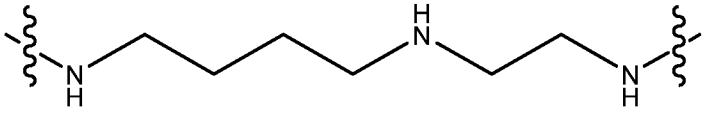

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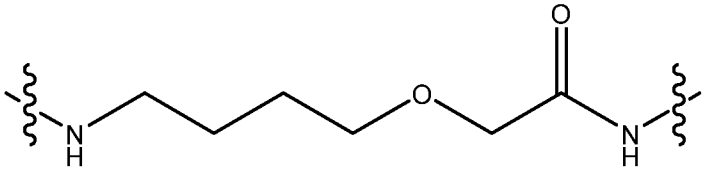

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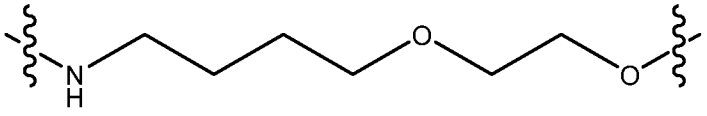

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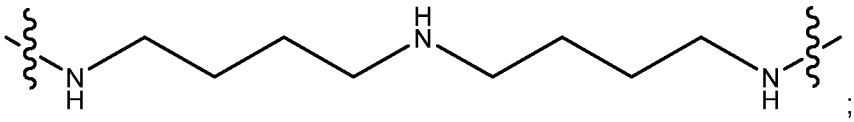

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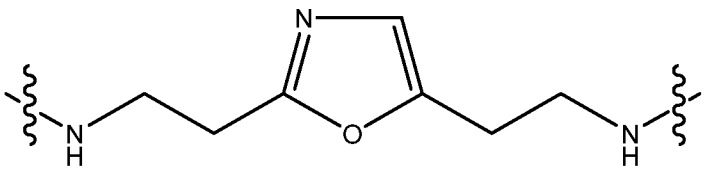

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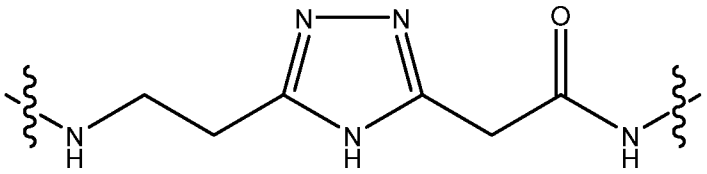

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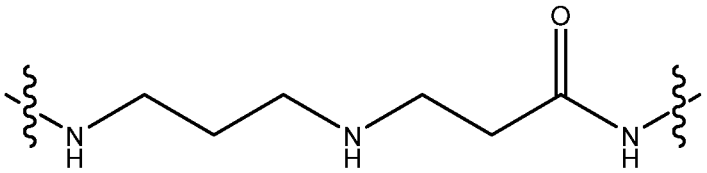

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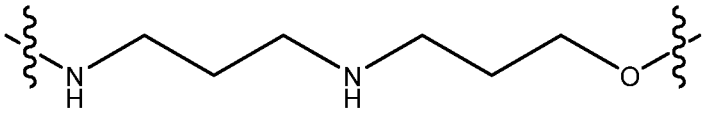

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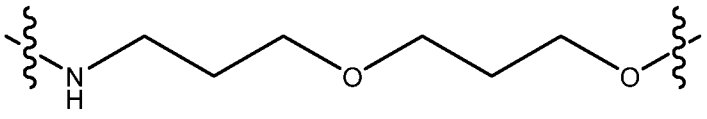


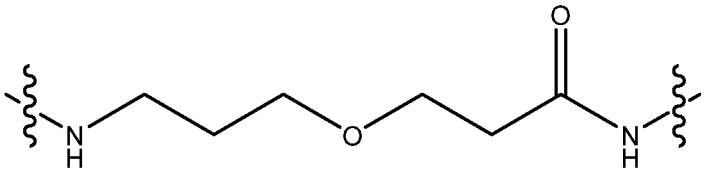


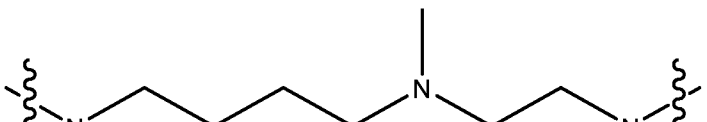


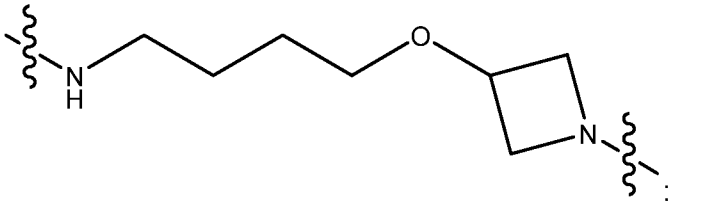


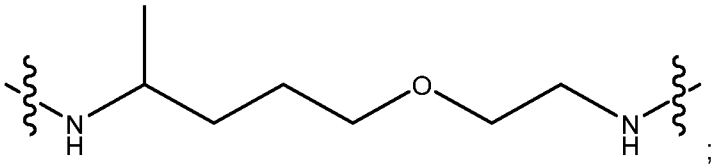


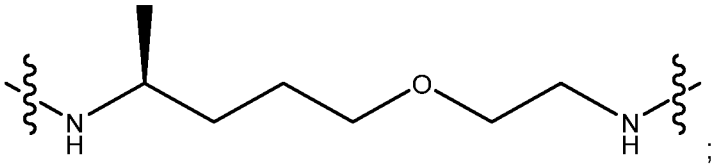


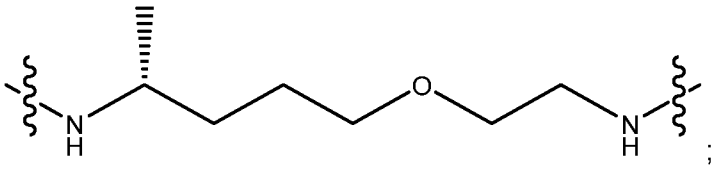


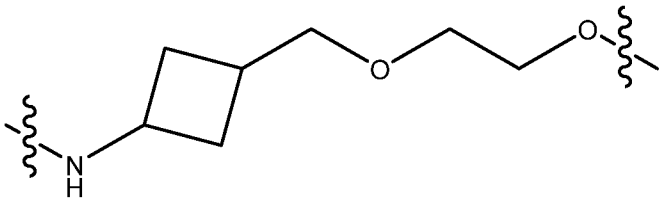


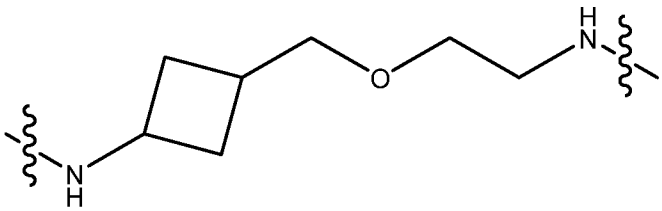


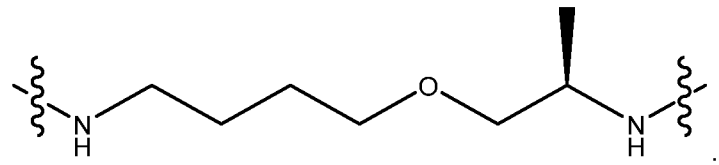

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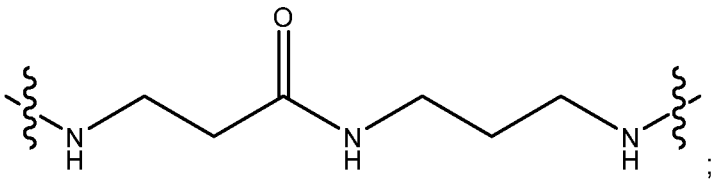

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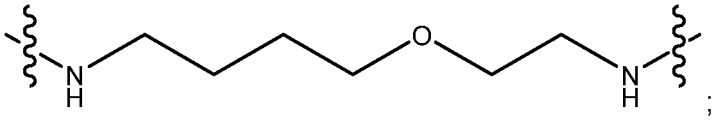

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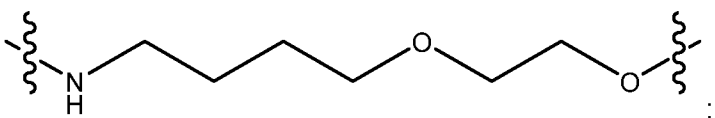

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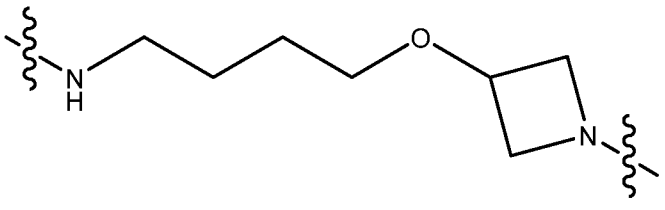

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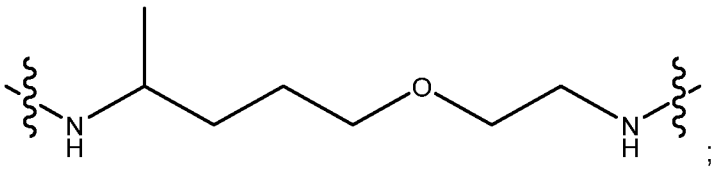
(13) L is a linker selected from:

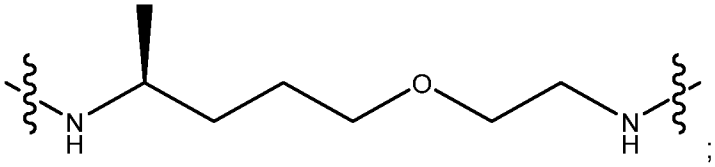

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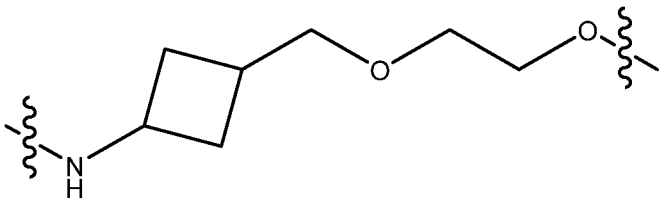

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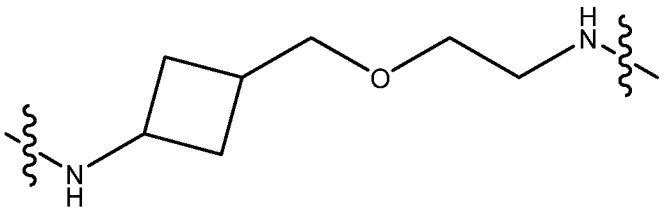

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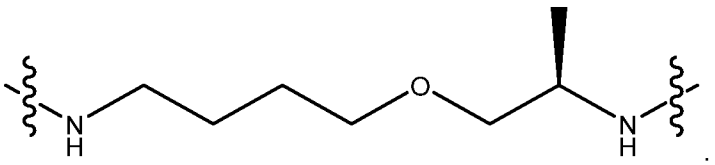

;


;

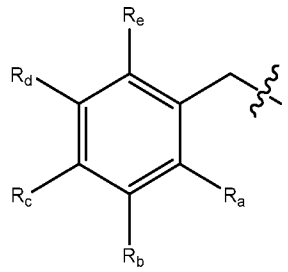

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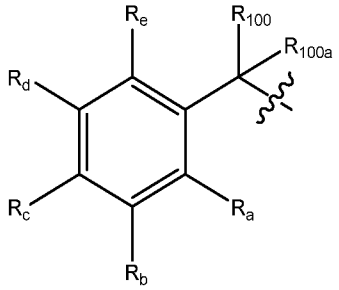

; or


.

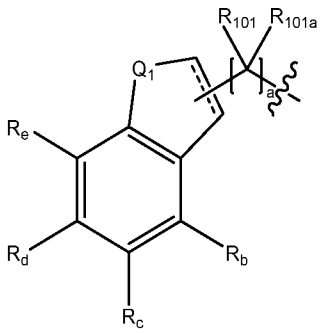
(14) R_L is selected from one of formulae Ic, Id, Ie, If or Ii shown below:



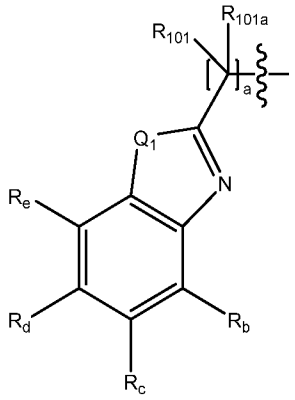
Ic



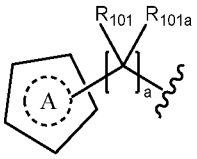
Id



Ie

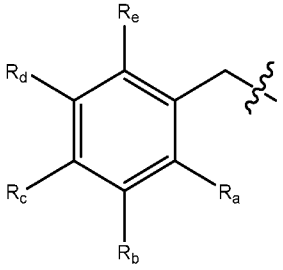


If

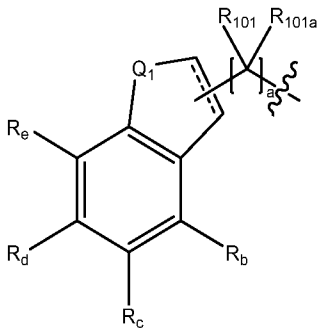


Ij

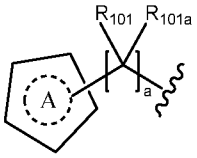
(15) R_L is selected from one of formulae Ic, Ie or If shown below:



Ic

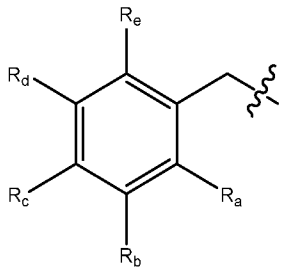


Ie

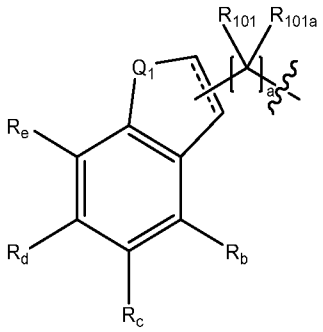


Ij

(16) R_L is selected from one of formulae Ic or Ie shown below:

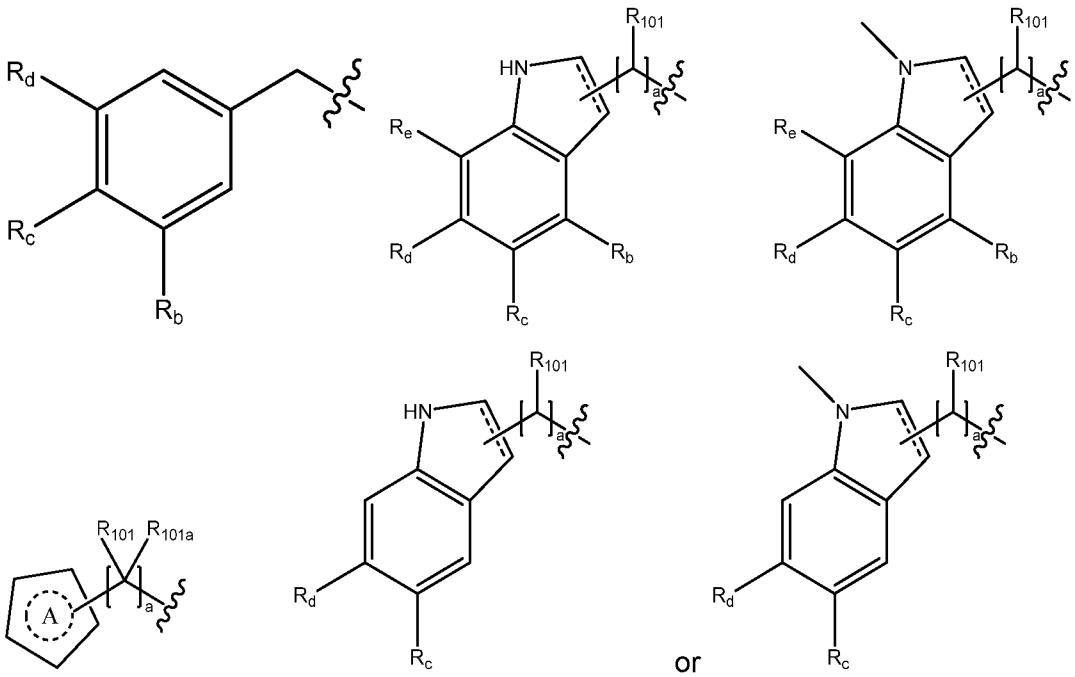


Ic



Ie

(17) R_L is selected from one of formulae shown below:

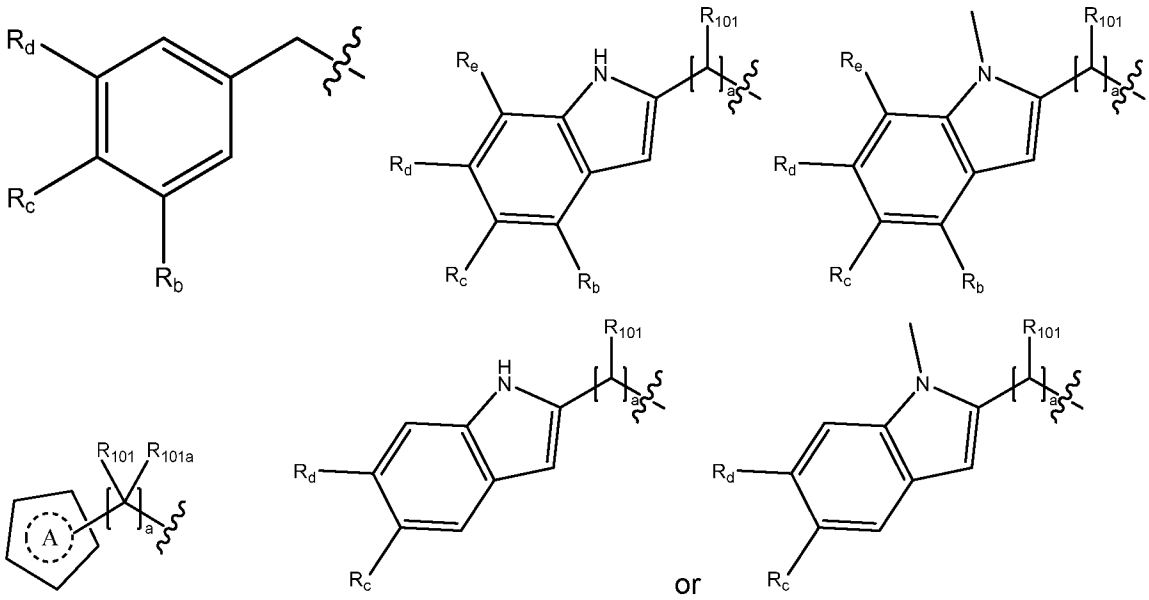


wherein:

denotes the point of attachment; and

denotes an optional double bond;

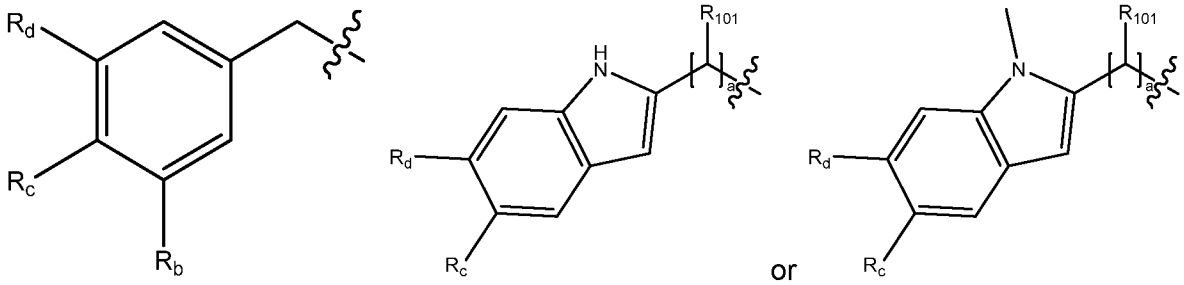
(18) R_L is selected from one of formulae shown below:



wherein:

denotes the point of attachment;

(19) R_L is selected from one of formulae shown below:



wherein:

denotes the point of attachment;

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

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

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

(23) R_a and R_e are both hydrogen;

(24) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, (3-6C)cycloalkyl,

$-[CH_2]_{0-2}$-(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]$_2$,

$-[CH_2]_{0-2}-NH_2$,

$-[CH_2]_{0-2}$-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)OH,

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

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

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

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

$-[CH_2]_{0-2}-N(R_g)SO_2$-(1-4C)alkyl (wherein R_g is hydrogen or methyl),

a group of the formula:

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

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, cycloalkyl or $-[CH_2]-$ 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;

(25) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, (3-6C)cycloalkyl,

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

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

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

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

$-[CH_2]_{0-2}-NH_2$,

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

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

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

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

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

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

$-[CH_2]_{0-2}-N(R_f)C(O)-(1-2C)alkyl$ (wherein R_f is hydrogen or methyl),

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

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

-$[CH_2]_{0-2}$-$N(R_g)SO_2$-(1-2C)alkyl (wherein R_g is hydrogen or methyl),

a group of the formula:

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

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, cycloalkyl or -$[CH_2]$- 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, $-C(O)N[(1\text{-}2C)alkyl]_2$, -NH(1-2C)alkyl, $-N[(1\text{-}2C)alkyl]_2$, $-S(O)_q$-(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, $-S(O)_2N[(1\text{-}2C)alkyl]_2$, 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;

(26) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, (3-6C)cycloalkyl,

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

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

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

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

-$[CH_2]_{0-1}$-NH_2,

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

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

-$[CH_2]_{0-1}$-$S(O)_q$-(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)OH,

-$[CH_2]_{0-1}$-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:

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

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, cycloalkyl or -$[CH_2]$- 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;

(27) R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, (3-6C)cycloalkyl,

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

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

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

-$[CH_2]_{0-1}$-NH_2,

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

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

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

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

-$[CH_2]_{0-1}$-N(H)C(O)-(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, cycloalkyl or -$[CH_2]$- 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, (3-6C)cycloalkyl,

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

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

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

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

a group of the formula:

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

wherein Y_1 is absent, -O-, -NH- or -NMe-; and

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

and wherein:

any alkyl, alkoxy, cycloalkyl or -[CH_2]- 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]$_2$, -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl or -N(R_f)C(O)-(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, (1-3C)alkyl, (1-3C)alkoxy, -C(O)NH_2,

a group of the formula:

$$-Y_1-[CH_2]-Z_1$$

wherein Y_1 is absent; and

Z_1 is 5 or 6-membered heteroaryl;

and wherein:

any alkyl, alkoxy, cycloalkyl or -[CH_2]- 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]$_2$, -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl or -N(R_f)C(O)-(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, fluoro, chloro, bromo, cyano, methyl, ethyl, methoxy, ethoxy, -C(O)NH_2, -CH_2-oxazole, -CH_2OH, -CH_2OCH_3, -CH_2CN, -CH_2CH_2OH, -CF3, -OCF_3, -O-CH_2CH_2OH, -O-CH_2CF_3, -CH_2-C(O)NH_2, -CH(CH_3)CN or -C(CH_3)$_2$CN;

(32) R_b and R_d are each independently selected from hydrogen, fluoro, chloro cyano, methyl, ethyl, methoxy, ethoxy, -C(O)NH_2, -CH_2-oxazole, -CH_2OH, -CH_2CN, -CH_2CH_2OH, -CF3, -OCF_3, -O-CH_2CH_2OH or -CH_2-C(O)NH_2;

(33) One of R_b and R_d is hydrogen or halogen and the other is selected from any one of the options defined in paragraphs (24) to (32);

(34) One of R_b and R_d is hydrogen or halogen and the other is selected from hydrogen, fluoro, chloro cyano, methyl, ethyl, methoxy, ethoxy, -C(O)NH_2, -CH_2-oxazole, -CH_2OH, -CH_2CN, -CH_2CH_2OH, -CF3, -OCF_3, -O-CH_2CH_2OH or -CH_2-C(O)NH_2;

(35) R_c is selected from hydrogen, halo, cyano, -C(O)NH_2, (1-4C)alkyl, (3-6C)cycloalkyl

-[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(1-2C)alkyl,

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

-$[CH_2]_{0-2}$-NH_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)OH,

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

-$[CH_2]_{0-2}$-$N(R_h)$C(O)-(1-2C)alkyl (wherein R_h is hydrogen or methyl),

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

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

-$[CH_2]_{0-2}$-$N(R_i)SO_2$-(1-2C)alkyl (wherein R_i is hydrogen or methyl),

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, cycloalkyl or -$[CH_2]$- 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;

(36) R_c is selected from hydrogen, halo, cyano, -$C(O)NH_2$, (1-4C)alkyl, (3-6C)cycloalkyl

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

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

-$[CH_2]_{0-1}$-NH_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)OH,

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

-$[CH_2]_{0-1}$-$N(R_h)C(O)$-(1-2C)alkyl (wherein R_h is hydrogen or methyl),

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

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

-$[CH_2]_{0-1}$-$N(R_i)SO_2$-(1-2C)alkyl (wherein R_i is hydrogen or methyl),

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, cycloalkyl or -$[CH_2]$- 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, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl;

(37) R_c is selected from hydrogen, halo, cyano, $-C(O)NH_2$, (1-4C)alkyl, (3-6C)cycloalkyl

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

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

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

$-[CH_2]_{0-1}-NH_2$,

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

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

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

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

(38) R_c is selected from hydrogen, halo, cyano, $-C(O)NH_2$, (1-4C)alkyl, (3-6C)cycloalkyl

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

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

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

$-[CH_2]_{0-1}-NH_2$,

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

a group of the formula:

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

wherein Y_2 is absent, -O-, -NH- or -NMe-; 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, cycloalkyl or $-[CH_2]-$ 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, $-N[(1-2C)alkyl]_2$, -C(O)(1-2C)alkyl or -C(O)O-(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;

(39) R_c is selected from hydrogen, halo, cyano, $-C(O)NH_2$, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkoxy,

a group of the formula:

$$-Y_2-Z_2$$

wherein Y_2 is absent, -O-, -NH- or -NMe-; 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, cycloalkyl or $-[CH_2]-$ 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]$_2$, -C(O)(1-2C)alkyl or -C(O)O-(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;

(40) R_c is selected from hydrogen, halo, cyano, -C(O)NH_2, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkoxy,

a group of the formula:

$$-Y_2-Z_2$$

wherein Y_2 is absent or -O -; and

Z_2 is (3-4C)cycloalkyl or phenyl;

and wherein:

any alkyl, alkoxy, cycloalkyl or -[CH_2]- 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]$_2$, -C(O)(1-2C)alkyl or -C(O)O-(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;

(41) R_c is selected from hydrogen, halo, cyano, -C(O)NH_2, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkoxy,

a group of the formula:

$$-Y_2-Z_2$$

wherein Y_2 is absent or -O -; and

Z_2 is (3-4C)cycloalkyl or phenyl;

and wherein:

any alkyl, alkoxy, cycloalkyl or -[CH_2]- moiety within a R_c substituent group is optionally substituted by one or more substituents selected from fluoro, chloro, hydroxy, cyano, or amino; and

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

(42) R_c is selected from hydrogen, fluoro, chloro, bromo, cyano, -C(O)NH_2, methyl, -CF_3, ethyl, propyl, methoxy, -OCF_3, ethoxy, propoxy, cyclopropyl, cyclobutyl, cyclopentyl, phenyl, -O-cyclopropyl, -O-cyclobutyl, -O-cyclopentyl, -phenyl-(1-2Calkyl)-OH or -phenyl-(1-2Calkyl)-CN;

(43) R_c is selected from hydrogen, -CF_3, -OCF_3, cyclopropyl, phenyl, -O-cyclobutyl or -phenyl-CH_2-OH;

(44) R_{100} is methyl optionally substituted by hydroxy, fluoro, chloro or bromo;

(45) R_{100} is methyl optionally substituted by hydroxy or chloro;

(46) R_{100a} is hydrogen;

(47) R_{100a} is methyl;

(48) R_{100} and R_{100a} are linked to form a cyclopropyl ring;

(49) R_{100} and R_{100a} are linked to form a cyclobutyl ring;

(50) R_{101} is hydrogen or methyl optionally substituted by hydroxy or halo;

(51) R_{101} is hydrogen or methyl optionally substituted by hydroxy, fluoro, chloro or bromo;

(52) R_{101} is hydrogen or methyl optionally substituted by hydroxy or chloro;

(53) R_{101a} is hydrogen;

(54) R_{101a} is methyl;

(55) R_{101} and R_{101a} are linked to form a cyclopropyl ring;

(56) R_{101} and R_{101a} are linked to form a cyclobutyl ring;

(57) integer a is 0, 1 or 2;

(58) integer a is 0 or 1

(59) integer a is 1

(60) Q_1 is selected from -NR_{102}-, -O- or -S-;

(61) Q_1 is selected from -NR_{102}- or -O-;

(62) Q_1 is -NR_{102}-;

(63) R_{102} is hydrogen or methyl;

(64) R_{102} is hydrogen

(65) ------ represents a double bond;

(66) Q_2 is N or CR_a;

Q_3 is N or CR_b;

Q_4 is N or CR_c;

Q_5 is N or CR_d;

Q_6 is N or CH;

R_a, R_b, R_c, R_d and R_e are each as defined in any one of paragraphs (20) to (23), (24) to (34) and (35) to (43) above;

with the proviso that one to three of Q_2, Q_3, Q_4, Q_5 or Q_6 is/are N;

(67) Q_2 is N or CH;

Q_3 is N or CR_b;

Q_4 is N or CR_c;

Q_5 is N or CR_d;

Q_6 is N or CH;

R_b, R_c and R_d are each as defined in any one of paragraphs (24) to (34) and (35) to (43) above;

with the proviso that one to three of Q_2, Q_3, Q_4, Q_5 or Q_6 is/are N;

(68) Q_2 is N;

Q_3 is CR_b;

Q_4 is CR_c;

Q_5 is CR_d;

Q_6 is CH;

R_b, R_c and R_d are each as defined in any one of paragraphs (24) to (34) and (35) to (43) above;

(69) Q_2 is CH;

Q_3 is N;

Q_4 is CR_c;

Q_5 is CR_d;

Q_6 is CH;

R_c and R_d are each as defined in any one of paragraphs (24) to (34) and (35) to (43) above;

with the proviso that one to three of Q_2, Q_3, Q_4, Q_5 or Q_6 is/are N;

(70) Q_2 is CH;

Q_3 is CR_b;

Q_4 is CR_c;

Q_5 is N;

Q_6 is CH;

R_b and R_c are each as defined in any one of paragraphs (24) to (34) and (35) to (43) above;

(71) Q_2 is CH;

Q_3 is CR_b;

Q_4 is CR_c;

Q_5 is CR_d;

Q_6 is N;

R_b, R_c and R_d are each as defined in any one of paragraphs (24) to (34) and (35) to (43) above;

(72) Q_7 is N or CR_f;

Q_8 is N or CR_f;

Q_9 is N or CR_f;

Q_{10} is N or CR_f;

with the proviso that one or two of Q_7, Q_8, Q_9 or Q_{10} is/are N;

each R_f present is independently selected from hydrogen, methyl fluoro, chloro or bromo;

(73) Q_7 is N or CR_f;

Q_8 is N or CR_f;

Q_9 is N or CR_f;

Q_{10} is N or CR_f;

with the proviso that one or two of Q_7, Q_8, Q_9 or Q_{10} is/are N;

each R_f present is hydrogen;

(74) Q_7 is N;

Q_8 is CH;

Q_9 is CH;

Q_{10} is CH;

(75) Ring A is a five-membered heteroaryl ring comprising one, two or three heteroatoms selected from N, O or S, optionally substituted by one R_b (as defined herein) and/or one or two R_c substituents (as defined herein);

(76) Ring A is a five-membered heteroaryl ring comprising one or two heteroatoms selected from N, O or S, optionally substituted by one R_b (as defined in any one of paragraphs (24) to (34) above) and/or one or two R_c substituents (as defined in any one of paragraphs (35) to (43) above);

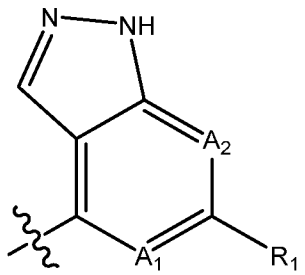
(77) Ring A is a five-membered heteroaryl ring comprising one or two heteroatoms selected from N or O, optionally substituted by one R_b (as defined in any one of paragraphs (30) to (34) above) and/or one or two R_c substituents (as defined in any one of paragraphs (40) to (43) above);

(78) Ring A is a five-membered heteroaryl ring comprising two heteroatoms selected from N or O, optionally substituted by one R_b (as defined in paragraph (34) above) and/or one or two R_c substituents (as defined in paragraph (43) above);

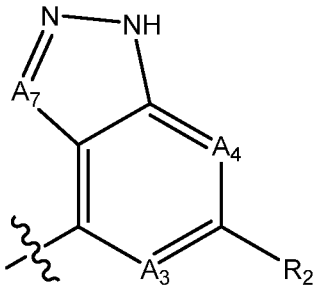
(79) Ring A is a pyrazole ring substituted with one, two or three groups independently selected from phenyl, methyl, chloro;

(80) Ring A is a pyrazole ring substituted with one phenyl group and one chloro group;

(81) R_R is selected from one of formulae Im or In shown below:



Im

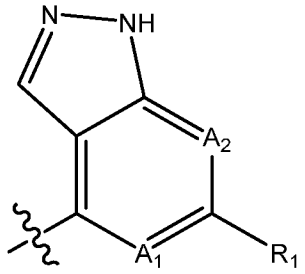


In

wherein:

~~~ denotes the point of attachment;

(82) R_R is formula Im shown below:



Im

wherein:

~~~ denotes the point of attachment;

(83) A_1 and A_2 are both CH;

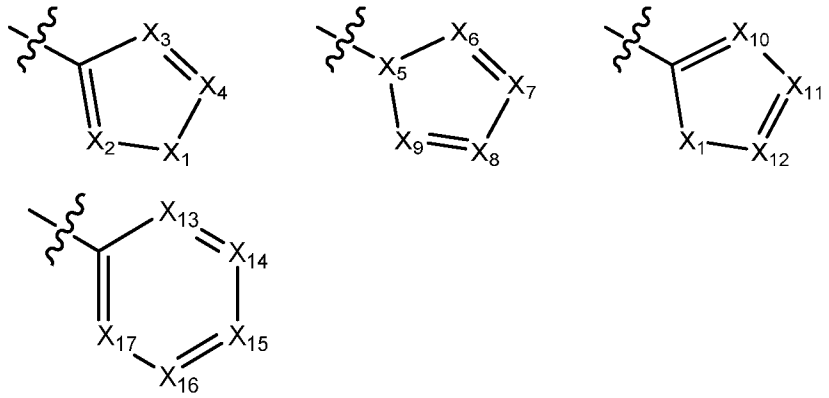
(84) one of A_1 and A_2 is N and the other is CH;

(85) R_1 is a 5- or 6-membered heteroaryl ring comprising one, two, three or four heteroatoms which is optionally substituted on any available carbon atom by one or more R_{1A} substituent groups and on any available nitrogen atom by one or more R_{1B} substituent groups;

(86) R_1 is a 5- or 6-membered heteroaryl ring comprising one, two, three or four heteroatoms selected from N, O or S which is optionally substituted on any available carbon atom by one or more R_{1A} substituent groups and on any available nitrogen atom by one or more R_{1B} substituent groups;

(87) R_1 is a 5- or 6-membered heteroaryl ring comprising one, two, or three heteroatoms selected from N, O or S which is optionally substituted on any available carbon atom by one or more R_{1A} substituent groups and on any available nitrogen atom by one or more R_{1B} substituent groups;

(88) R_1 is selected from:



wherein:

~~~ denotes the point of attachment;

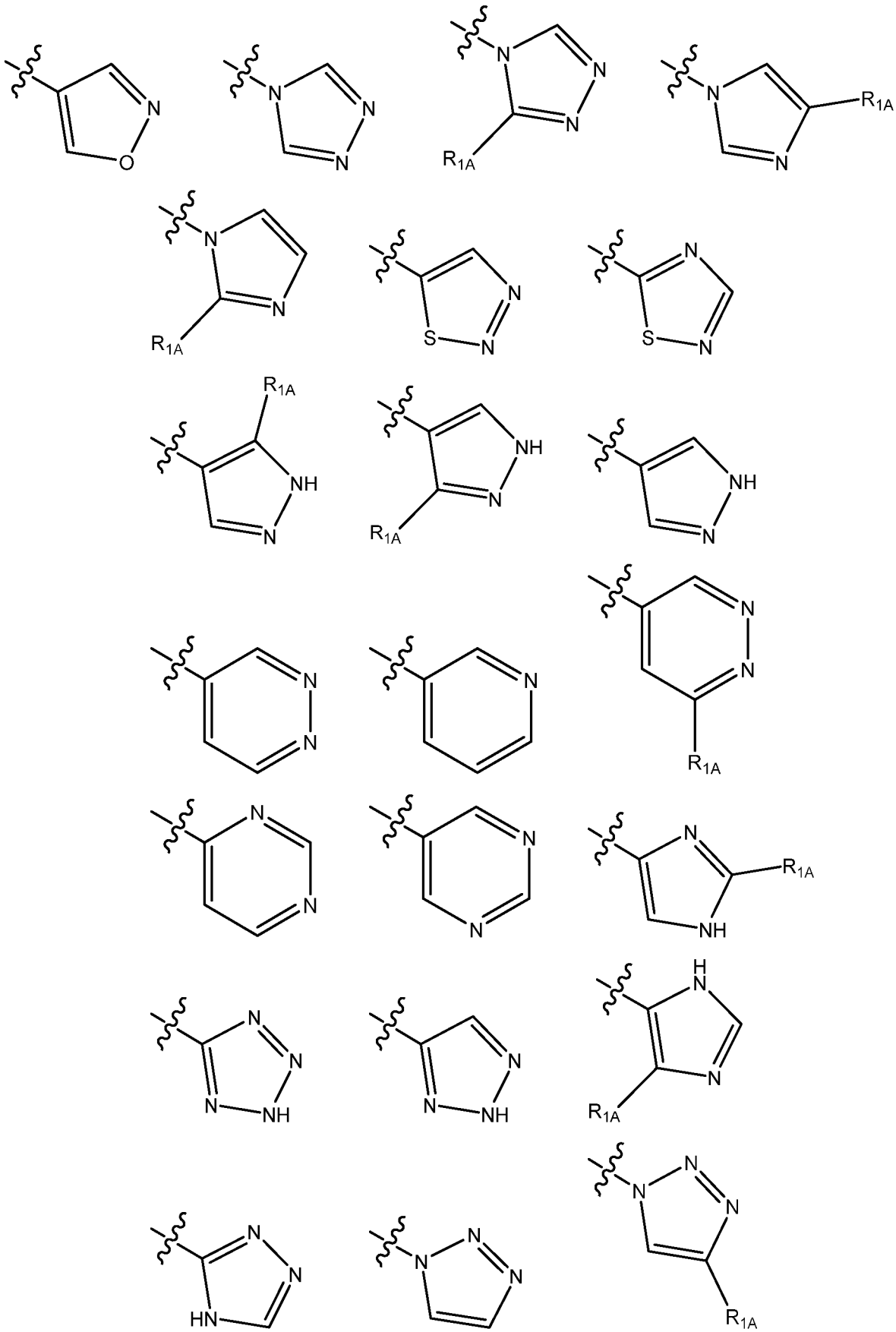
X_1 is NH, NR_{1B}, O or S;

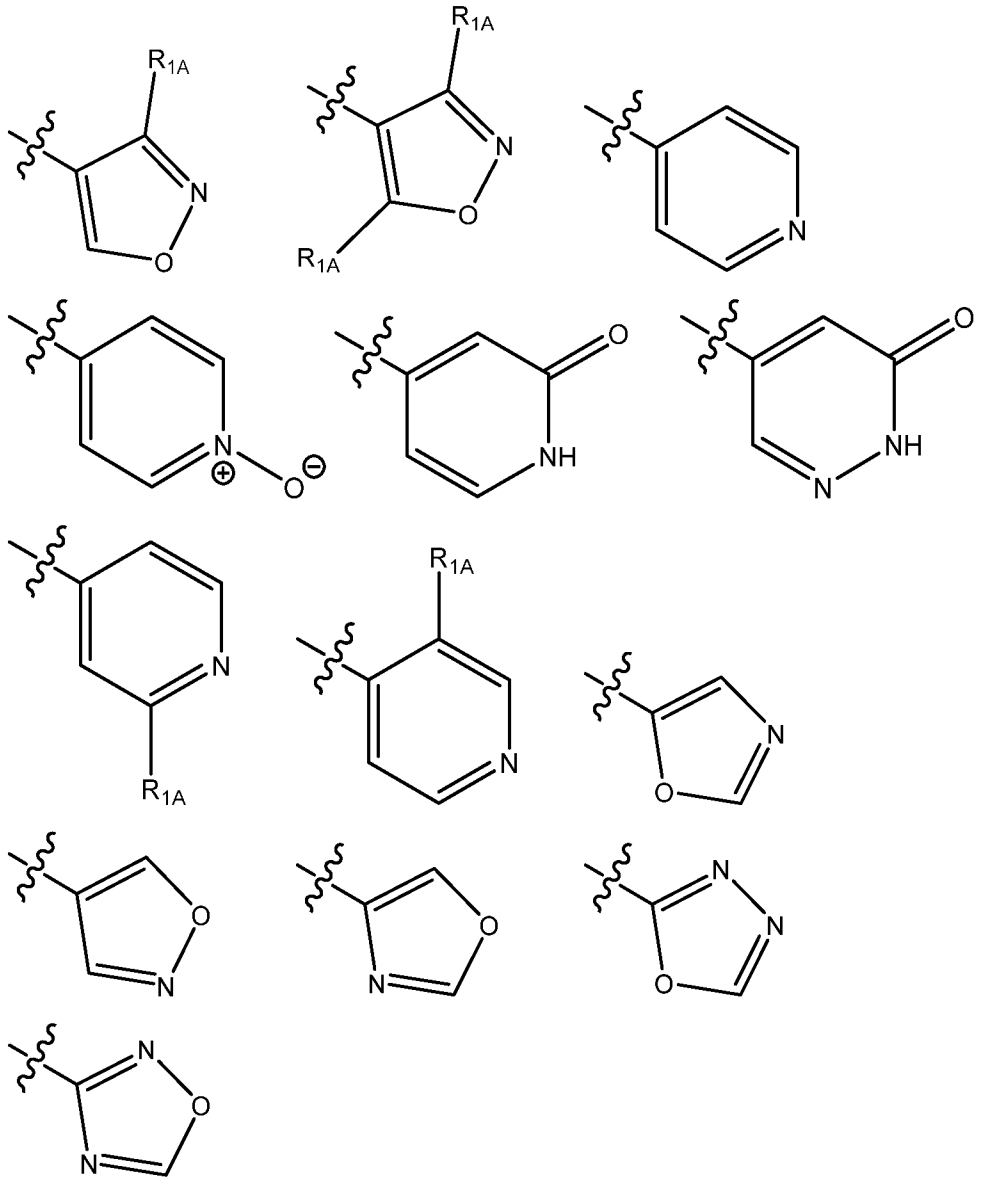
X_5 is N;

X_2, X_3, X_4, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16} or X_{17} are selected from CH, CR_{1A}, N or N^+-O^-;

and R_{1A} and R_{1B} are both as defined herein;

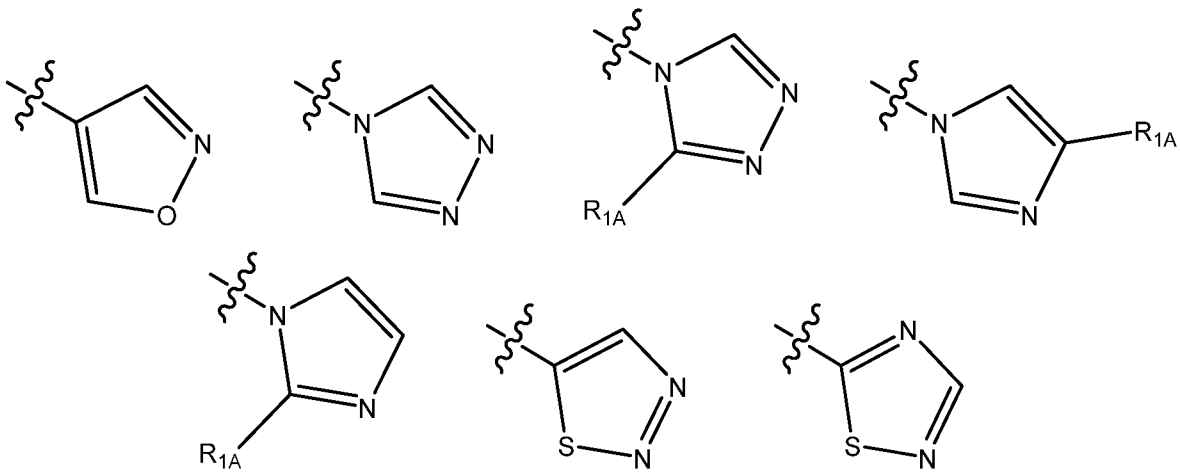
(89) R_1 is selected from:
~~~

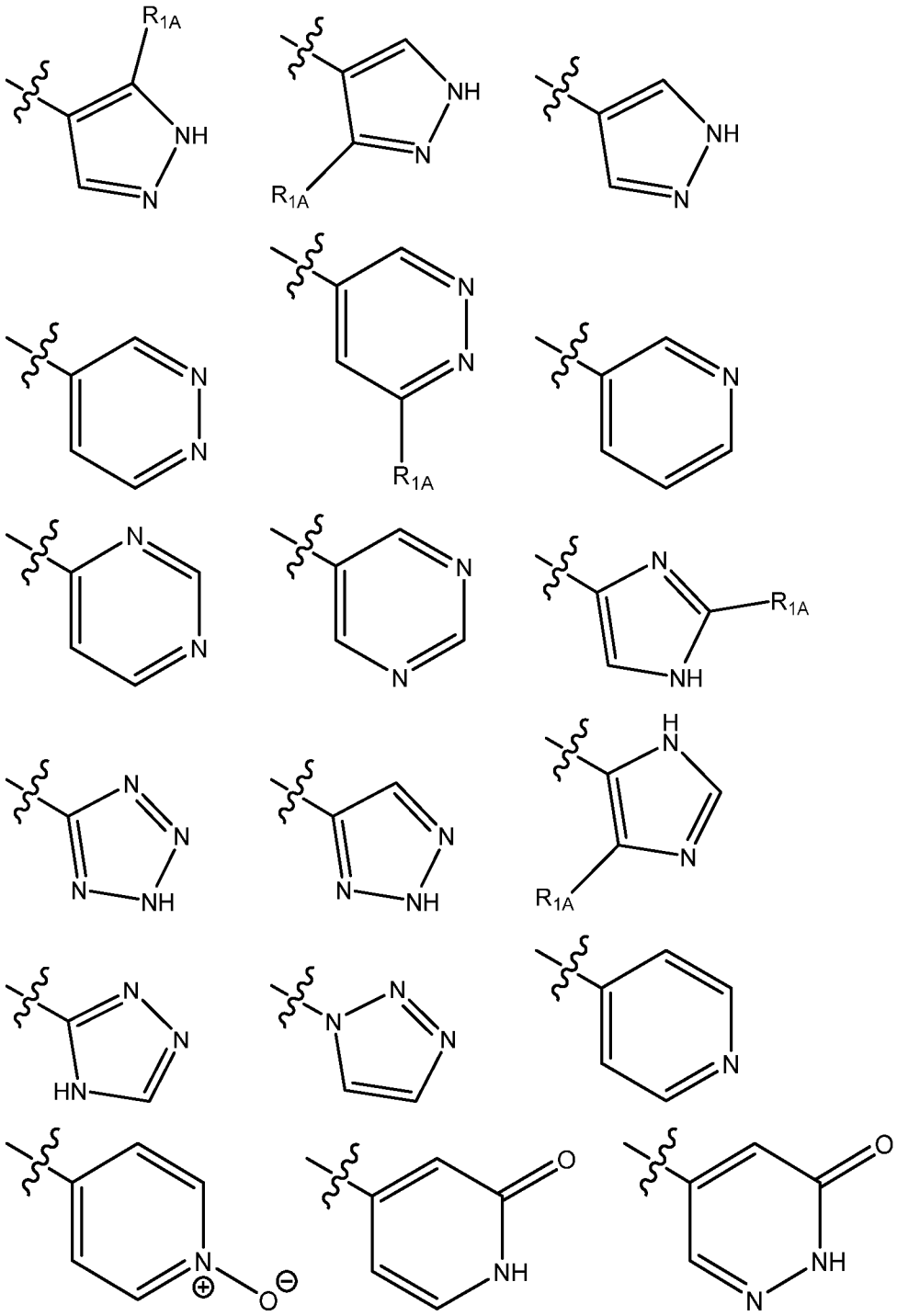


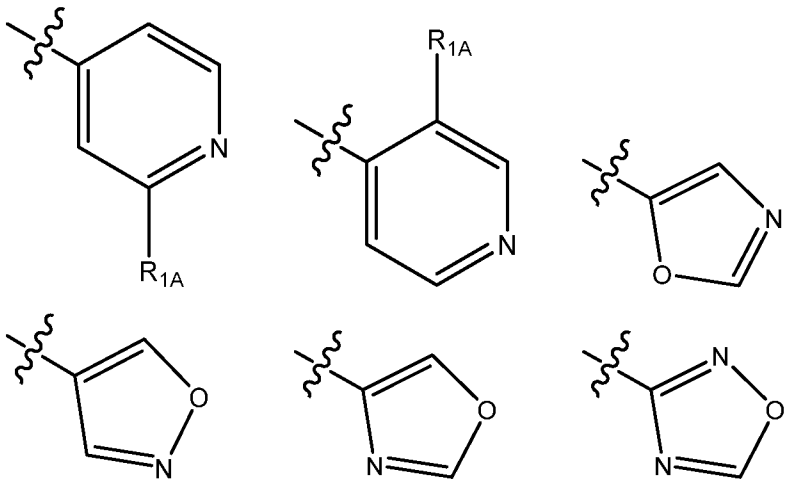


wherein R_{1A} is as defined herein;

(90) R_1 is selected from:

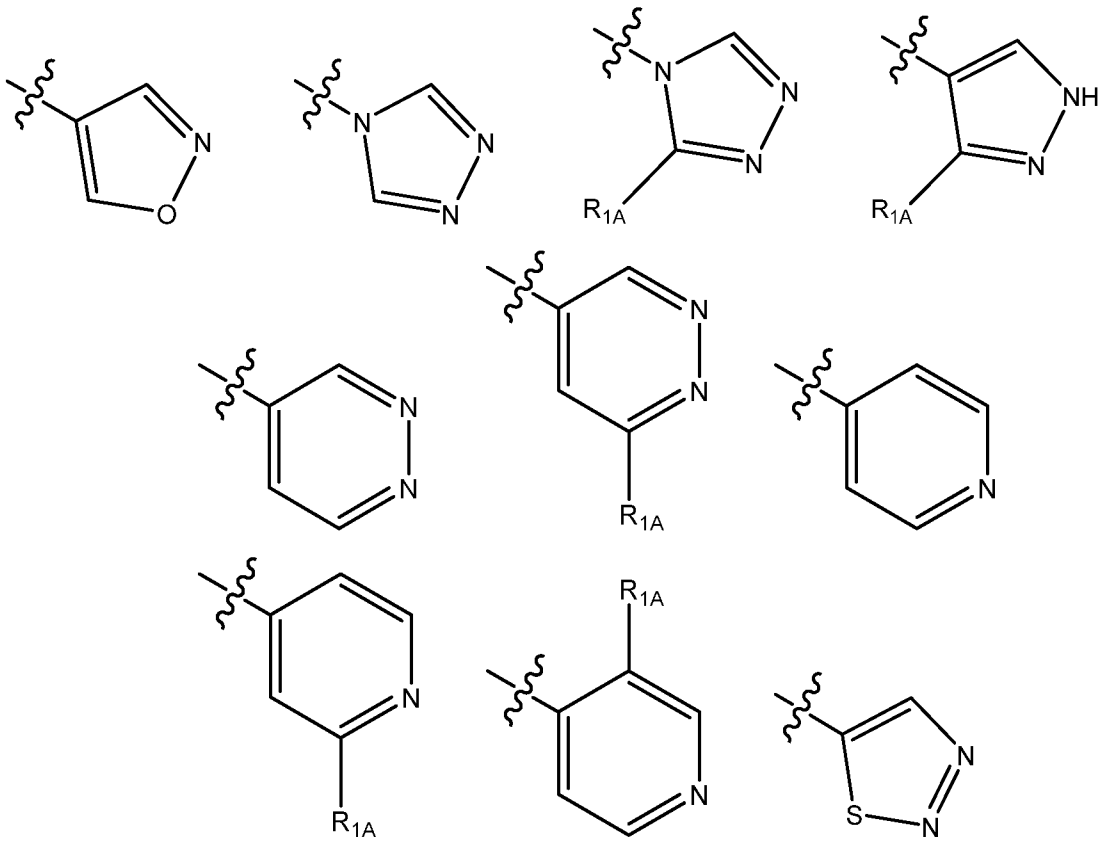



R1A
NH
N
R1A
NH
N
NH
N
N
N
N
R1A
N
N
N
N
N
N
R1A
NH
N
N
N
NH
N
N
NH
H
N
N
R1A
N
N
HN
N
N
N
N
O
N
O
NH
O
NH
N



wherein R_{1A} is as defined herein;

(91) R_1 is selected from:



wherein R_{1A} is as defined herein;

(92) X_1 is NH, NMe, O or S;

(93) X_1 is NH, O or S;

(94) X_1 is NH;

(95) X_1 is O;

(96) X_1 is S;

(97) X_5 is N;

(98) X_2, X_3 and X_4 are each independently selected from CH, CR_{1A} or N, wherein R_{1A} is as defined herein;

(99) X_2, X_3 and X_4 are each independently selected from CH, C-(1-2C)alkyl, C-CN, C-OH, C-NH_2, C-O-(1-2C)alkyl, C-halo or N;

(100) X_2, X_3 and X_4 are each independently selected from CH, C-CH_3, C-CH_2CH_3, C-CN, C-OH, C-NH_2, C-O-CH_3, C-O-CH_2CH_3, C-F, C-Cl, C-Br or N;

(101) X_2, X_3 and X_4 are each independently selected from CH, C-CH_3, C-CN, C-O-CH_3, or N;

(102) X_2, X_3 and X_4 are all N;

(103) One or two of X_2, X_3 and X_4 are N and the others are each independently selected from CH, C-CH_3, C-CN, or C-O-CH_3;

(104) One of X_2, X_3 and X_4 is N and the others are each independently selected from CH, C-CH_3, C-CN or C-O-CH_3;

(105) Two of X_2, X_3 and X_4 is N and the other is CH;

(106) X_6, X_7, X_8 and X_9 are each independently selected from CH, CR_{1A} or N, wherein R_{1A} is as defined herein;

(107) X_6, X_7, X_8 and X_9 are each independently selected from CH, C-(1-2C)alkyl, C-CN, C-OH, C-NH_2, C-O-(1-2C)alkyl, C-halo or N;

(108) X_6, X_7, X_8 and X_9 are each independently selected from CH, C-CH_3, C-CH_2CH_3, C-CN, C-OH, C-NH_2, C-O-CH_3, C-O-CH_2CH_3, C-F, C-Cl, C-Br or N;

(109) X_6, X_7, X_8 and X_9 are each independently selected from CH, C-CH_3, C-CN, C-OH or N;

(110) One or two of X_6, X_7, X_8 and X_9 are N and the others are each independently selected from CH, C-CH_3, C-CN or C-OH;

(111) Two of X_6, X_7, X_8 and X_9 are N and the others are each independently selected from CH, C-CH_3, C-CN or C-OH;

(112) Two of X_6, X_7, X_8 and X_9 are N and the others are both CH;

(113) X_{10}, X_{11} and X_{12} are each independently selected from CH, CR_{1A} or N, wherein R_{1A} is as defined herein;

(114) X_{10}, X_{11} and X_{12} are each independently selected from CH, C-(1-2C)alkyl, C-CN, C-OH, C-NH_2, C-O-(1-2C)alkyl, C-halo or N;

(115) X_{10}, X_{11} and X_{12} are each independently selected from CH, C-CH_3, C-CH_2CH_3, C-CN, C-OH, C-NH_2, C-O-CH_3, C-O-CH_2CH_3, C-F, C-Cl, C-Br or N;

(116) One or two of X_{10}, X_{11} and X_{12} N and the others are each independently selected from CH or C-CH_3;

(117) Two of X_{10}, X_{11} and X_{12} N and the other is CH;

(118) X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are each independently selected from CH, CR_{1A} or N, wherein R_{1A} is as defined herein;

(119) X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are each independently selected from CH, C-(1-2C)alkyl, C-CN, C-OH, C(O), C-NH_2, C-O-(1-2C)alkyl, C-halo, N or N-oxide;

(120) X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are each independently selected from CH, C-CH_3, C-CH_2CH_3, C-CN, C-OH, C(O), C-NH_2, C-O-CH_3, C-O-CH_2CH_3, C-F, C-Cl, C-Br, N or N-oxide;

(121) One or two of X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are N and the others are each independently selected from CH, C-CH_3, C-CH_2CH_3, C-CN, C-OH, C(O), C-NH_2, C-O-CH_3, C-O-CH_2CH_3, C-F, C-Cl, C-Br, N or N-oxide;

(122) One or two of X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are N and the others are each independently selected from CH, C-CH_3, C-CN, C-OH, C(O), C-NH_2, C-O-CH_3, C-F, C-Cl, C-Br or N-oxide;

(123) One of X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are N and the others are each independently selected from CH, C-CH_3, C-CN, C(O), C-NH_2, C-O-CH_3, C-F or C-Cl;

(124) Two of X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are N and the others are each independently selected from CH, C-CN, C-OH, or C-NH_2;

(125) Two of X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are N, one is C-OH or C--NH_2, and the others are CH;

(126) Two of X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are N and the others are CH;

(127) each R_{1A} group present is selected from hydroxy, cyano, amino, halo, -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]$_2$, or -C(O)(1-2C)alkyl, -C(O)O-(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;

(128) each R_{1A} group present is selected from hydroxy, cyano, amino, halo, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(Me), -C(O)N[Me]$_2$, -NH(Me), -N(Me)$_2$, or -C(O)(Me), -C(O)O-(Me); and wherein any (1-2C)alkoxy, (1-2C)alkyl, methyl, (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;

(129) each R_{1A} group present is selected from hydroxy, cyano, amino, halo, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl, (3-4C)cycloalkyl, (3-4C)cycloalkoxy, -C(O)NH(Me), -C(O)N[Me]$_2$, -NH(Me), -N(Me)$_2$, or -C(O)(Me), -C(O)O-(Me); and wherein any (1-2C)alkoxy, (1-2C)alkyl, methyl, (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;

(130) each R_{1A} group present is selected from hydroxy, cyano, amino, chloro, fluoro, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl; and wherein any (1-2C)alkoxy, (1-

2C)alkyl 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;

(131) each R_{1A} group present is selected from -OH, -CN, NH_2, -F, -Cl, =O, $-OCH_3$, or $-CH_3$;

(132) each R_{1A} group present is selected from -OH, -CN, NH_2, -F, =O, $-OCH_3$, or $-CH_3$;

(133) each R_{1B} group is methyl, ethyl, cyclopropyl or cyclobutyl;

(134) each R_{1B} group is methyl;

(135) A_3 is selected from CH;

(136) A_3 is selected from CR_3;

(137) A_3 is selected from N;

(138) A_4 is selected from CH;

(139) A_4 is selected from CR_4;

(140) A_4 is selected from N;

(141) A_5 and A_6 are both C;

(142) one of A_5 and A_6 is N and the other is C;

(143) A_7 is selected from CH;

(144) A_7 is selected from CR_7;

(145) A_7 is selected from N;

(146) R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)cyanoalkyl, (1-4C)hydroxyalkyl, (1-4C)haloalkyl, (1-4C)aminoalkyl,

$-[CH_2]_{0-2}$-(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)OH,

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

$-[CH_2]_{0-2}-N(R_{2a})C(O)$-(1-4C)alkyl (wherein R_{2a} is hydrogen or methyl),

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

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

$-[CH_2]_{0-2}-N(R_{2b})SO_2$-(1-4C)alkyl (wherein R_{2b} is hydrogen or methyl),

a 4- to 7-membered heterocyclyl,

(3-6C)cycloalkyl,

(3-6C)cycloalkyl(1-2C)alkyl,
phenyl, or
phenyl(1-2C)alkyl;
and wherein any cycloalkyl, heterocyclyl or phenyl group present is optionally substituted by one or more hydroxy, cyano, amino, halo, -C(O)OH, -C(O)NH_2, (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, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl (wherein R_f is hydrogen or methyl), -S(O)$_2$NH(1-2C)alkyl, -S(O)$_2$N[(1-2C)alkyl]$_2$, or -NHSO$_2$-(1-2C)alkyl;

(147) R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)cyanoalkyl, (1-4C)hydroxyalkyl, (1-4C)haloalkyl, (1-4C)aminoalkyl,
-[CH$_2$]$_{0-2}$-(1-4C)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[(1-4C)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)OH,
-[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 4- to 7-membered heterocyclyl,
(3-6C)cycloalkyl,
(3-6C)cycloalkyl(1-2C)alkyl,
phenyl, or
phenyl(1-2C)alkyl;
and wherein any cycloalkyl, heterocyclyl or phenyl group present is optionally substituted by one or more hydroxy, cyano, amino, halo, -C(O)OH, -C(O)NH_2, (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, -C(O)O-

(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl (wherein R_f is hydrogen or methyl), -S(O)$_2$NH(1-2C)alkyl, -S(O)$_2$N[(1-2C)alkyl]$_2$, or -NHSO$_2$-(1-2C)alkyl;

(148) R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)cyanoalkyl, (1-4C)hydroxyalkyl, (1-4C)haloalkyl, (1-4C)aminoalkyl,
-[CH$_2$]$_{0-1}$-(1-4C)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[(1-4C)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$_2$]$_{0-2}$-C(O)OH,
-[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 4- to 7-membered heterocyclyl,
(3-6C)cycloalkyl,
(3-6C)cycloalkyl(1-2C)alkyl,
phenyl, or
phenyl(1-2C)alkyl;
and wherein any cycloalkyl, heterocyclyl or phenyl group present is optionally substituted by one or more hydroxy, cyano, amino, halo, -C(O)OH, -C(O)NH$_2$, (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, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl (wherein R_f is hydrogen or methyl), -S(O)$_2$NH(1-2C)alkyl, -S(O)$_2$N[(1-2C)alkyl]$_2$, or -NHSO$_2$-(1-2C)alkyl;

(149) R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)cyanoalkyl, (1-4C)hydroxyalkyl, (1-4C)haloalkyl, (1-4C)aminoalkyl,
-[CH$_2$]$_{0-1}$-(1-4C)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[(1-4C)alkyl]$_2$,
-$[CH_2]_{0-1}$-C(O)(1-2C)alkyl,
-$[CH_2]_{0-2}$-C(O)OH,
-$[CH_2]_{0-1}$-C(O)O-(1-2C)alkyl,
-$[CH_2]_{0-1}$-N(H)C(O)-(1-2C)alkyl,
a 4- to 7-membered heterocyclyl,
(3-6C)cycloalkyl,
(3-6C)cycloalkyl(1-2C)alkyl,
phenyl, or
phenyl(1-2C)alkyl;
and wherein any cycloalkyl, heterocyclyl or phenyl group present is optionally substituted by one or more hydroxy, cyano, amino, halo, -C(O)OH, -C(O)NH_2, methoxy, methyl, -C(O)NH(Me), -C(O)N(Me)$_2$, -NH(Me), -N(Me)$_2$, -S(O)$_q$-(Me) (wherein q is 0, 1 or 2), -C(O)(Me), -C(O)O-(Me), -N(H)C(O)-(Me), -S(O)$_2$NH(Me), -S(O)$_2$N(Me)$_2$, or -NHSO$_2$-(Me);

(150) R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, halo, cyano, (1-2C)alkyl, (1-2C)cyanoalkyl, (3-4C)cyanoalkyl, (1-2C)hydroxyalkyl, (1-2C)haloalkyl, (1-2C)aminoalkyl,
-$[CH_2]_{0-1}$-(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]$_2$,
-$[CH_2]_{0-1}$-C(O)(1-2C)alkyl,
-$[CH_2]_{0-2}$-C(O)OH,
-$[CH_2]_{0-1}$-C(O)O-(1-2C)alkyl,
-$[CH_2]_{0-1}$-N(H)C(O)-(1-2C)alkyl,
a 4- to 6-membered heterocyclyl,
(4-6C)cycloalkyl,
(4-6C)cycloalkyl(1-2C)alkyl,
phenyl, or
phenyl(1-2C)alkyl;
and wherein any cycloalkyl, heterocyclyl or phenyl group present is optionally substituted by one or more hydroxy, cyano, amino, halo, -C(O)OH, -C(O)NH_2, methoxy, methyl, -C(O)NH(Me), -C(O)N(Me)$_2$, -NH(Me), -N(Me)$_2$, -S(O)$_q$-(Me) (wherein

q is 0, 1 or 2), -C(O)(Me), -C(O)O-(Me), -N(H)C(O)-(Me), -$S(O)_2$NH(Me), -$S(O)_2$N$(Me)_2$, or -$NHSO_2$-(Me);

(151) R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, halo, cyano, (1-2C)alkyl, (1-2C)cyanoalkyl, (3-4C)cyanoalkyl, (1-2C)hydroxyalkyl, (1-2C)haloalkyl, (1-2C)aminoalkyl,
-$[CH_2]_{0-1}$-(1-2C)alkoxy,
-$[CH_2]_{0-2}$-$C(O)NH_2$,
-$[CH_2]_{0-1}$-C(O)N[(1-2C)alkyl]$_2$,
-$[CH_2]_{0-1}$-C(O)OH,
a 4- to 6-membered heterocyclyl,
(4-6C)cycloalkyl,
phenyl,
and wherein any cycloalkyl, heterocyclyl or phenyl group present is optionally substituted by one or more hydroxy, cyano, amino, halo, -C(O)OH, -$C(O)NH_2$, methoxy, methyl, -C(O)NH(Me), -$C(O)N(Me)_2$, -NH(Me), -$N(Me)_2$, -$S(O)_q$-(Me) (wherein q is 0, 1 or 2), -C(O)(Me), -C(O)O-(Me), -N(H)C(O)-(Me), -$S(O)_2$NH(Me), -$S(O)_2$N$(Me)_2$, or -$NHSO_2$-(Me);

(152) R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, chloro, fluoro, cyano, methyl, ethyl, -CH_2CN, -$C(CH_3)_2$CN, -CH_2OH, (1-2C)haloalkyl, -CH_2NH_2, -OCH_3, -$C(O)NH_2$, -C(O)N$(Me)_2$, CH_2CH_2-C(O)OH, -C(O)OH, -morpholino, -oxetane, -tetrahydrofuran or -tetrahyrdopyran;

(153) R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, cyano, -$C(O)NH_2$, -C(O)N$(Me)_2$, CH_2CH_2-C(O)OH, -C(O)OH, -morpholino, -oxetane, -tetrahydrofuran, -tetrahyrdopyran, -CH_2CN or -$C(CH_3)_2$CN,;

(154) R_3 is selected from fluoro, chloro, methyl or methoxy;

(155) R_3 is chloro;

(156) R_4 is selected from fluoro, chloro, methyl or methoxy;

(157) R_4 is selected from fluoro, chloro or methyl;

(158) R_7 is selected from methyl or -NH(Me);

(159) R_7 is -NH(Me);

(160) A_8 is selected from CH, CR_8, O, S or N;

(161) A_9 is selected from CH, CR_9, O, S or N;

(162) A_{10} is selected from CH, CR_{10}, O, S, NH or N;

(163) R_8, R_9 and R_{10} are selected from methyl, amino or -NH(Me).

[0070] In a particular group of compounds of the invention, when L is a group of formula II defined herein, either:

(i) X_A is not NH, when L_A is an unsubstituted (4C)alkylene (butylene), X_B is -O-, L_B is an unsubstituted (2C)alkylene (ethylene), and X_C is -O- or -NH-;

(ii) L_A is not an unsubstituted (4C)alkylene (butylene), when X_A is NH, X_B is -O-, L_B is an unsubstituted (2C)alkylene (ethylene), and X_C is -O- or -NH-;

(iii) X_B is not -O-, when X_A is NH, L_A is an unsubstituted (4C)alkylene (butylene), L_B is an unsubstituted (2C)alkylene (ethylene), and X_C is -O- or -NH-;

(iv) L_B is not an unsubstituted (2C)alkylene (ethylene), when X_A is NH, L_A is an unsubstituted (4C)alkylene (butylene), X_B is -O-, and X_C is -O- or -NH-;

(v) X_C is not -O- or -NH-, when X_A is NH, L_A is an unsubstituted (4C)alkylene (butylene), X_B is -O-, and L_B is an unsubstituted (2C)alkylene (ethylene).

[0071] In a further group of compounds of the invention, when L is a group of formula II defined herein, L_A is suitably selected from:

(i) a (4C)alkylene substituted by one or more R_{LA} substituent groups;

(ii) a (2-3C)alkylene or a (5C)alkylene optionally substituted by one or more R_{LA} substituent groups; or

(iii) a (0-3C)alkylene-(3-6C)cycloalkylene-(0-3C)alkylene- group optionally substituted by one or more R_{LA} substituent groups.

[0072] In a further group of compounds of the invention, when L is a group of formula II defined herein, L_A is suitably selected from:

(i) a (4C)alkylene substituted by one or more R_{LA} substituent groups;

(ii) a (2-3C)alkylene or a (5C)alkylene optionally substituted by one or more R_{LA} substituent groups.

[0073] 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).

[0074] 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.

[0075] 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 $-Y_1-[CH_2]_{0-3}-Z_1$.

[0076] 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 $-Y_2-[CH_2]_{0-3}-Z_2$.

[0077] In a particular group of compounds of formula I:

[0078] 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

[0079] 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 $-Y_2-[CH_2]_{0-3}-Z_2$.

[0080] 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 $-Y_2-[CH_2]_{0-3}-Z_2$.

[0081] 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, unless specified otherwise.

[0082] 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, unless specified otherwise. 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].

[0083] Suitably, in any of the definitions of formula I set out herein, L is as defined in formula I above or as defined in any one of paragraphs (1) to (13) above. More suitably, L is as defined in any one of paragraphs (4) to (13) above. Even more suitably, L is as defined in any one of paragraphs (6) to (13) above. Yet even more suitably, L is as defined in any one of paragraphs (8) to (13) above. Yet still even more suitably, L is as defined in any one of paragraphs (10) to (13) above. Most suitably, L is as defined in any one of paragraphs (12) or (13) above.

[0084] Suitably, in any of the definitions of formula I set out herein, R_L is as defined in any one of paragraphs (14) to (19) above. More suitably, R_L is as defined in any one of paragraphs (15) to (19) above. Even more suitably, R_L is as defined in any one of paragraphs (16) to (19) above. Yet even more suitable, R_L is as defined in any one of paragraphs (17), (18) or (19) above. Most suitably, R_L is as defined in any one of paragraphs (18) or (19) above.

[0085] 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 (20) to (23) above. More suitably, R_a and R_e are as defined in any

one of paragraphs (21), (22) or (23) above. Even more suitably, R_a and R_e are as defined in any one of paragraphs (22) or (23) above. Most suitably, R_a and R_e are as defined in paragraph (23) above.

[0086] In a particular group of compounds of formula I, R_a and R_e are as defined in paragraph (23) above, and L and R_L, and any group associated therewith, are each as defined in formula I above.

[0087] 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 (24) to (34) above. More suitably, R_b and R_d are as defined in any one of paragraphs (26) to (34) above. Even more suitably, R_b and R_d are as defined in any one of paragraphs (28) to (34) above. Yet more suitably, R_b and R_d are as defined in any one of paragraphs (30) to (34) above. Yet even more suitably, R_b and R_d are as defined in any one of paragraphs (31), (32), (33) or (34) above. Yet still even more suitably, R_b and R_d are as defined in any one of paragraphs (32), (33) or (34) above. Most suitably, R_b and R_d are as defined in any one of paragraphs (33) or (34) above.

[0088] In a particular group of compounds of formula I, R_b and R_d are as defined in paragraph (24) above, and L and R_L, and any group associated therewith, 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 (26) above, and L and R_L, and any group associated therewith, 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 (28) above, and L and R_L, and any group associated therewith, 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 (30) above, and L and R_L, and any group associated therewith, 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 (31) above, and L and R_L, and any group associated therewith, 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 (32) above, and L and R_L, and any group associated therewith, 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 (33) above, and L and R_L, and any group associated therewith, 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 (34) above, and L and R_L, and any group associated therewith, are each as defined in formula I above.

[0096] Suitably, in any of the definitions of formula I set out herein, R_c is as defined in any one of paragraphs (35) to (43) above. More suitably, R_c is as defined in any one of paragraphs (37) to (43) above. Even more suitably, R_c is as defined in any one of paragraphs (39) to (43) above. Yet more suitable, R_c is as defined in any one of paragraphs (40), (41), (42) or (43) above. Yet even more suitably, R_c is as defined in paragraphs (41), (42) or (43) above. Yet even more suitably, R_c is as defined in paragraphs (42) or (43) above.

[0097] In a particular group of compounds of formula I, R_c is as defined in paragraph (35) above, and L and R_L, and any group associated therewith, are each as defined in formula I above.

[0098] In a particular group of compounds of formula I, R_c is as defined in paragraph (37) above, and L and R_L, and any group associated therewith, 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 (39) above, and L and R_L, and any group associated therewith, 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 (40) above, and L and R_L, and any group associated therewith, 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 (41) above, and L and R_L, and any group associated therewith, 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 (42) above, and L and R_L, and any group associated therewith, 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 (43) above, and L and R_L, and any group associated therewith, are each as defined in formula I above.

[00104] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

R_a and R_e are both as defined in any one of paragraphs (20) to (23) above;

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00105] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

R_a and R_e are both as defined in any one of paragraphs (21) to (23) above;

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00106] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

R_a and R_e are both as defined in any one of paragraphs (22) or (23) above;

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00107] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00108] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (26) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (28) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (30) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (31) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (32) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (33) or (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) 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 (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (36) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (38) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (40) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (41) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (42) or (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in paragraph (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (26) to (34) above; and

R_c is as defined in any one of paragraphs (36) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (28) to (34) above; and

R_c is as defined in any one of paragraphs (38) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (30) to (34) above; and

R_c is as defined in any one of paragraphs (40) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (31) to (34) above; and

R_c is as defined in any one of paragraphs (40) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (32) to (34) above; and

R_c is as defined in any one of paragraphs (41) to (43) above.

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

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (33) or (34) above; and

R_c is as defined in any one of paragraphs (42) or (43) above.

[00127] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) 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 (34) above; and

R_c is as defined in paragraph (43) above.

[00128] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (4) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00129] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (6) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00130] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (8) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00131] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (10) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00132] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (11) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00133] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (12) or (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00134] In a particular group of compounds of formula I defined herein:

L is as defined in paragraph (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00135] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (15) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00136] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (16) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00137] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (17) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00138] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00139] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in paragraph (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00140] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (4) to (13) above;

R_L is as defined in any one of paragraphs (15) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (26) to (34) above; and

R_c is as defined in any one of paragraphs (36) to (43) above.

[00141] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (6) to (13) above;

R_L is as defined in any one of paragraphs (16) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (28) to (34) above; and

R_c is as defined in any one of paragraphs (38) to (43) above.

[00142] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (8) to (13) above;

R_L is as defined in any one of paragraphs (17) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (30) to (34) above; and

R_c is as defined in any one of paragraphs (40) to (43) above.

[00143] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (10) to (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (31) to (34) above; and

R_c is as defined in any one of paragraphs (40) to (43) above.

[00144] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (11) to (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (32) to (34) above; and

R_c is as defined in any one of paragraphs (41) to (43) above.

[00145] In a particular group of compounds of formula I defined herein:

L is as defined in any one of paragraphs (12) or (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (33) or (34) above; and

R_c is as defined in any one of paragraphs (42) or (43) above.

[00146] In a particular group of compounds of formula I defined herein:

L is as defined in paragraph (13) above;

R_L is as defined in paragraph (19) 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 (34) above; and

R_c is as defined in paragraph (43) above.

[00147] Suitably, in any of the definitions of formula I set out herein, R_{100} is as defined in formula I above, or as defined in any one of paragraphs (44) or (45) above.

[00148] Suitably, in any of the definitions of formula I set out herein, R_{100a} is as defined in formula I above, or as defined in any one of paragraphs (46) or (47) above.

[00149] Suitably, in any of the definitions of formula I set out herein, R_{100} and R_{100a} are as defined in formula I above, or as defined in any one of paragraphs (48) or (49) above.

[00150] Suitably, in any of the definitions of formula I set out herein, R_{101} is as defined in formula I above, or as defined in any one of paragraphs (50), (51) or (52) above.

[00151] Suitably, in any of the definitions of formula I set out herein, R_{101a} is as defined in formula I above, or as defined in any one of paragraphs (53) or (54) above.

[00152] Suitably, in any of the definitions of formula I set out herein, R_{101} and R_{101a} are as defined in formula I above, or as defined in any one of paragraphs (55) or (56) above.

[00153] Suitably, in any of the definitions of formula I set out herein, integer a is as defined in formula I above, or as defined in any one of paragraphs (57), (58) or (59) above.

[00154] Suitably, in any of the definitions of formula I set out herein, Q_1 is as defined in formula I above, or as defined in any one of paragraphs (60), (61) or (62) above.

[00155] Suitably, in any of the definitions of formula I set out herein, R_{102} is as defined in formula I above, or as defined in any one of paragraphs (63) or (64) above.

[00156] Suitably, in any of the definitions of formula I set out herein, Q_2, Q_3, Q_4, Q_5 and Q_6 is as defined in formula I above, or as defined in any one of paragraphs (66) to (71) above. More, suitably, Q_2, Q_3, Q_4, Q_5 and Q_6 is as defined in formula I above, or as defined in any one of paragraphs (67) to (71) above. Even more suitably, Q_2, Q_3, Q_4, Q_5 and Q_6 is as defined in formula I above, or as defined in any one of paragraphs (68) to (71) above. Yet more suitably, Q_2, Q_3, Q_4, Q_5 and Q_6 is as defined in formula I above, or as defined in any one of paragraphs (69) to (71) above. Most suitably, Q_2, Q_3, Q_4, Q_5 and Q_6 is as defined in formula I above, or as defined in any one of paragraphs (70) or (71) above.

[00157] Suitably, in any of the definitions of formula I set out herein, Q_7, Q_8, Q_9 and Q_{10} is as defined in formula I above, or as defined in any one of paragraphs (72) to (74) above. More suitably, in any of the definitions of formula I set out herein, Q_7, Q_8, Q_9 and Q_{10} is as defined in formula I above, or as defined in any one of paragraphs (73) or (74) above.

[00158] Suitably, in any of the definitions of formula I set out herein, ring A is as defined in formula I above, or as defined in any one of paragraphs (75) to (80) above. More suitably, ring

A is as defined in any one of paragraphs (76) to (80) above. Even more suitably, ring A is as defined in any one of paragraphs (77) to (80) above. Yet more suitably, ring A is as defined in any one of paragraphs (78), (79) or (80) above. Most suitable, ring A is as defined in anyone of paragraph (79) or (80) above.

[00159] Suitably, in any of the definitions of formula I set out herein, R_R is as defined in formula I above or as defined in any one of paragraphs (81) or (82) above.

[00160] In a particular group of compounds of formula I, R_R is as defined in paragraph (81) above, and L and R_L, and any group associated therewith, are each as defined in formula I above.

[00161] In a particular group of compounds of formula I, R_R is as defined in paragraph (82) above, and L and R_L, and any group associated therewith, are each as defined in formula I above.

[00162] Suitably, in any of the definitions of formula I set out herein, A_1 and A_2 are as defined in paragraph (83) or (84) above.

[00163] Suitably, in any of the definitions of formula I set out herein, R_1 is as defined in any one of paragraphs (85) to (91) above. More suitably, R_1 is as defined in any one of paragraphs (86) to (91) above. Even more suitably, R_1 is as defined in any one of paragraphs (87) to (91) above. Yet more suitably, R_1 is as defined in any one of paragraphs (88) to (91) above. Yet even more suitably, R_1 is as defined in any one of paragraphs (89) to (91) above. Most suitably, R_1 is as defined in any one of paragraphs (90) or (91) above.

[00164] Suitably, in any of the definitions of formula I set out herein, X_1 is as defined in any one of paragraphs (92) to (96) above. More suitably, X_1 is as defined in any one of paragraphs (94), (95) or (96) above.

[00165] Suitably, in any of the definitions of formula I set out herein, X_5 is as defined in paragraph (97) above.

[00166] Suitably, in any of the definitions of formula I set out herein, X_2, X_3 and X_4 are as defined in any one of paragraphs (98) to (105) above. More suitably, X_2, X_3 and X_4 are as defined in any one of paragraphs (100) to (105) above. Even more suitably, X_2, X_3 and X_4 are as defined in any one of paragraphs (102) to (105) above.

[00167] Suitably, in any of the definitions of formula I set out herein, X_6, X_7, X_8 and X_9 are as defined in any one of paragraphs (106) to (112) above. More suitably, X_6, X_7, X_8, and X_9 are as defined in any one of paragraphs (108) to (112) above. Even more suitably, X_6, X_7, X_8 and X_9 are as defined in any one of paragraphs (110) to (112) above. Yet even more suitably, X_6, X_7, X_8 and X_9 are as defined in any one of paragraphs (111) or (112) above.

[00168] Suitably, in any of the definitions of formula I set out herein, X_{10}, X_{11} and X_{12} are as defined in any one of paragraphs (113) to (117) above. More suitably, X_{10}, X_{11} and X_{12} are as defined in any one of paragraphs (115) to (117) above. Even more suitably, X_{10}, X_{11} and X_{12} are as defined in any one of paragraphs (116) or (117) above.

[00169] Suitably, in any of the definitions of formula I set out herein, X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are as defined in any one of paragraphs (118) to (126) above. More suitably, X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are as defined in any one of paragraphs (120) to (126) above. Even more suitably, X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are as defined in any one of paragraphs (122) to (126) above. Yet even more suitably, X_{13}, X_{14}, X_{15}, X_{16} and X_{17} are as defined in any one of paragraphs (124) to (126) above.

[00170] Suitably, in any of the definitions of formula I set out herein, R_{1A} is as defined in any one of paragraphs (127) to (132). More suitably, R_{1A} is as defined in any one of paragraphs (129) to (132). Even more suitably, R_{1A} is as defined in any one of paragraphs (130) to (132). Even more suitably, R_{1A} is as defined in any one of paragraphs (131) or (132). Most suitably, R_{1A} is as defined in paragraph (132).

[00171] Suitably, in any of the definitions of formula I set out herein, R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00172] Suitably, in any of the definitions of formula I set out herein, A_3 is as defined in any one of paragraphs (135), (136) or (137) above.

[00173] Suitably, in any of the definitions of formula I set out herein, A_4 is as defined in any one of paragraphs (138), (139) or (140) above.

[00174] Suitably, in any of the definitions of formula I set out herein, A_5 and A_6 are as defined in any one of paragraphs (141) or (142) above.

[00175] Suitably, in any of the definitions of formula I set out herein, A_7 is as defined in any one of paragraphs (143), (144) or (145) above.

[00176] Suitably, in any of the definitions of formula I set out herein, R_2 is as defined in any one of paragraphs (146) to (153) above. More suitably, R_2 is as defined in any one of paragraphs (147) to (153) above. Even more suitably, R_2 is as defined in any one of paragraphs (148) to (153) above. Yet more suitably, R_2 is as defined in any one of paragraphs (149) to (153) above. Yet even more suitably, R_2 is as defined in any one of paragraphs (150) to (153) above. Yet still even more suitably, R_2 is as defined in any one of paragraphs (151), (152) or (153) above. Most suitably, R_2 is as defined in any one of paragraphs (152) or (153) above.

[00177] Suitably, in any of the definitions of formula I set out herein, R_3 is as defined in any one of paragraphs (154) or (155) above.

[00178] Suitably, in any of the definitions of formula I set out herein, R_4 is as defined in any one of paragraphs (156) or (157) above.

[00179] Suitably, in any of the definitions of formula I set out herein, R_7 is as defined in any one of paragraphs (158) or (159) above.

[00180] Suitably, in any of the definitions of formula I set out herein, A_8 is as defined in paragraph (160) above.

[00181] Suitably, in any of the definitions of formula I set out herein, A_9 is as defined in paragraph (161) above.

[00182] Suitably, in any of the definitions of formula I set out herein, A_{10} is as defined in paragraph (162) above.

[00183] Suitably, in any of the definitions of formula I set out herein, R_8, R_9 and R_{10} are as defined in paragraph (163) above.

[00184] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (85) to (91) above, or R_2 is as defined in any one of paragraphs (146) to (153) above;

L is as defined in any one of paragraphs (1) to (13) above; and

R_L, and any groups associated therewith, is as defined herein.

[00185] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (86) to (91) above, or R_2 is as defined in any one of paragraphs (148) to (153) above;

L is as defined in any one of paragraphs (1) to (13) above; and

R_L, and any groups associated therewith, is as defined herein.

[00186] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (87) to (91) above, or R_2 is as defined in any one of paragraphs (149) to (153) above;

L is as defined in any one of paragraphs (1) to (13) above; and

R_L, and any groups associated therewith, is as defined herein.

[00187] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (88) to (91) above, or R_2 is as defined in any one of paragraphs (150) to (153) above;

L is as defined in any one of paragraphs (1) to (13) above; and

R_L, and any groups associated therewith, is as defined herein.

[00188] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (89) to (91) above, or R_2 is as defined in any one of paragraphs (151) to (153) above;

L is as defined in any one of paragraphs (1) to (13) above; and

R_L, and any groups associated therewith, is as defined herein.

[00189] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (90) or (91) above, or R_2 is as defined in any one of paragraphs (152) or (153) above;

L is as defined in any one of paragraphs (1) to (13) above; and

R_L, and any groups associated therewith, is as defined herein.

[00190] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in paragraph (91) above, or R_2 is as defined in paragraph (153) above;

L is as defined in any one of paragraphs (1) to (13) above; and

R_L, and any groups associated therewith, is as defined herein.

[00191] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (86) to (91) above, or R_2 is as defined in any one of paragraphs (148) to (153) above;

L is as defined in any one of paragraphs (4) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

R_a and R_e are both as defined in any one of paragraphs (20) to (23) above;

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00192] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (87) to (91) above, or R_2 is as defined in any one of paragraphs (149) to (153) above;

L is as defined in any one of paragraphs (8) to (13) above;

R_L is as defined in any one of paragraphs (15) to (19) above;

R_a and R_e are both as defined in any one of paragraphs (21) to (23) above;

R_b and R_d are both as defined in any one of paragraphs (26) to (34) above; and

R_c is as defined in any one of paragraphs (36) to (43) above.

[00193] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (88) to (91) above, or R_2 is as defined in any one of paragraphs (150) to (153) above;

L is as defined in any one of paragraphs (9) to (13) above;

R_L is as defined in any one of paragraphs (16) to (19) above;

R_a and R_e are both as defined in any one of paragraphs (22) or (23) above;

R_b and R_d are both as defined in any one of paragraphs (28) to (34) above; and

R_c is as defined in any one of paragraphs (38) to (43) above.

[00194] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (89) to (91) above, or R_2 is as defined in any one of paragraphs (151) to (153) above;

L is as defined in any one of paragraphs (10) to (13) above;

R_L is as defined in any one of paragraphs (17) to (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (30) to (34) above; and

R_c is as defined in any one of paragraphs (40) to (43) above.

[00195] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (90) or (91) above, or R_2 is as defined in any one of paragraphs (152) or (153) above;

L is as defined in any one of paragraphs (11) to (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above;

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

R_b and R_d are both as defined in any one of paragraphs (32) to (34) above; and

R_c is as defined in any one of paragraphs (42) or (43) above.

[00196] In a particular group of compounds of formula I defined herein:

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in paragraph (91) above, or R_2 is as defined in paragraph (153) above;

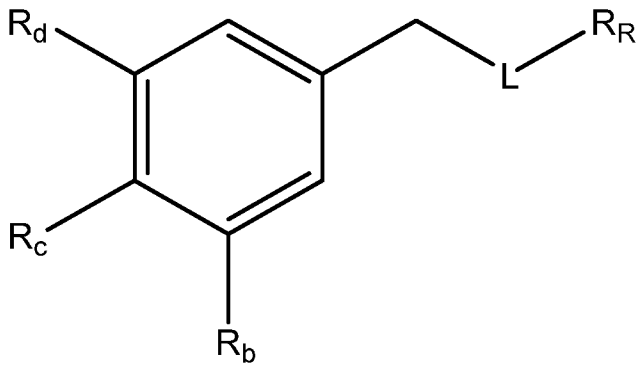
L is as defined in any one of paragraphs (12) or (13) above;

R_L is as defined in paragraph (19) above;

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

R_c is as defined in paragraph (43) above.

[00197] In a particular group of compounds of the invention, the compound is a compound of formula I defined herein in which R_L is as defined in paragraph (16) above R_a and R_e are as defined in paragraph (23) above, i.e. the compounds have the formula Ip shown below, or a pharmaceutically acceptable salt thereof:



(Ip)

wherein L, R_R, R_b, R_c and R_d, and any groups associated therewith, each have any one of the definitions set out hereinbefore.

[00198] In a particular group of compounds of formula Ip:

L is as defined in any one of paragraphs (1) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (86) to (91) above, or R_2 is as defined in any one of paragraphs (148) to (153) above;

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00199] In a particular group of compounds of formula Ip:

L is as defined in any one of paragraphs (4) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (87) to (91) above, or R_2 is as defined in any one of paragraphs (149) to (153) above;

R_b and R_d are both as defined in any one of paragraphs (26) to (34) above; and

R_c is as defined in any one of paragraphs (36) to (43) above.

[00200] In a particular group of compounds of formula Ip:

L is as defined in any one of paragraphs (6) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (88) to (91) above, or R_2 is as defined in any one of paragraphs (150) to (153) above;

R_b and R_d are both as defined in any one of paragraphs (28) to (34) above; and

R_c is as defined in any one of paragraphs (38) to (43) above.

[00201] In a particular group of compounds of formula Ip:

L is as defined in any one of paragraphs (8) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (89) to (91) above, or R_2 is as defined in any one of paragraphs (151) to (153) above;

R_b and R_d are both as defined in any one of paragraphs (30) to (34) above; and

R_c is as defined in any one of paragraphs (40) to (43) above.

[00202] In a particular group of compounds of formula Ip:

L is as defined in any one of paragraphs (10) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (90) or (91) above, or R_2 is as defined in any one of paragraphs (152) or (153) above;

R_b and R_d are both as defined in any one of paragraphs (31) to (34) above; and

R_c is as defined in any one of paragraphs (40) to (43) above.

[00203] In a particular group of compounds of formula Ip:

L is as defined in any one of paragraphs (11) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (90) or (91) above, or R_2 is as defined in any one of paragraphs (152) or (153) above;

R_b and R_d are both as defined in any one of paragraphs (32) to (34) above; and

R_c is as defined in any one of paragraphs (41) to (43) above.

[00204] In a particular group of compounds of formula Ip:

L is as defined in any one of paragraphs (12) or (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in paragraph (91) above, or R_2 is as defined in paragraph (153) above;

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

R_b and R_d are both as defined in any one of paragraphs (33) or (34) above; and

R_c is as defined in any one of paragraphs (42) or (43) above.

[00205] In a particular group of compounds of formula Ip defined herein:

L is as defined in paragraph (13) above;

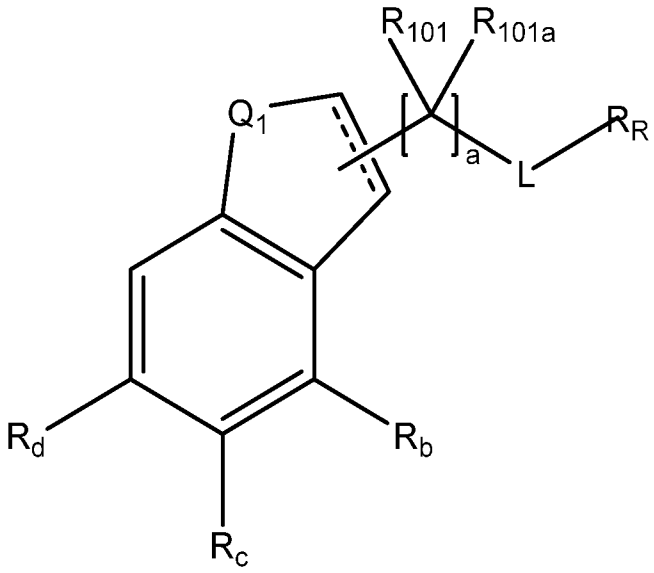
R_R is as defined in paragraph (82) above;

R_1 is as defined in paragraph (91) above;

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

R_c is as defined in paragraph (43) above.

[00206] In a particular group of compounds of the invention, the compound is a compound of formula I defined herein in which R_L is as defined in paragraph (16) above and R_e is as defined in paragraph (23) above, i.e. the compounds have the formula Iq shown below, or a pharmaceutically acceptable salt thereof:



(Iq)

wherein L, R_R, a, R_{101}, R_{101a}, Q_1, R_b, R_c and R_d each have any one of the definitions set out herein.

[00207] In a particular group of compounds of formula Iq:

L is as defined in any one of paragraphs (1) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (86) to (91) above, or R_2 is as defined in any one of paragraphs (148) to (153) above;

Integer a is as defined in paragraph (57) to (59) above;

R_{101} is as defined in any one of paragraphs (50) to (52) above;

R_{101a} is as defined in any one of paragraphs (53) or (54) above;

Q_1 is as defined in any one of paragraphs (60) to (62) above;

R_b and R_d are both as defined in any one of paragraphs (24) to (34) above; and

R_c is as defined in any one of paragraphs (34) to (43) above.

[00208] In a particular group of compounds of formula Iq:

L is as defined in any one of paragraphs (4) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (87) to (91) above, or R_2 is as defined in any one of paragraphs (149) to (153) above;

Integer a is as defined in paragraph (58) or (59) above;

R_{101} is as defined in any one of paragraphs (51) or (52) above;

R_{101a} is as defined in any one of paragraphs (53) or (54) above;

Q_1 is as defined in any one of paragraphs (61) to (62) above;

R_b and R_d are both as defined in any one of paragraphs (26) to (34) above; and

R_c is as defined in any one of paragraphs (36) to (43) above.

[00209] In a particular group of compounds of formula Iq:

L is as defined in any one of paragraphs (6) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (88) to (91) above, or R_2 is as defined in any one of paragraphs (150) to (153) above;

Integer a is as defined in paragraph (58) or (59) above;

R_{101} is as defined in any one of paragraphs (51) or (52) above;

R_{101a} is as defined in any one of paragraphs (53) or (54) above;

Q_1 is as defined in any one of paragraphs (61) to (62) above;

R_b and R_d are both as defined in any one of paragraphs (28) to (34) above; and

R_c is as defined in any one of paragraphs (38) to (43) above.

[00210] In a particular group of compounds of formula Iq:

L is as defined in any one of paragraphs (8) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (89) to (91) above, or R_2 is as defined in any one of paragraphs (151) to (153) above;

Integer a is as defined in paragraph (58) or (59) above;

R_{101} is as defined in any one of paragraphs (51) or (52) above;

R_{101a} is as defined in any one of paragraphs (53) or (54) above;

Q_1 is as defined in any one of paragraphs (61) to (62) above;

R_b and R_d are both as defined in any one of paragraphs (30) to (34) above; and

R_c is as defined in any one of paragraphs (40) to (43) above.

[00211] In a particular group of compounds of formula Iq:

L is as defined in any one of paragraphs (10) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (90) or (91) above, or R_2 is as defined in any one of paragraphs (152) or (153) above;

Integer a is as defined in paragraph (58) or (59) above;

R_{101} is as defined in any one of paragraphs (51) or (52) above;

R_{101a} is as defined in any one of paragraphs (53) or (54) above;

Q_1 is as defined in any one of paragraphs (61) to (62) above;

R_b and R_d are both as defined in any one of paragraphs (31) to (34) above; and

R_c is as defined in any one of paragraphs (40) to (43) above.

[00212] In a particular group of compounds of formula Iq:

L is as defined in any one of paragraphs (11) to (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in any one of paragraphs (90) or (91) above, or R_2 is as defined in any one of paragraphs (152) or (153) above;

Integer a is as defined in paragraph (58) or (59) above;

R_{101} is as defined in any one of paragraphs (51) or (52) above;

R_{101a} is as defined in any one of paragraphs (53) or (54) above;

Q_1 is as defined in any one of paragraphs (61) to (62) above;

R_{102} is as defined in any one of paragraphs (63) or (64) above;

R_b and R_d are both as defined in any one of paragraphs (32) to (34) above; and

R_c is as defined in any one of paragraphs (41) to (43) above.

[00213] In a particular group of compounds of formula Iq:

L is as defined in any one of paragraphs (12) or (13) above;

R_R is as defined in any one of paragraphs (81) or (82) above;

R_1 is as defined in paragraph (91) above, or R_2 is as defined in paragraph (153) above;

Integer a is as defined in paragraph (58) or (59) above;

R_{101} is as defined in any one of paragraphs (51) or (52) above;

R_{101a} is as defined in any one of paragraphs (53) or (54) above;

Q_1 is as defined in any one of paragraphs (61) to (62) above;

R_{102} is as defined in any one of paragraphs (63) or (64) above;

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

R_b and R_d are both as defined in any one of paragraphs (33) or (34) above; and

R_c is as defined in any one of paragraphs (42) or (43) above.

[00214] In a particular group of compounds of formula Iq defined herein:

L is as defined in paragraph (13) above;

R_R is as defined in paragraph (82) above;

R_1 is as defined in paragraph (91) above;

Integer a is as defined in paragraph (58) or (59) above;

R_{101} is as defined in any one of paragraphs (51) or (52) above;

R_{101a} is as defined in any one of paragraphs (53) or (54) above;

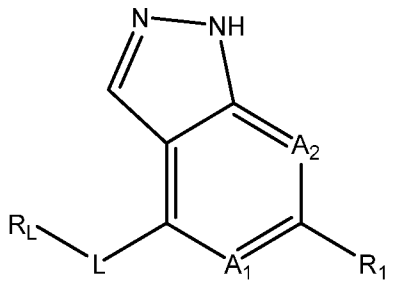
Q_1 is as defined in any one of paragraphs (61) to (62) above;

R_{102} is as defined in paragraph (64) above;

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

R_c is as defined in paragraph (43) above.

[00215] In a particular group of compounds of the invention, the compound is a compound of formula I defined herein in which R_R is as defined in paragraph (81) above, i.e. the compounds have the formula Ir shown below, or a pharmaceutically acceptable salt thereof:



(Ir)

wherein A_1, A_2, L, R_L and R_1 each have any one of the definitions set out herein.

[00216] In a particular group of compounds of formula Ir:

A_1 and A_2 are as defined in any one of paragraphs (83) or (84) above;

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

R_1 is as defined in any one of paragraphs (85) to (91) above;

R_{1A} is as defined in any one of paragraphs (127) to (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00217] In a particular group of compounds of formula Ir:

A_1 and A_2 are as defined in any one of paragraphs (83) or (84) above;

L is as defined in any one of paragraphs (4) to (13) above;

R_L is as defined in any one of paragraphs (15) to (19) above;

R_1 is as defined in any one of paragraphs (86) to (91) above;

R_{1A} is as defined in any one of paragraphs (128) to (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00218] In a particular group of compounds of formula Ir:

A_1 and A_2 are as defined in any one of paragraphs (83) or (84) above;

L is as defined in any one of paragraphs (6) to (13) above;

R_L is as defined in any one of paragraphs (16) to (19) above;

R_1 is as defined in any one of paragraphs (87) to (91) above;

R_{1A} is as defined in any one of paragraphs (129) to (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00219] In a particular group of compounds of formula Ir:

A_1 and A_2 are as defined in any one of paragraphs (83) or (84) above;

L is as defined in any one of paragraphs (8) to (13) above;

R_L is as defined in any one of paragraphs (17) to (19) above;

R_1 is as defined in any one of paragraphs (88) to (91) above;

R_{1A} is as defined in any one of paragraphs (130) to (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00220] In a particular group of compounds of formula Ir:

A_1 and A_2 are as defined in any one of paragraphs (83) or (84) above;

L is as defined in any one of paragraphs (10) to (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above;

R_1 is as defined in any one of paragraphs (89) to (91) above;

R_{1A} is as defined in any one of paragraphs (131) or (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00221] In a particular group of compounds of formula Ir:

A_1 and A_2 are as defined in any one of paragraphs (83) or (84) above;

L is as defined in any one of paragraphs (12) or (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above;

R_1 is as defined in any one of paragraphs (90) or (91) above;

R_{1A} is as defined in any one of paragraphs (131) or (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00222] In a particular group of compounds of formula Ir:

A_1 and A_2 are as defined in paragraph (83) above;

L is as defined in paragraph (13) above;

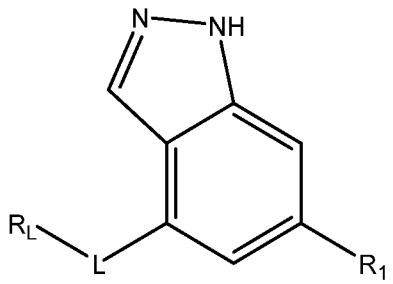
R_L is as defined in paragraph (19) above;

R_1 is as defined in paragraph (91) above;

R_{1A} is as defined in paragraph (132) above; and

R_{1B} is as defined in paragraph (134) above.

[00223] In a particular group of compounds of the invention, the compound is a compound of formula I defined herein in which R_R is as defined in paragraph (81) above and A_1 and A_2 are as defined in paragraph (83) above, i.e. the compounds have the formula Is shown below, or a pharmaceutically acceptable salt thereof:



(Is)

wherein L, R_L and R_1 each have any one of the definitions set out herein.

[00224] In a particular group of compounds of formula Is:

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above;

R_1 is as defined in any one of paragraphs (85) to (91) above;

R_{1A} is as defined in any one of paragraphs (127) to (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00225] In a particular group of compounds of formula Is:

L is as defined in any one of paragraphs (4) to (13) above;

R_L is as defined in any one of paragraphs (15) to (19) above;

R_1 is as defined in any one of paragraphs (86) to (91) above;

R_{1A} is as defined in any one of paragraphs (128) to (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00226] In a particular group of compounds of formula Is:

L is as defined in any one of paragraphs (6) to (13) above;

R_L is as defined in any one of paragraphs (16) to (19) above;

R_1 is as defined in any one of paragraphs (87) to (91) above;

R_{1A} is as defined in any one of paragraphs (129) to (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00227] In a particular group of compounds of formula Is:

L is as defined in any one of paragraphs (8) to (13) above;

R_L is as defined in any one of paragraphs (17) to (19) above;

R_1 is as defined in any one of paragraphs (88) to (91) above;

R_{1A} is as defined in any one of paragraphs (130) to (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00228] In a particular group of compounds of formula Is:

L is as defined in any one of paragraphs (10) to (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above;

R_1 is as defined in any one of paragraphs (89) to (91) above;

R_{1A} is as defined in any one of paragraphs (131) or (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00229] In a particular group of compounds of formula Is:

L is as defined in any one of paragraphs (12) or (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above;

R_1 is as defined in any one of paragraphs (90) or (91) above;

R_{1A} is as defined in any one of paragraphs (131) or (132) above; and

R_{1B} is as defined in any one of paragraphs (133) or (134) above.

[00230] In a particular group of compounds of formula Is:

L is as defined in paragraph (13) above;

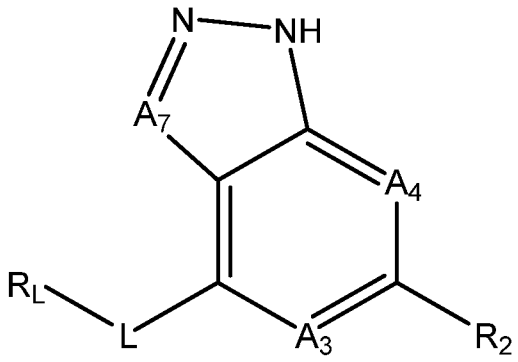
R_L is as defined in paragraph (19) above;

R_1 is as defined in paragraph (91) above;

R_{1A} is as defined in paragraph (132) above; and

R_{1B} is as defined in paragraph (134) above.

[00231] In a particular group of compounds of the invention, the compound is a compound of formula I defined herein in which R_R is as defined in paragraph (81) above, i.e. the compounds have the formula It shown below, or a pharmaceutically acceptable salt thereof:



(It)

wherein A_3, A_4, A_7, L, R_L and R_2 each have any one of the definitions set out herein.

[00232] In a particular group of compounds of formula It:

A_3 is as defined in any one of paragraphs (135), (136) or (137) above;

A_4 is as defined in any one of paragraphs (138), (139) or (140) above;

A_7 is as defined in any one of paragraphs (143), (144) or (145) above;

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above; and

R_2 is as defined in any one of paragraphs (146) to (153) above;

[00233] In a particular group of compounds of formula It:

A_3 is as defined in any one of paragraphs (135), (136) or (137) above;

A_4 is as defined in any one of paragraphs (138), (139) or (140) above;

A_7 is as defined in any one of paragraphs (143), (144) or (145) above;

L is as defined in any one of paragraphs (4) to (13) above;

R_L is as defined in any one of paragraphs (15) to (19) above; and

R_2 is as defined in any one of paragraphs (148) to (153) above.

[00234] In a particular group of compounds of formula It:

A_3 is as defined in any one of paragraphs (135), (136) or (137) above;

A_4 is as defined in any one of paragraphs (138), (139) or (140) above;

A_7 is as defined in any one of paragraphs (143), (144) or (145) above;

L is as defined in any one of paragraphs (6) to (13) above;

R_L is as defined in any one of paragraphs (16) to (19) above; and

R_2 is as defined in any one of paragraphs (150) to (153) above.

[00235] In a particular group of compounds of formula It:

A_3 is as defined in any one of paragraphs (135), (136) or (137) above;

A_4 is as defined in any one of paragraphs (138), (139) or (140) above;

A_7 is as defined in any one of paragraphs (143), (144) or (145) above;

L is as defined in any one of paragraphs (8) to (13) above;

R_L is as defined in any one of paragraphs (17) to (19) above; and

R_2 is as defined in any one of paragraphs (151) to (153) above.

[00236] In a particular group of compounds of formula It:

A_3 is as defined in any one of paragraphs (135), (136) or (137) above;

A_4 is as defined in any one of paragraphs (138), (139) or (140) above;

A_7 is as defined in any one of paragraphs (143), (144) or (145) above;

L is as defined in any one of paragraphs (10) to (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above; and

R_2 is as defined in any one of paragraphs (152) or (153) above.

[00237] In a particular group of compounds of formula It:

A_3 is as defined in paragraph (135) above;

A_4 is as defined in paragraph (138) above;

A_7 is as defined in any one of paragraphs (143) or (145) above;

L is as defined in any one of paragraphs (12) or (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above; and

R_2 is as defined in any one of paragraphs (152) or (153) above.

[00238] In a particular group of compounds of formula It:

A_3 is as defined in paragraph (135) above;

A_4 is as defined in paragraph (138) above;

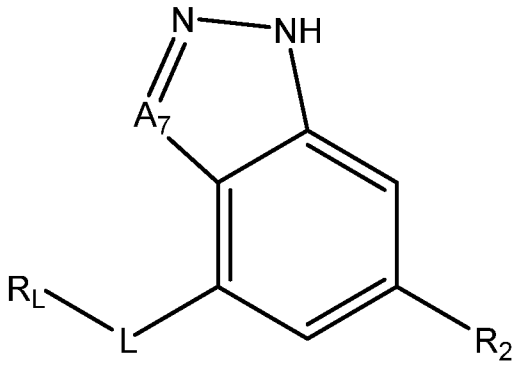
A_7 is as defined in any one of paragraphs (143) or (145) above;

L is as defined in paragraph (13) above;

R_L is as defined in any paragraph (19) above; and

R_2 is as defined in paragraph (153) above.

[00239] In a particular group of compounds of the invention, the compound is a compound of formula I defined herein in which R_R is as defined in paragraph (81) above, A_3 is as defined in paragraph (135) above, A_4 is as defined in paragraph (139) above and A_5 and A_6 are as defined in paragraph (141) above, i.e. the compounds have the formula Iu shown below, or a pharmaceutically acceptable salt thereof:



(Iu)

wherein A_7, L, R_L and R_2 each have any one of the definitions set out herein.

[00240] In a particular group of compounds of formula Iu:

A_7 is as defined in any one of paragraphs (143), (144) or (145) above;

L is as defined in any one of paragraphs (1) to (13) above;

R_L is as defined in any one of paragraphs (14) to (19) above; and

R_2 is as defined in any one of paragraphs (146) to (153) above;

[00241] In a particular group of compounds of formula Iu:

A_7 is as defined in any one of paragraphs (143), (144) or (145) above;

L is as defined in any one of paragraphs (4) to (13) above;

R_L is as defined in any one of paragraphs (15) to (19) above; and

R_2 is as defined in any one of paragraphs (148) to (153) above.

[00242] In a particular group of compounds of formula Iu:

A_7 is as defined in any one of paragraphs (143), (144) or (145) above;

L is as defined in any one of paragraphs (6) to (13) above;

R_L is as defined in any one of paragraphs (16) to (19) above; and

R_2 is as defined in any one of paragraphs (150) to (153) above.

[00243] In a particular group of compounds of formula Iu:

A_7 is as defined in any one of paragraphs (143), (144) or (145) above;

L is as defined in any one of paragraphs (8) to (13) above;

R_L is as defined in any one of paragraphs (17) to (19) above; and

R_2 is as defined in any one of paragraphs (151) to (153) above.

[00244] In a particular group of compounds of formula Iu:

A_7 is as defined in any one of paragraphs (143), (144) or (145) above;

L is as defined in any one of paragraphs (10) to (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above; and

R_2 is as defined in any one of paragraphs (152) or (153) above.

[00245] In a particular group of compounds of formula Iu:

A_7 is as defined in any one of paragraphs (143) or (145) above;

L is as defined in any one of paragraphs (12) or (13) above;

R_L is as defined in any one of paragraphs (18) or (19) above; and

R_2 is as defined in any one of paragraphs (152) or (153) above.

[00246] In a particular group of compounds of formula Iu:

A_7 is as defined in any one of paragraphs (143) or (145) above;

L is as defined in paragraph (13) above;

R_L is as defined in any paragraph (19) above; and

R_2 is as defined in paragraph (153) above.

[00247] 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:
3-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;

4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1H-indazole-6-carboxamide;
N-(3-((6-(1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
N-(3-((6-(1H-1,2,4-triazol-1-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
3-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-cyano-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methyl-1H-imidazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-cyano-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chlorobenzyl)amino)propanamide;
N-(2-(4-(2-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)-1H-1,2,3-triazol-1-yl)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-(2-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)oxazol-5-yl)acetamide;
N-(2-(5-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)-4H-1,2,4-triazol-3-yl)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-((4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butyl)amino)acetamide;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-(3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamido)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-methylpropanamide;
3-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methylpyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methoxypyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(2-(4-(((6-chloro-1H-benzo[d]imidazol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N1-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)-N4-(3-chloro-4-(trifluoromethoxy)benzyl)butane-1,4-diamine;
N-(3-((6-(2H-1,2,3-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridin-3-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-methyl-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(isoxazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(4-methyl-1H-imidazol-1-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
4-(4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1H-indazol-6-yl)pyridine 1-oxide ;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(2-oxo-1,2-dihydropyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((4-chloro-5-phenyl-1H-pyrazol-3-yl)methyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(hydroxymethyl)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((6-chloro-1-methyl-1H-indol-2-yl)methyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((6-chloro-1H-indol-2-yl)methyl)amino)propanamide;

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((1-methyl-5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-cyano-4-cyclobutoxybenzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(2-hydroxyethyl)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((4-cyclobutoxy-3-(hydroxymethyl)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(2-hydroxyethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-5-(hydroxymethyl)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(hydroxymethyl)-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-cyano-4-cyclopropylbenzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-cyano-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(cyanomethyl)benzyl)amino)propanamide;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)acetamide;
6-(4H-1,2,4-triazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
N-(2-(4-(((6-chloro-1-methyl-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(2-(4-(((1-methyl-5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(2-(4-(((6-chloro-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(2-(4-(((5-cyclobutoxy-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-(2-((6-(isoxazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butan-1-amine;
N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-(2-((6-(pyridazin-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butan-1-amine;

4-(2-((6-(pyridazin-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
N-(2-(4-(((5-cyclobutoxy-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(pyridazin-4-yl)-1H-indazol-4-amine;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1H-indazole-6-carboxylic acid;
4-((4-((4-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)butyl)amino)butyl)amino)-1H-indazole-6-carboxylic acid;
N-(3-((1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-N,N-dimethyl-1H-indazole-6-carboxamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(hydroxymethyl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(2-(2-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)oxazol-5-yl)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-(5-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)-4H-1,2,4-triazol-3-yl)acetamide;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-((3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propyl)amino)propanamide;
N1-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propyl)-N3-(3-chloro-4-(trifluoromethoxy)benzyl)propane-1,3-diamine;
N-(2-(4-(((6-chloro-1-methyl-1H-benzo[d]imidazol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
3-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propoxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)propan-1-amine;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-(3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propoxy)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-methyl-4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N1-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)-N4-(3-chloro-4-(trifluoromethoxy)benzyl)-N1-methylbutane-1,4-diamine;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyrimidin-5-yl)-1H-indazol-4-yl)amino)propyl)propanamide;

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-cyanopyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyrimidin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-methoxy-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((4-cyclopropyl-3-(hydroxymethyl)benzyl)amino)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-morpholino-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((6-(2H-tetrazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methyl-1H-imidazol-1-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(oxetan-3-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(tetrahydrofuran-3-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((5-(4H-1,2,4-triazol-4-yl)-1H-indazol-7-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
methyl 4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxylate;
4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxylic acid;
6-(3-methyl-4H-1,2,4-triazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine ;
6-(2-methoxypyridin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
methyl 3-(4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)propanoate;
3-(4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)propanoic acid;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(tetrahydro-2H-pyran-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(4-methyl-1H-imidazol-5-yl)-1H-indazol-4-yl)amino)propyl)propanamide;

6-(3-methoxy-1H-pyrazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
6-(pyridazin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
6-(pyrimidin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carbonitrile;
6-(isoxazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
N-(2-(4-(((5-cyclobutoxy-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(isoxazol-4-yl)-1H-indazol-4-amine;
N-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine;
6-(pyridazin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-benzo[d][1,2,3]triazol-4-amine;
4-(2-((6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-(2-((6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butan-1-amine;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-fluorophenyl)acetonitrile;
(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)methanol;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)acetonitrile;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-methylphenyl)acetonitrile;
N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
N-(3-fluoro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
(3-fluoro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol;

(3-chloro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol;
(3-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)methanol;
2-(3-fluoro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile;
2-(3-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)acetonitrile;
2-(3-methyl-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile;
4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-cyclobutoxy-1H-indol-2-yl)methyl)butan-1-amine;
N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)methanol;
2-(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-methylphenyl)acetonitrile;
2-(3-chloro-5-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile;
4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)butan-1-amine;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-cyclobutoxy-1H-indol-2-yl)methyl)butan-1-amine;
(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-fluorophenyl)methanol;
N-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine;
N-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(isoxazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;

4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-(3-fluoro-4-(trifluoromethoxy)benzyl)butan-1-amine;
(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-chlorophenyl)methanol;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-chlorophenyl)acetonitrile;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)butan-1-amine;
2-(3-chloro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile;
2-(3-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
N-(3-fluoro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
(3-chloro-5-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol;
N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
(3-fluoro-5-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol;
4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
2-(3-(((4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
6-(4H-1,2,4-triazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-benzo[d][1,2,3]triazol-4-amine;
6-(isoxazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-benzo[d][1,2,3]triazol-4-amine;
4-(2-((6-(isoxazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
2-(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)acetonitrile;
2-(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;

2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
2-(3-(((4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
2-(3-(((4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)butan-1-amine;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
2-(3-(((4-(2-((6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(5-cyano-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((6-(1,3,4-oxadiazol-2-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-chloro-6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(5-methyl-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-cyano-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((6-(1H-1,2,3-triazol-1-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-fluoropyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(oxazol-5-yl)-1H-indazol-4-yl)amino)propyl)propanamide;

3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-methylpyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
7-chloro-N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(pyridin-4-yl)-1H-indazol-4-amine;
4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carbonitrile;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(6-oxo-1,6-dihydropyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-chloropyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(2-oxo-1,2-dihydropyrimidin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
4-(2-(((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)methyl)amino)ethoxy)-N-(3,5-difluoro-4-(trifluoromethoxy)benzyl)butan-1-amine;
N-(3-(((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)methyl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(1,2,4-oxadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-3-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(oxazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-7-fluoro-6-(pyridin-4-yl)-1H-indazol-4-amine;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-cyano-4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-methyl-6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-7-methyl-6-(pyridin-4-yl)-1H-indazol-4-amine;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-fluoro-6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-chloro-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
7-chloro-N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;

N-(3-((6-(1,2,4-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(2-aminopyridin-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)amino)propyl)propanamide;
5-chloro-N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(3-((6-(6-aminopyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(6-aminopyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(1,2,4-oxadiazol-3-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N4-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-N3-methyl-6-(4H-1,2,4-triazol-4-yl)-1H-indazole-3,4-diamine;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((3-(methylamino)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
(S)-(3-(((5-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol;
(S)-5-(4-((2-((4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)pentyl)oxy)ethyl)amino)-1H-indazol-6-yl)pyridazin-3-ol;
(S)-2-(3-(((5-(2-((6-(6-hydroxypyridazin-4-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
(S)-5-(4-((2-((4-((3-(oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)pentyl)oxy)ethyl)amino)-1H-indazol-6-yl)pyridazin-3-ol;
(S)-3-(((5-(2-((6-(isoxazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)benzamide;
4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxylic acid;
2-(4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)acetic acid;
5-(4-(2-((3-((3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzyl)amino)cyclobutyl)methoxy)ethoxy)-1H-indazol-6-yl)pyridazin-3-ol;
5-(4-(2-((3-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)cyclobutyl)methoxy)ethoxy)-1H-indazol-6-yl)pyridazin-3-ol;

3-(4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)propanoic acid;
2-(3-(((4-(2-((1H-indazol-4-yl)amino)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenoxy)ethanol;
(3-(((3-((2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)methyl)cyclobutyl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol;
2-(4-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)acetonitrile;
2-(3-(((3-((2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)methyl)cyclobutyl)amino)methyl)-5-(trifluoromethoxy)phenoxy)ethan-1-ol;
2-(4-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)-2-methylpropanenitrile;
(S)-(3-(((5-(2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol; and
(R)-(3-(((4-(2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol.

[00248] 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.

[00249] Suitably, the present invention excludes any individual compounds not possessing the biological activity defined herein.

Salts and Solvates

[00250] 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.

[00251] 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.

[00252] In one embodiment, the compounds of Formula I and sub-formulae thereof are isolated as pharmaceutically acceptable salts.

[00253] 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.

[00254] 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.

[00255] 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.

[00256] 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

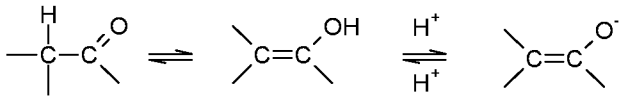
[00257] It is also to be understood that certain compounds of the Formula I and sub-formulae thereof may exhibit polymorphism, and that the invention encompasses all such forms that possess the biological activity described herein.

N-oxides

[00258] 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

[00259] 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

[00260] 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 centre, 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 centre 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".

[00261] 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

[00262] 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

[00263] 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.

[00264] Accordingly, the present invention includes those compounds of the Formula I and sub-formulae thereof as defined herein 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.

[00265] 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.

[00266] 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.

[00267] 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.

[00268] 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.

[00269] 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.

[00270] 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.

[00271] 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 herein, 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

[00272] According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the invention as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in association with a pharmaceutically acceptable diluent or carrier.

[00273] 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).

[00274] 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.

[00275] 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.

[00276] 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.

[00277] 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.

[00278] 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.

[00279] 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.

[00280] 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

[00281] The compounds of the present invention can be prepared by any suitable technique known in the art.

[00282] 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.

[00283] 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.

[00284] 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.

[00285] 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.

[00286] 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.

[00287] 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, such 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.

[00288] 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.

[00289] 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.

[00290] Resins may also be used as a protecting group.

[00291] 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;

(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.

Therapeutic Uses and Applications

[00292] 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.

[00293] 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].

[00294] 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.

[00295] 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.

[00296] 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.

[00297] 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.

[00298] 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.

[00299] 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.

[00300] 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.

[00301] 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.

[00302] 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.

[00303] 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.

[00304] 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.

[00305] 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.

[00306] 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).

[00307] 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.

[00308] 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.*

[00309] 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.

[00310] 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.

[00311] In a particular aspect of the invention, the proliferative disorder is colon/colorectal, cholangiocarcinoma, ovarian or prostate cancer.

[00312] In a particular aspect of the invention, the proliferative disorder is colorectal cancer.

[00313] 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.

[00314] 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.

[00315] 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.

[00316] 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.

[00317] 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.

[00318] 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.

[00319] 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 colon/colorectal cancer, cholangiocarcinoma, gastric cancer, skin cancer (e.g. basal cell carcinoma), ovarian, prostate, breast cancer, liver cancer, pancreatic cancer, brain cancer, blood cancers (leukaemia's, myelomas), bladder cancer, bone cancer, head and neck cancer, renal cancer and lung cancer.

[00320] More suitably, the cancer is selected from colon/colorectal cancer, prostate cancer, ovarian cancer, basal cell carcinoma or cholangiocarcinoma.

[00321] In a particular aspect of the present invention, the cancer is basal cell carcinoma.

[00322] In a particular aspect of the present invention, the cancer is colorectal cancer.

[00323] In a particular aspect of the present invention, the cancer is cholangiocarcinoma.

[00324] In a further aspect of the present invention, the cancer is prostate cancer.

[00325] In a further aspect of the present invention, the cancer is ovarian cancer.

[00326] In another aspect of the present invention, the cancer is a hematopoietic tumour.

[00327] It is hypothesised that the compounds of the present invention will be particularly suited to the treatment of wnt pathway driven cancers, e.g. wnt pathway mutated colorectal cancer or cholangiocarcinoma (Di Maira *et al*, 2019).

[00328] 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.

[00329] CK2α 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).

[00330] 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.

[00331] 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.

[00332] 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.

[00333] Suitably, the virus is a coronavirus, e.g. SARS-CoV2.

Routes of Administration

[00334] 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).

[00335] 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.

[00336] The compounds of the present invention are particularly suitable for oral administration.

Combination Therapies

[00337] The compounds of the invention and salts, solvates thereof defined herein 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.

[00338] 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.

[00339] In a particular embodiment, the antiproliferative treatment defined herein may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy.

[00340] In a further particular embodiment, the antiproliferative treatment defined herein may involve, in addition to the compound of the invention, standard chemotherapy for the cancer concerned.

[00341] In a particular embodiment, the antiproliferative treatment defined herein 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).

[00342] 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 herein and the other pharmaceutically-active agent within its approved dosage range.

[00343] 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 herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and another anti-tumour agent.

[00344] 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 herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and any one of the anti-tumour agents listed herein above.

[00345] 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.

[00346] 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.

[00347] 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

[00348] 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.

[00349] 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.

EXAMPLES

[00350] 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.

[00351] 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)

[00352] Where examples and preparations cite analytical data, the following analytical methods were used unless otherwise specified.

[00353] 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% $NH3{\cdot}H_2O$ 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% $NH3{\cdot}H_2O$ 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% $NH_3{\bullet}H_2O$ 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.

Method 10 (AM10): (5-95CD_4MIN_220 & 254_POS): Instrument: SHIMADZU LCMS-2020; Column: XBridge C18 2.1 × 50mm × 5 μm; Run Time: 1.0 min; Solvents A) 0.025% $NH3{\cdot}H_2O$ in water（v/v） B) Acetonitrile. The gradient runs with 5% B. Gradient: 5-95% B with A 3.6 min @ 0.6 mL/min; hold at 95% B to 3.70 min; 5% B at 3.71 min and hold at 5% B to 4.00 min @ 1.2 ml/min, 40°C.

Method 11 (AM11): (5–95 A–B_0.8 min_220 & 254 nm): Instrument: SHIMADZU LCMS-2020; Column: Kinetex EVO C18 30 × 2.1 mm × 5 μm; Run Time: 1 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, 0.6 min @ 1.5 mL/min; hold at 95% B to 0.78 min; 5% B at 0.79 min and hold at 5% B to 0.8 min @ 2 mL/min, 50°C.

Method 12 (AM12): (5–95 A–B_1 min_220 & 254 nm): Instrument: SHIMADZU LCMS-2020; Column: Kinetex EVO C18 30 × 2.1 mm × 5 μm; Run Time: 1 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 @ 1.5 mL/min; hold at 95% B to 0.95 min; 5% B at 0.96 min and hold at 5% B to 1.0 min @ 2 mL/min, 50°C.

Method 13 (AM13): (0-60 A–B_0.8 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, 0.6 min @ 1.5 mL/min; hold at 60% B to 0.78 min; 0% B at 0.79 min and hold at 0% B to 0.8 min @ 2 mL/min, 50°C.

Method 14 (AM14): (5-95 C–D_1 min_R_220&254_POS): Instrument: SHIMADZU LCMS-2020; Column: XBridge C18 2.1 × 30 mm × 3.5 μm; Run Time: 1.0 min; Solvents A) 0.025% $NH3 \cdot H_2O$ in water（v/v） B) Acetonitrile. The gradient runs with 5% B. Gradient: 5-95% B with A 0.8 min @ 1.5 mL/min; hold at 95% B to 0.94 min; 5% B at 0.95 min and hold at 5% B to 1.0 min @ 2 ml/min, 40°C.

Method 15 (AM15): (5–95 N_1 min_220 & 254 nm): Instrument: SHIMADZU LCMS-2020; Column: Kinetex EVO C18 30 × 2.1 mm × 5 μm; Run Time: 1 min; Solvents: A) 10mM NH4•HCO3 in water, B) Acetonitrile. The gradient runs with 5% B; Gradient: 5–95% B with A, 0.8 min @ 1.5 mL/min; hold at 95% B to 0.95 min; 5% B at 0.96 min and hold at 5% B to 1.0 min @ 2 mL/min, 40°C.

Method 16 (AM16): (5–95 C–D_1.2 min_220 & 254 nm): Instrument: SHIMADZU LCMS-2020; Column: XBridge C18 2.1 × 50 mm × 5 μm; Run Time: 1.2 min; Solvents A) 0.025% $NH_3 \cdot H_2O$ in water（v/v） B) Acetonitrile. The gradient runs with 5% B. Gradient: 5-95% B with A 0.8 min @ 1.5 mL/min, hold at 95% B to 1.10 min; 5% B at 1.11 min and hold at 5% B to 1.2 min @ 2 ml/min, 40°C.

Method 21 (AM21): (5–95 A–B_4 min_220 & 254 nm): Instrument: SHIMADZU LCMS-2020; Column: Kinetex EVO C18 30 × 2.1 mm × 5 μm; Run Time: 4 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 3.6 min @ 0.6 mL/min; hold at 95% B to 3.70 min; 5% B at 3.71 min and hold at 5% B to 4.00 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. The spectra were processed using interpretation software ACD Spectrus processor or equivalent software.

Purification Methods (PM)

Chromatography

Purification method	Column	Eluent	Eluent Ratio
PM1	SiO2	Petroleum ether	1

PM2	SiO2	PE:Ethyl acetate	1:1
PM3	SiO2	PE:Ethyl acetate	2:1
PM4	SiO2	PE:Ethyl acetate	3:1
PM5	SiO2	PE:Ethyl acetate	4:1
PM6	SiO2	PE:Ethyl acetate	5:1
PM7	SiO2	PE:Ethyl acetate	10:1
PM8	SiO2	PE:Ethyl acetate	13:1
PM9	SiO2	PE:Ethyl acetate	15:1
PM10	SiO2	PE:Ethyl acetate	16:1
PM11	SiO2	PE:Ethyl acetate	20:1
PM12	SiO2	PE:Ethyl acetate	30:1
PM13	SiO2	PE:Ethyl acetate	40:1
PM14	SiO2	PE:Ethyl acetate	50:1
PM15	SiO2	PE:Ethyl acetate	60:1
PM16	SiO2	PE:Ethyl acetate	80:1
PM17	SiO2	PE:Ethyl acetate	100:1
PM18	SiO2	PE:Ethyl acetate	200:1
PM19	SiO2	DCM:Methanol	100:1 to 10:1
PM20	SiO2	PE:Ethyl acetate	8:1 to 2:1
PM21	SiO2	PE:Ethyl acetate	100:1 to 30:1
PM22	SiO2	Petroleum ether:Ethyl acetate to Ethyl acetate: Methanol	1:1 to 10:1
PM23	SiO2	Petroleum ether:Ethyl acetate	1:1 to 0:1
PM24	SiO2	Petroleum ether:Ethyl acetate	1:0 to 1:1
PM25	SiO2	Petroleum ether:Ethyl acetate	1:1 to 1:2
PM26	SiO2	Petroleum ether:Ethyl acetate	1:0 to 2:1
PM27	SiO2	Petroleum ether:Ethyl acetate	1:0 to 3:1

PM28	SiO2	Petroleum ether:Ethyl acetate	1:0 to 4:1
PM29	SiO2	Petroleum ether:Ethyl acetate	1:0 to 5:1
PM30	SiO2	Petroleum ether:Ethyl acetate	3:1 to 0:1
PM31	SiO2	Petroleum ether:Ethyl acetate	1:0 to 20:1
PM32	SiO2	Petroleum ether:Ethyl acetate	2:1 to 0:1
PM33	SiO2	Petroleum ether:Ethyl acetate	2:1 to 1:1
PM34	SiO2	Petroleum ether:Ethyl acetate	3:1 to 1:1
PM35	SiO2	Petroleum ether:Ethyl acetate	5:1 to 1:1
PM36	SiO2	Petroleum ether:Ethyl acetate	5:1 to 3:1
PM37	SiO2	Petroleum ether:Ethyl acetate	10:1 to 0:1
PM38	SiO2	Petroleum ether:Ethyl acetate	10:1 to 1:1
PM39	SiO2	Petroleum ether:Ethyl acetate	10:1 to 2:1
PM40	SiO2	Petroleum ether:Ethyl acetate	10:1 to 3:1
PM41	SiO2	Petroleum ether:Ethyl acetate	10:1 to 5:1
PM42	SiO2	Petroleum ether:Ethyl acetate	20:1 to 1:1
PM43	SiO2	Petroleum ether:Ethyl acetate	20:1 to 2:1
PM44	SiO2	Petroleum ether:Ethyl acetate	20:1 to 3:1
PM45	SiO2	Petroleum ether:Ethyl acetate	20:1 to 5:1
PM46	SiO2	Petroleum ether:Ethyl acetate	20:1 to 10:1
PM47	SiO2	Petroleum ether:Ethyl acetate	30:1 to 4:1
PM48	SiO2	Petroleum ether:Ethyl acetate	50:1 to 5:1
PM49	SiO2	Petroleum ether:Ethyl acetate	50:1 to 30:1
PM50	SiO2	Petroleum ether:Ethyl acetate	50:1 to 10:1
PM51	SiO2	Petroleum ether:Ethyl acetate	100:1 to 5:1
PM52	SiO2	DCM:Ethyl acetate	1:1
PM53	SiO2	DCM:Ethyl acetate	1:0 to 0:1
PM54	SiO2	Petroleum ether:Ethyl acetate	3:1 to 1:2

PM55	SiO2	Petroleum ether:Ethyl acetate	5:1 to 2:1
PM56	SiO2	Petroleum ether:Ethyl acetate	10:1 to 8:1
PM57	SiO2	Petroleum ether:Ethyl acetate	20:1 to 6:1
PM58	SiO2	Petroleum ether:Ethyl acetate	20:1 to 9:1
PM59	SiO2	Petroleum ether:Ethyl acetate	20:1 to 12:1
PM60	SiO2	Petroleum ether:Ethyl acetate	100:1 to 20:1

Reverse-phase HPLC conditions

Purification Method (PM)	Column	Mobile phase	Gradient
PM61	Phenomenex Synergi C18 150 × 25 mm × 10 mm	water (0.1% FA)-ACN]	10%-90%, 20 min
PM62	Waters Xbridge 150 mm × 25 mm × 5 μm	water (10 mM NH4HCO3) - ACN	18%-48%, 10 min
PM63	Phenomenex Synergi C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	25%-39%, 15 min
PM64	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% FA)–ACN	20%-80%, 20 min
PM65	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	21%-51%, 10 min
PM66	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.075% TFA)-ACN	28%-58%, 9 min
PM67	Phenomenex Synergi C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	10%-90%, 20 min
PM68	Phenomenex Synergi C18 150 × 25 mm × 10 mm	water (0.225% FA)-ACN	18%-48%, 10 min
PM69	Phenomenex Synergi C18 150 × 25 mm × 10 mm	water (0.1% HCl)-ACN	10%-90%, 20 min
PM70	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	80%-90%, 10 min
PM71	Phenomenex Synergi Max-RP 250 × 50 mm × 10 mm	water (10 mM NH4HCO3) - ACN	60%-90%, 35 min
PM72	Phenomenex Synergi C18 150 × 25 mm × 10 mm	water (0.05% FA) - ACN	14%-34%, 10 min
PM73	Phenomenex Synergi C18 150 × 25 mm × 10 mm	water (0.05% HCl)-ACN	64%-84%, 10 min
PM74	Phenomenex luna C18 150 × 25 mm × 5 mm	water (0.075% TFA)-ACN	50%-80%, 9 min
PM75	Phenomenex Synergi Max-RP 250 × 50 mm × 10 mm	water (0.1% TFA)-ACN	30%-60%, 25 min
PM76	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	20%-40%, 10 min
PM77	Phenomenex Synergi C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	20%-40%, 10 min
PM78	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 mm	water (0.1% TFA)-ACN	20%-40%, 10 min

PM79	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 mm	water (0.225% FA)-ACN	20%-40%, 10 min
PM80	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	32%-62%, 11 min
PM81	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	25%-55%, 7 min
PM82	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	25%-55%, 10 min
PM83	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	35%-45%, 7 min
PM84	Phenomenex Synergi C18 150 × 25 mm × 10 mm	water (0.05% HCl)-ACN	58%-78%, 10 min
PM85	Boston Green ODS 150 × 30 mm × 5 mm	water (0.225% FA)-ACN	50%-80%, 10 min
PM86	Waters Xbridge 150 mm × 25 mm × 5 μm	water (NH4OH v/v)-ACN	4%-34%, 9 min
PM87	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	30%-45%, 15 min
PM88	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% FA)-ACN	45%-70%, 20 min
PM89	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	45%-70%, 20 min
PM90	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	45%-70%, 20 min
PM91	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	45%-70%, 20 min
PM92	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	50%-70%, 10 min
PM93	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	50%-70%, 10 min
PM94	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	48%-78%, 10 min
PM95	Phenomenex Synergi Max-RP 250 × 50 mm × 10 mm	water (0.1% TFA)-ACN	32%-62%, 10 min
PM96	Phenomenex luna C18 150 × 40 mm × 15 mm	water (0.1% TFA)-ACN	20%-50%, 10 min
PM97	Waters Xbridge 150 mm × 25 mm × 5 μm	water (10 mM NH4HCO3) - ACN	20%-50%, 10 min
PM98	Phenomenex Synergi Max-RP 250 × 50 mm × 10 mm	water (0.1% TFA)-ACN	37%-67%, 10 min
PM99	Waters Xbridge 150 mm × 25 mm × 5 μm	water (10 mM NH4HCO3) - ACN	18%-51%, 11 min
PM100	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	40%-70%, 20 min
PM101	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	45%-70%, 25 min
PM102	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	45%-70%, 25 min
PM103	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	45%-60%, 22 min
PM104	Phenomenex luna C18 150 × 40 mm × 15 mm	water (0.1% TFA)-ACN	52%-82%, 10 min
PM105	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% FA)-ACN]	40%-71%, 20 min

PM106	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	30%-50%, 20 min
PM107	Waters Xbridge 150 mm × 25 mm × 5 μm	water (0.1% ammonium hydroxide)-ACN	0%-20%, 9 min
PM108	SepaFlash SW120 spherical C18 20 - 45 μm, 100 A	water (0.1% NH3.H2O)-ACN	45%-65%, 15 min
PM109	SepaFlash SW080 spherical C18 20 - 45 μm, 100 A	water (0.1% NH3.H2O)-ACN	40%-65%, 15 min
PM110	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	50%-60%, 25 min
PM111	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	48%-58%, 7 min
PM112	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	20%-30%, 15 min
PM113	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	5%-35%, 10 min
PM114	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	50%-60%, 7 min
PM115	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	42%-60%, 20 min
PM116	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	30%-50%, 15 min
PM117	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	50%-70%, 25 min
PM118	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	65%-90%, 25 min
PM119	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	65%-75%, 20 min
PM120	Phenomenex luna C18 150 × 40 mm × 15 mm	water (0.1% TFA)-ACN	65%-95%,10 min
PM121	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	58%-78%,10 min
PM122	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	35%-45%, 7min
PM123	Phenomenex luna C18 150 × 40 mm × 15 mm	water (0.1% TFA)-ACN	62%-92%, 10 min
PM124	Phenomenex luna C18 150 × 40 mm × 15 mm	water (0.1% TFA)-ACN	65%-75%, 7 min
PM125	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	62%-72%, 10 min
PM126	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% FA)-ACN]	50%-60% 10 min
PM127	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	50%-60%, 20 min
PM128	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	40%-60%, 20 min
PM129	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	52%-72%, 9 min
PM130	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	50%-65%, 15 min
PM131	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	70%-85%, 15 min
PM132	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	50%-70%, 15 min

PM133	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	45%-60%, 15 min
PM134	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	45%-60%, 15 min
PM135	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	65%-80%, 15 min
PM136	SepaFlash SW080 spherical C18 20 - 45 μm, 100 A	water (0.1% NH3.H2O)-ACN	30%-50%, 12 min
PM137	SepaFlash SW330 spherical C18 20 - 45 μm, 100 A	water (0.1% TFA)-ACN	25%-45%, 15 min
PM138	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	60%-75%, 15 min
PM139	SepaFlash SW080 spherical C18 20 - 45 μm, 100 A	water (0.1% TFA)-ACN	70%-90%, 15 min
PM140	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% HCl)-ACN	35%-50%, 15 min
PM141	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	60%-70%, 10 min
PM142	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	40%-65%, 20 min
PM143	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% FA)-ACN]	40%-65%, 20 min
PM144	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	35%-55%, 20 min
PM145	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	65%-75%, 25 min
PM146	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	46%-76%, 10 min
PM147	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	80%-90%, 20 min
PM148	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	75%-85%, 20 min
PM149	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	70%-80%, 20 min
PM150	Boston Green ODS 150 × 30 mm × 5 mm	water (0.225% FA)-ACN	51%-81%, 10 min
PM151	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	60%-80%, 10 min
PM152	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	45%-75%,10 min
PM153	Waters Xbridge 150 mm × 25 mm × 5 μm	water (0.225% FA)-ACN	22%-52%, 10 min
PM154	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	22%-52%, 10 min
PM155	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	25%-65%, 10 min
PM156	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	29%-59%, 10 min
PM157	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	62%-92%, 8 min
PM158	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	80%-90%, 10 min
PM159	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	75%-85%, 10 min

PM160	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	72%-89%, 15 min
PM161	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	20%-50%, 20 min
PM162	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	50%-70%, 20 min
PM163	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	30%-40%, 20 min
PM164	Phenomenex luna C18 150 × 25 mm × 10 mm	water (0.1% TFA)-ACN	35%-65%, 10 min
PM165	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	50%-73%, 20 min
PM166	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	43%-70%, 20 min
PM167	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	18%-38%, 10 min
PM168	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	35%-55%, 10 min
PM169	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	45%-60%, 20 min
PM170	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% FA)-ACN]	40%-55%, 20 min
PM171	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	57%-70%, 15 min
PM172	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	82%-95%, 15 min
PM173	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	60%-80%, 15 min
PM174	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	48%-65%, 15 min
PM175	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	60%-78%, 15 min
PM176	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	60%-70%, 10 min
PM177	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	35%-45%, 15 min
PM178	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	60%-70%, 15 min
PM179	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	75%-90%, 15 min
PM180	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	55%-65%, 15 min
PM181	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	80%-100%, 15 min
PM182	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	48%-60%, 15 min
PM183	Boston pH-lex 150 mm × 25 mm × 10 mm	water (0.1% TFA)-ACN	92%-100%, 10 min
PM184	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% FA)-ACN]	55%-71%, 20 min
PM185	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	20%-30%, 10 min
PM186	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% FA)-ACN]	50%-72%, 20 min

PM187	Phenomenex Gemini 150 mm ´ 25 mm ´ 10 mm	water (0.04% NH3.H2O + 10 mM NH4HCO3) - ACN	62%-92%, 10 min
PM188	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	36%-56%, 10 min
PM189	SepaFlash SW120 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	40%-60%, 15 min
PM190	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% NH3.H2O)-ACN	70%-78%, 22 min
PM191	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water-ACN	30%-45%, 20 min
PM192	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	45%-65%, 15 min
PM193	SepaFlash SW040 spherical C18 20 - 45 μm, 100 A	water (0.1% NH3.H2O)-ACN	45%-65%, 15 min
PM194	SepaFlash SW080 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	70%-85%, 15 min
PM195	Waters Xbridge 150 mm × 25 mm × 5 μm	water (0.1% NH3.H2O)-ACN	5%-35%, 9 min
PM196	SepaFlash SW040 spherical C18 20 - 45 μm, 100 A	water (0.1% NH3.H2O)-ACN	50%-60%, 15 min
PM197	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	20%-30%, 15 min
PM198	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% FA)-ACN]	50%-70%, 15 min
PM199	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	50%-70%, 15 min
PM200	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% HCl)-ACN	50%-70%, 15 min
PM201	SepaFlash SW220 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	70%-90%, 30 min
PM202	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	65%-85%, 15 min
PM203	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	70% - 90%, 12 min
PM204	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	40%-50%, 15 min
PM205	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 mm	water (0.225% FA)-ACN	18%-38%, 10 min
PM206	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.05% HCl)-ACN	14% - 34%, 10 min
PM207	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	25%-45%, 10 min
PM208	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	25%-45%, 10 min
PM209	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	22%-52%, 9 min
PM210	Waters Xbridge 150 mm × 25 mm × 5 μm	water (10 mM NH4HCO3) - ACN	22%-52%, 9 min
PM211	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.05% HCl)-ACN	21%-41%, 10 min
PM212	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.05% HCl)-ACN	17%-37%, 10 min
PM213	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	8%-38%, 10 min

PM214	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	25%-35%, 7 min
PM215	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	27%-47%, 10 min
PM216	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.05% HCl)-ACN	15%-35%, 6.5 min
PM217	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	32%-52%, 10 min
PM218	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.075% TFA)-ACN	15%-45%, 9 min
PM219	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	15%-45%, 9 min
PM220	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	22%-32%, 7 min
PM221	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	24%-44%, 9 min
PM222	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	12%-42%,10 min
PM223	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	28%-38%, 7 min
PM224	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)-ACN	20%-50%, 9 min
PM225	Waters Xbridge 150 mm × 25 mm × 5 μm	water (10 mM NH4HCO3) - ACN	20%-50%, 9 min
PM226	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	12%-32%, 10 min
PM227	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 mm	water (0.225% FA)-ACN	12%-32%, 10 min
PM228	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	25%-40%, 9 min
PM229	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	8%-38%, 7 min
PM230	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	12%-42%, 7 min
PM231	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	14%-44%, 10 min
PM232	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	15%-45%, 10 min
PM233	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	18%-28%, 7 min
PM234	Waters Xbridge 150 mm × 25 mm × 5 μm	water (10 mM NH4HCO3) - ACN	18%-48%, 11min
PM235	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	22%-52%, 8 min
PM236	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	23%-53%, 8 min
PM237	Waters Xbridge 150 mm × 25 mm × 5 μm	water (10 mM NH4HCO3) - ACN	23%-53%, 11 min
PM238	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	45%-55%, 15 min
PM239	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	42%-71%, 25 min
PM240	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.05% HCl)-ACN	4%-34%, 10 min

PM241	SepaFlash SW330 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	25%-40%, 15 min
PM242	Waters Xbridge 150 mm × 25 mm × 5 μm	water (0.05% ammonium hydroxide)-ACN	10%-37%, 10 min
PM243	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	12%-42%, 10 min
PM244	Welch Xtimate C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	12%-42%, 10 min
PM245	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	18%-48%, 11 min
PM246	Welch Xtimate C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	14% - 44%, 10 min
PM247	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	35%-50%, 12 min
PM248	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	40%-55%, 11 min
PM249	Waters Xbridge 150 mm × 25 mm × 5 μm	water (ammonium hydroxide v/v)-ACN	18%-48%, 8 min
PM250	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	18%-48%, 8 min
PM251	Welch Ultimate C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	20%-50%, 2 min
PM252	Welch Ultimate C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	20%-50%, 7 min
PM253	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	20%-50%, 7 min
PM254	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.225% FA)-ACN	3%-33%, 11 min
PM255	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	15%-45%, 7 min
PM256	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	40%-57%, 15 min
PM257	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	40%-55%, 15 min
PM258	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	9%-39%, 10 min
PM259	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	16%-46%, 10 min
PM260	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	1%-24%, 10 min
PM261	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	1%-30%, 10 min
PM262	Phenomenex Synergi Max-RP C18 250 × 50 mm × 10 μm	water (0.1% TFA)-ACN	8%-38%, 10 min
PM263	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	17%-47%, 10 min
PM264	Welch Xtimate C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	8%-38%, 10 min
PM265	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	15%-25%, 7 min
PM266	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	15%-45%, 2 min
PM267	Waters Xbridge 150 mm × 25 mm × 5 μm	water (10 mM NH4HCO3) - ACN	27%-57%, 9 min

PM268	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (10 mM NH4HCO3) - ACN	20%-50%, 8 min
PM269	Zhongpu RD-C18 150 mm × 25 mm × 3 mm	water (0.225% FA)-ACN	21%-51%, 10 min
PM270	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 mm	water (0.225% FA)-ACN	25%-45%, 10 min
PM271	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	14%-44%, 11.5 min
PM272	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	10%-40%, 8 min
PM273	Phenomenex Synergi C18 150 × 25 mm × 10 µm	water (0.1% TFA)-ACN	30%-50%, 10 min
PM274	Shim-pack C18 150 × 25 mm × 10 mm	water (0.225% FA)-ACN	17%-37%, 10 min
PM275	Shim-pack C18 150 × 25 mm × 10 mm	water (0.225% FA)-ACN	23%-43%, 10 min
PM276	Welch Ultimate XB-CN 250 × 70 mm × 10 mm	Hexane-EtOH	35%-75%, 15 min
PM277	Phenomenex Luna C18 150 × 25 mm × 10 µm	water (0.1% NH3.H2O)-ACN	35%-75%, 15 min
PM278	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	33%-63%, 11.5 min
PM279	Welch Ultimate XB-CN 250 × 70 mm × 10 mm	water (0.1% NH3.H2O)-ACN	30%-70%, 15min
PM280	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	30%-60%, 7 min
PM281	Phenomenex Luna C18 150 × 25 mm × 10 µm	water (0.1% TFA)-ACN	30%-60%, 7 min
PM282	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (ammonium hydroxide v/v)-ACN	28%-58%, 7 min
PM283	Phenomenex Luna C18 150 × 25 mm × 10 µm	water (0.225% FA)-ACN	15%-45%, 11 min
PM284	Welch Ultimate XB-CN 250 × 70 mm × 10 mm	water (0.1% NH3.H2O)-ACN	15%-55%, 15 min
PM285	Waters Xbridge 150 mm × 25 mm × 5 µm	water (ammonium hydroxide v/v)-ACN	12%-42%, 11min
PM286	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (ammonium hydroxide v/v)-ACN	8% - 38%, 11.5 min
PM287	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	25% - 55%, 11.5 min
PM288	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	29%-59%, 7 min
PM289	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 mm	water (0.225% FA)-ACN	22%-42%, 10 min
PM290	Shim-pack C18 150 × 25 mm × 10 mm	water (0.225% FA)-ACN	22%-42%, 10 min
PM291	Shim-pack C18 150 × 25 mm × 10 mm	water (0.225% FA)-ACN	24%-46%, 11 min
PM292	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	9%-39%, 8 min
PM293	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (10 mM NH4HCO3) - ACN	17%-47%, 8 min
PM294	Welch Ultimate XB-CN 250 × 70 mm × 10 mm	Hexane-EtOH	20%-60%, 15 min

PM295	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	15%-45%, 6 min
PM296	Phenomenex Gemini 150 × 25 mm × 10 μm	water (0.05% ammonium hydroxide)-ACN	15%-45%,12 min
PM297	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.05% HCl)-ACN	13%-39%, 8 min
PM298	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.05% HCl)-ACN	20%-40%, 9 min
PM299	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	7%-37%, 10 min
PM300	Waters Vinridis Silica 2-EP OBD 50 mm × 150 mm × 5 mm	Hexane-EtOH	15%-55%, 15 min
PM301	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	15%-55%, 10 min
PM302	Welch Ultimate XB-SiOH 250 × 50 mm × 10 mm	Hexane-EtOH (0.1% NH3.H2O)	20%-60%, 15 min
PM303	Welch Ultimate XB-CN 250 × 70 mm × 10 mm	Hexane-EtOH (0.1% NH3.H2O)	20%-60%, 15 min
PM304	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (10 mM NH4HCO3) - ACN	19%-49%, 8 min
PM305	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	12%-42%, 9 min
PM306	Welch Xtimate C18 150 × 40 mm × 10 mm	water (0.05% ammonium hydroxide)-ACN	20%-30%, 7 min
PM307	Welch Xtimate C18 150 × 40 mm × 10 mm	water (0.05% ammonium hydroxide)-ACN	38%-68%, 10 min
PM308	Waters Xbridge 150 mm × 25 mm × 10 μm	water (0.05% ammonium hydroxide)-ACN	37%-57%, 10 min
PM309	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	22%-42%, 10 min
PM310	Phenomenex Luna C18 150 × 25 mm × 10 μm	water (0.1% TFA)-ACN	20%-50%, 10 min
PM311	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	32%-42%, 7 min
PM312	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	30%-40%, 7 min
PM313	Phenomenex Luna C18 150 × 40 mm × 15 μm	water (0.225% FA)-ACN	18%-48%, 10 min
PM314	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	38%-48%, 7 min
PM315	Phenomenex Luna C18 150 × 40 mm × 15 μm	water (0.1% TFA)-ACN	30%-50%, 10 min
PM316	Waters Xbridge 150 mm × 25 mm × 5 μm	water (0.05% ammonium hydroxide)-ACN	40%-70%, 10 min
PM317	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.1% TFA)-ACN	28%-38%, 7min
PM318	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (0.225% FA)-ACN	28%-58%, 8.5 min
PM319	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	18%-48%, 7 min
PM320	Waters Xbridge 150 mm × 25 mm × 10 μm	water (0.05% ammonium hydroxide)-ACN	20%-50%, 11 min
PM321	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	24%-54%, 7 min

PM322	Welch Ultimate XB-SiOH 250 × 50 mm × 10 mm	Hexane-EtOH (0.1% NH3.H2O)	30%-70%, 15 min
PM323	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	17%-47%, 7 min
PM324	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	20%-50%, 7 min
PM325	Phenomenex Luna C18 150 × 40 mm × 15 μm	water (0.1% NH3.H2O)-ACN	30%-70%, 15 min
PM326	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	16%-46%, 7 min
PM327	Welch Ultimate XB-CN 250 × 70 mm × 10 mm	Hexane-EtOH (0.1% NH3.H2O)	15%-55%, 15 min
PM328	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	8%-38%, 5 min
PM329	Welch Ultimate XB-CN 250 × 70 mm × 10 mm	Hexane-EtOH (0.1% NH3.H2O)	10%-50%, 10 min
PM330	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	22%-52%, 7 min
PM331	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	23%-53%, 11.5 min
PM332	Unisil 3-100 C18 Ultra 150 × 50 mm × 3 mm	water (0.225% FA)-ACN	15%-35%, 10 min
PM333	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	7%-37%, 7 min
PM334	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (10 mM NH4HCO3) - ACN	15%-45%, 8 min
PM335	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	3% - 33%, 7 min
PM336	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (10 mM NH4HCO3) - ACN	14%-44%, 8 min
PM337	Phenomenex Gemini-NX C18 75 × 30 mm × 3 mm	water (0.05% ammonium hydroxide)-ACN	7%-37%, 11.5min
PM338	Waters Xbridge 150 mm × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	28%-58%, 11 min
PM339	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	35%-60%, 15 min
PM340	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	30%-55%, 10 min
PM341	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	55%-70%, 15 min
PM342	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	32%-50%, 15 min
PM343	Welch Xtimate C18 150 × 40 mm × 10 mm	water (0.1% NH3.H2O)-ACN	45%-75%, 8 min
PM344	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	32%-45%, 15 min
PM345	Phenomenex Synergi C18 150 × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	28%-58%, 8 min
PM346	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	40%-50%, 10 min
PM347	Welch Xtimate C18 150 × 40 mm × 10 mm	water (0.1% NH3.H2O)-ACN	28%-58%, 8 min
PM348	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	53%-65%, 10 min

PM349	Waters Xbridge 150 mm × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	34%-64%, 9 min
PM350	Waters Xbridge 150 mm × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	31%-61%, 9 min
PM351	Waters Xbridge 150 mm × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	24%-54%, 9 min
PM352	Waters Xbridge 150 mm × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	45%-75%, 8 min
PM353	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	35%-52%, 15 min
PM354	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% NH3.H2O)-ACN	45%-70%, 10 min
PM355	Welch Xtimate C18 150 × 40 mm × 10 mm	water (0.1% NH3.H2O)-ACN	25%-55%, 8 min
PM356	Waters Xbridge 150 mm × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	32%-62%, 9 min
PM357	Welch Xtimate C18 150 × 25 mm × 5 mm	water (0.05% ammonium hydroxide)-ACN	31%-61%, 2 min
PM358	Welch Xtimate C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	10%-40%, 10 min
PM359	Welch Xtimate C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	15%-45%, 10 min
PM360	Welch Xtimate C18 150 × 25 mm × 5 mm	water (10 mM NH4HCO3) - ACN	24%-54%, 2 min
PM361	Welch Xtimate C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	15%-35%, 10 min
PM362	Welch Ultimate C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	20%-50%, 10 min
PM363	Welch Ultimate C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	17%-47%, 10 min
PM364	Waters Xbridge 150 mm × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	22%-52%, 10 min
PM365	Welch Xtimate C18 150 × 25 mm × 5 mm	water (0.1% NH3.H2O)-ACN	30%- 60%, 8 min
PM366	SepaFlash SW040 spherical C18 20 - 45 mm, 100 A	water (0.1% TFA)-ACN	38%-53%, 15 min
PM367	YMC Triart C18 150 × 25 mm × 5 mm	water (0.1% TFA)-ACN	33%-53%, 10 min
PM368	Waters Xbridge 150 mm × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	35%-65%, 9 min
PM369	Waters Xbridge 150 mm × 25 mm × 10 μm	water (10 mM NH4HCO3) - ACN	36%-66%, 9 min
PM370	Welch Xtimate C18 150 × 25 mm × 5 mm	water (0.1% NH3.H2O)-ACN	21%-51%, 2 min

Abbreviations

[00354] Wherein the following abbreviations have been used, the following meanings apply:

ACN is acetonitrile,

AcOH is acetic acid,

AM is analytical method,

aq. is aqueous,

atm. is atmosphere,

Boc_2O is di-tert-butyl dicarbonate,

B_2pin_2 is 4,4,4′,4′,5,5,5′,5′-Octamethyl-2,2′-bi-1,3,2-dioxaborolane,

Brettphos G3 Pd is [(2-Di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′- triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′ -biphenyl)]palladium(II) methanesulfonate methanesulfonate,

CDI is 1,1'-carbonyldiimidazole,

$CHCl_3$-*d* is deuterated chloroform,

CO is carbon monoxide gas,

Cs_2CO_3 is cesium carbonate,

CuI is copper iodide,

DCE is dichloroethane,

DCM is dichloromethane,

DHP is 3,4-dihydropyran,

DIPEA is N,N-diisopropylethylamine,

DMAP is dimethylaminopyridine,

DME is 1,2-dimethoxyethane,

DMF is N,N-dimethylformamide,

DMF-DMA is N,N-dimethylformamide dimethyl acetal,

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_2 is hydrogen gas,

H_2O is water,

HPLC is high performance liquid chromatography,

KF is potassium fluoride,

K_2CO_3 is potassium carbonate,

K_3PO_4 is tripotassium phosphate,

K_2SO_4 is potassium sulphate,

LAH is lithium aluminum hydride,

LCMS is Liquid Chromatography Mass Spectrometry,

LDA is lithium diisopropylamide,

$LiOH.H_2O$ 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 are molecular sieves,

MTBE is methyltertbutylether,

N_2 is nitrogen gas,

$NaBH(AcO)_3$ is sodium triacetoxyborohydride,

$NaBH_4$ is sodium borohydride,

$NaBH_3CN$ is sodium cyanoborohydride,

Na_2CO_3 is sodium carbonate,

NaH is sodium hydride,

$NaHCO_3$ is sodium bicarbonate ,

NaN_3 is sodium azide,

NaOH is sodium hydroxide,

NaOMe is sodium methoxide,

Na_2SO_4 is anhydrous sodium sulfate,

NH_3 is ammonia,

NH_4Cl is ammonium chloride,

NCS is N-chlorosuccinimide,

Pd/C is palladium on carbon,

$Pd_2(dba)_3$ is tris(dibenzylideneacetone)dipalladium(0),

$Pd(PPh_3)_4$ 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,

PMB is p-methoxybenzyl,

$POCl_3$ is phosphorous oxychloride,

PPh_3 is triphenylphosphine,

RT is room temperature,

rt is retention time,

SEM is silylethoxymethyl,

$SOCl_2$ is thionyl chloride,

SiO_2 is silica,

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,

TMSCl is trimethylsilyl chloride,

T3P is propylphosphonic anhydride,

Trt is trityl,

TrtCl is trityl chloride; and

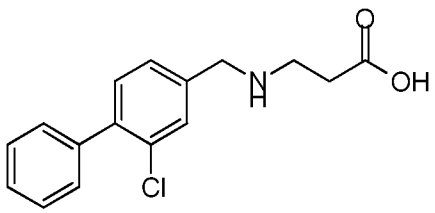
$TsOH.H_2O$ is p-toluenesulfonic acid monohydrate.

Preparation of Intermediates

[00355] The following Preparations describe the methods used for common intermediates required for synthesis of the Examples.

Synthesis of Intermediate D

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanoic acid, 1.39

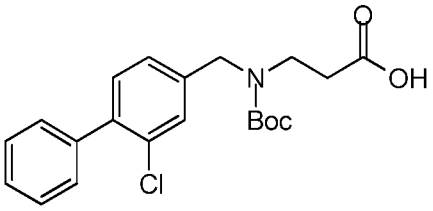


[00356] A solution of 3-Chloro-4-phenylbenzaldehyde (CAS 57592-44-6, 10 g, 46.15 mmol) (2-chloro-[1,1'-biphenyl]-4-carbaldehyde (Bioorganic and Medicinal Chemistry, 2017, 25 (13), 3471–3482)) and 3-aminopropanoic acid (12.34 g, 138.46 mmol) in MeOH (200 mL) was stirred at 34 °C for 1 h. $NaBH(AcO)_3$ (19.56 g, 92.31 mmol) was added slowly and the reaction mixture was stirred at 34 °C for 14 h. The reaction mixture was filtered and concentrated *in*

vacuo to give a residue that was purified (PM64) to afford **compound 1.39** (11.9 g, 41.07 mmol, 89% yield) as a colourless oil.

[00357] LCMS (AM3): rt = 0.758 min, (290.1 $[M+H]^+$), 50% purity.

3-((tert-butoxycarbonyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanoic acid, Intermediate D

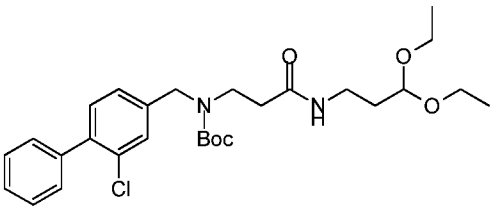


[00358] To a solution of **compound 1.39** (11.9 g, 41.07 mmol) in THF (75 mL) and H_2O (75 mL) was added $NaHCO_3$ (5.18 g, 61.60 mmol) and $(Boc)_2O$ (10.76 g, 49.28 mmol) sequentially at 30 °C, the mixture was stirred for 2 h. The reaction mixture was filtered and concentrated *in vacuo*, and the residue was purified (PM64) to afford **Intermediate D** (13.8 g, 35.40 mmol, 86.2% yield) as a yellow oil.

[00359] LCMS (AM3): rt = 0.997 min, (412.1 $[M+Na]^+$). 92% purity.

Synthesis of Intermediate H

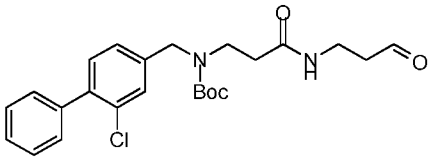
tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3,3-diethoxypropyl)amino)-3-oxopropyl)carbamate 1.77



[00360] To a solution of **Intermediate D** (10 g, 25.65 mmol), 3,3-diethoxypropan-1-amine (4.53 g, 30.78 mmol) and TEA (10.71 mL, 76.95 mmol) in THF (100 mL) was added T_3P (24.48 g, 38.47 mmol, 50% in EA) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. The mixture was diluted with water (500 mL) and extracted with EA (200 mL × 2). The combined organic phases were washed (brine, 200 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified (PM5) to give **compound 1.77** (11.2 g, 21.58 mmol, 84.1% yield) as a colourless oil.

[00361] LCMS (AM3): rt = 1.057 min, (541.2 $[M+Na]^+$), 76% purity.

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-oxopropyl)amino)propyl)carbamate; Intermediate H

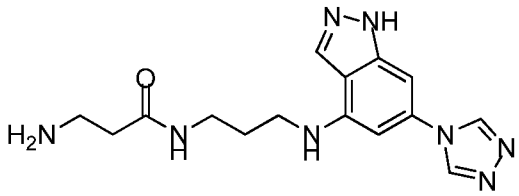


[00362] A solution of **compound 1.77** (1 g, 1.93 mmol) in AcOH (5 mL) and water (5 mL) was stirred at 30 °C for 2. The mixture was basified with sat. $NaHCO_3$ (aq.) to pH = 8 and then extracted with EA (50 mL × 2). The combined organic phases were washed (brine, 50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **Intermediate H** (850 mg, 1.91 mmol, 99.1% yield) as a colourless oil, which was used directly without further purification.

[00363] LCMS (AM3): rt = 0.961 min, (467.2 $[M+Na]^+$), 86.8% purity.

Synthesis of Intermediate N

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-aminopropanamide; Intermediate N

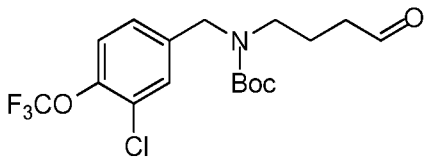


[00364] A mixture of **compound 1.279** (450 mg, 1.09 mmol) in a solution of HCl in MeOH (4 M, 10 mL) was stirred at 20 °C for 1 h. The mixture was concentrated *in vacuo* and the residue was purified (PM69) to afford **Intermediate N** (350 mg, 0.959 mmol, 87.9% yield, HCl salt) as a yellow solid.

[00365] LCMS (AM4): rt = 0.701 min, (329.1 $[M+H]^+$), 98.3% purity.

Synthesis of Intermediate I

tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(4-oxobutyl)carbamate, Intermediate I

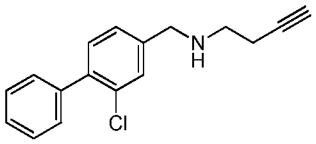


[00366] To a solution of tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(4-hydroxybutyl)carbamate (WO2022185041, 1.45 g, 3.64 mmol) in DCM (10 mL) was added DMP (1.86 g, 4.37 mmol) at 20 °C. The resulting mixture was stirred at 20 °C for 1 h. The mixture was concentrated *in vacuo* and purified (PM7) to afford **Intermediate I** (1.15 g, 2.91 mmol, 79.7% yield) as a light-yellow oil.

[00367] LCMS (AM3): rt = 1.036 min, (418.1 $[M+Na]^+$), 72.2% purity.

Synthesis of Intermediate J

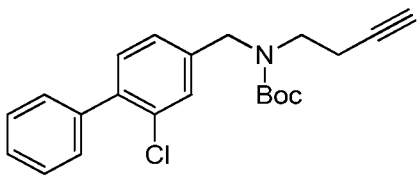
N-((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)but-3-yn-1-amine, 1.169



[00368] A mixture of but-3-yn-1-amine hydrochloride (974.47 mg, 9.23 mmol, HCl salt), NaOAc (946.56 mg, 11.54 mmol) and 3-Chloro-4-phenylbenzaldehyde (CAS 57592-44-6, 500 mg, 2.31 mmol) in MeOH (20 mL) was stirred at 20 °C for 12 h, then $NaBH(AcO)_3$ (1.96 g, 9.23 mmol) was added. The mixture was stirred at 20 °C for 3 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified (PM61) to afford **compound 1.169** (500 mg, 1.85 mmol, 80.3% yield) as a yellow oil.

[00369] LCMS (AM3): rt = 0.794 min, (270.5 $[M+H]^+$), 100% purity.

tert-Butyl but-3-yn-1-yl((2-chloro-[1,1'-biphenyl]-4-yl)methyl)carbamate, Intermediate J

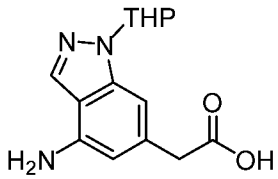


[00370] To a mixture of **compound 1.169** (500 mg, 1.85 mmol) and TEA (562.65 mg, 5.56 mmol) in THF (10 mL) was added Boc_2O (444.96 mg, 2.04 mmol) at 20 °C. The mixture was stirred at 20 °C for 12 h. The mixture was concentrated *in vacuo* and purified (PM6) to afford **Intermediate J** (370 mg, 1.00 mmol, 54% yield) as a colorless oil.

[00371] ^{1}**H NMR** (400 MHz, $CHCl_3$-*d*$CHCl_3$-*d*) δ: 7.48–7.29 (m, 7H), 7.19 (br s, 1H), 4.55 (s, 2H), 3.51-3.33 (m, 2H), 2.52–2.40 (m, 2H), 2.00 (t, *J* = 2.4 Hz, 1H), 1.54–1.45 (m, 9H) ppm.

Synthesis of Intermediate 1.3

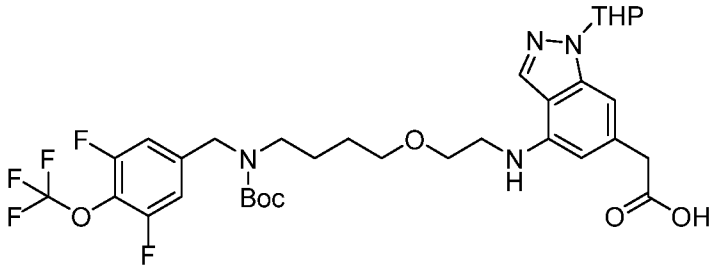
2-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)acetic acid 1.2



To a mixture of Pd/C (100 mg, 10% purity) in MeOH (40 mL) was added **compound 2.449** (270 mg, 884.42 μmol). The mixture was degassed and purged with H_2 (x3), then the mixture was stirred at 20 °C for 1 h under H_2 (15 psi). The mixture was filtered and the filtrate was concentrated *in vacuo* to afford **compound 1.2** (126 mg, 457.68 μmol, 51.75% yield) as a brown gum.

LCMS (AM11): rt = 0.300 min, (297.8 $[M+Na]^+$), 76.51% purity.

2-(4-((2-(4-((tert-butoxycarbonyl)(3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)acetic acid 1.3

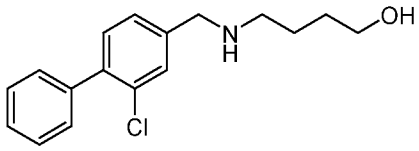


To a mixture of **compound 1.941** (130 mg, 294.53 μmol) and **compound 1.2** (117.36 mg, 323.98 μmol) in MeOH (4 mL) was added $MgSO_4$ (177.26 mg, 1.47 mmol) and AcOH (26.53 mg, 441.79 μmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (37.02 mg, 589.05 μmol) was added. The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water (20 mL) and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 20 mL × 2), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a residue, which was purified (PM70) to afford **compound 1.3** (120 mg, 162.01 μmol, 55.01% yield) as a yellow gum.

LCMS (AM11): rt = 0.527 min, (701.1, $[M+H]^+$), 94.60% purity.

Synthesis of Intermediate 1.7

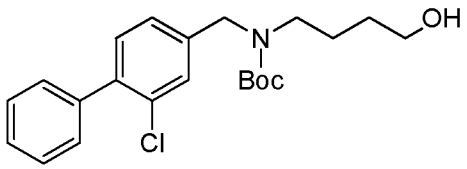
4-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)butan-1-ol 1.5



[00372] A mixture of 2-chloro-[1,1'-biphenyl]-4-carbaldehyde (10 g, 42.00 mmol) (Bioorganic and Medicinal Chemistry, 2017, 25 (13), 3471–3482), 4-aminobutan-1-ol (8.01 g, 89.88 mmol) and 4Å MS (20 g) in MeOH (200 mL) was stirred at RT for 18 h, and then $NaBH_3CN$ (9 g, 143.22 mmol) added. The mixture was stirred for 4 h at RT. The reaction mixture was filtered, the filtrate was concentrated *in vacuo* to give a residue that was added to H_2O (200 mL) and the aq. mixture was extracted with EA (200 mL x 3). The combined organic phases were washed (brine, 300 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified (PM19) to give **compound 1.5** (6.9 g, 23.77 mmol, 51.6% yield) as a light-brown gum.

[00373] **^{1}H NMR** ($CHCl_3$-*d*$CHCl_3$-*d*, 400 MHz) *δ*: 7.37–7.34 (m, 6H), 7.25–7.19 (m, 2H), 3.74 (s, 2H), 3.56 (m, 2H), 3.38 (bs, 2H), 2.68 (t, *J* = 5.6 Hz, 2H), 1.63–1.58 (m, 4H) ppm.

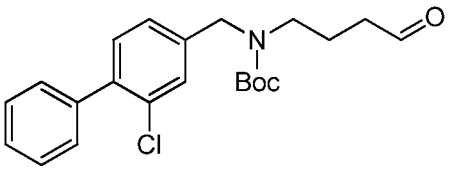
tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(4-hydroxybutyl)carbamate 1.6



[00374] To a mixture of **compound 1.5** (6.9 g, 23.77 mmol) in THF (45 mL) and H_2O (15 mL) was added $NaHCO_3$ (4.00 g, 47.62 mmol) and $(Boc)_2O$ (6 g, 27.49 mmol) at RT. The mixture was stirred for 18 h. To the reaction mixture was added H_2O (100 mL), extracted with EA (100 mL x 3) and the combined organic phases washed (brine, 100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was (PM20) to afford **compound 1.6** (7.0 g, 17.99 mmol, 75% yield) as a light-brown oil.

[00375] **LCMS** (AM1): rt = 0.839 min, (334.1 [M-^{t}Bu+2H]$^+$), 99.3% purity.

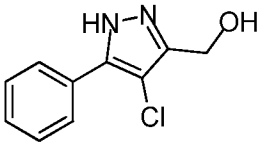
tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(4-oxobutyl)carbamate 1.7



[00376] To a solution of **compound 1.6** (1.5 g, 3.85 mmol) in DCM (30 mL) was added DMP (2 g, 4.72 mmol) at RT. The reaction mixture was then stirred for 15 h. The reaction mixture filtered, the filtrate concentrated *in vacuo* and purified (PM21) to afford **compound 1.7** (1.01 g, 62.9% yield) as a colourless oil.

Synthesis of Intermediate 1.67

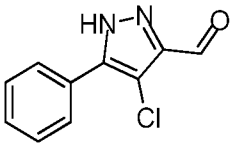
(4-Chloro-5-phenyl-1H-pyrazol-3-yl)methanol 1.66



[00377] To a mixture of 5-phenyl-1H-pyrazol-3-yl methanol (800 mg, 4.59 mmol) (Journal of Medicinal Chemistry, 1998, 41(13), 2390–2410) in ACN (10 mL) was added NCS (919.87 mg, 6.89 mmol) under N_2 at 25 °C. The mixture was stirred at 25 °C for 12 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The obtained residue was purified (PM65) to afford **compound 1.66** (250 mg, 1.14 mmol, 24.8% yield, 95% purity) as a white solid.

[00378] LCMS (AM3): rt = 0.813 min, (209.1 $[M+H]^+$), 94.39% purity.

4-Chloro-5-phenyl-1H-pyrazole-3-carbaldehyde 1.67

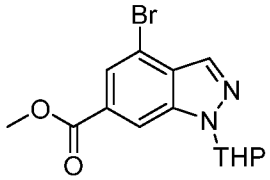


[00379] To a mixture of **compound 1.66** (250 mg, 1.20 mmol) in DCM (10 mL) was added manganese (IV) oxide (1.04 g, 11.98 mmol) under N_2 at 25 °C. The mixture was stirred at 25 °C for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue which was further purified (PM66) to afford **compound 1.67** (60 mg, 281.67 μmol, 23.5% yield, 97% purity) as a white solid.

[00380] LCMS (AM3): rt = 0.858 min, (207.0 $[M+H]^+$), 96.49% purity.

Synthesis of Intermediate 1.81

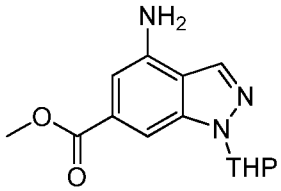
Methyl 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 1.79



[00381] To a mixture of Methyl 4-bromo-1H-indazole-6-carboxylate (CAS 885518-47-8 , 2 g, 7.84 mmol) in THF (20 mL) was added 3,4-dihydro-2H-pyran (1.32 g, 15.68 mmol, 1.43 mL) and 4-methylbenzenesulfonic acid (149 mg, 0.784 mmol) at RT. The mixture was heated to 50 °C and stirred for 12 h. The mixture was diluted with saturated aq. $NaHCO_3$ (30 mL) and extracted with EA (30 mL × 3). The combined organic phases were washed (brine, 150 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified (PM14) to afford **compound 1.79** (2.4 g, 7.08 mmol, 90.2% yield) as a white solid.

[00382] **^{1}H NMR** (400 MHz, $CHCl_3$-*d*$CHCl_3$-*d*) δ 8.30 (s, 1H), 8.08 (s, 1H), 8.00 (d, *J* = 1.2 Hz, 1H), 5.78 (dd, *J* = 9.2, 2.8 Hz, 1H), 4.07-3.95 (m, 4H), 3.83-3.73 (m, 1H), 2.60-2.44 (m, 1H), 2.20-2.07 (m, 2H), 1.82-1.70 (m, 3H) ppm.

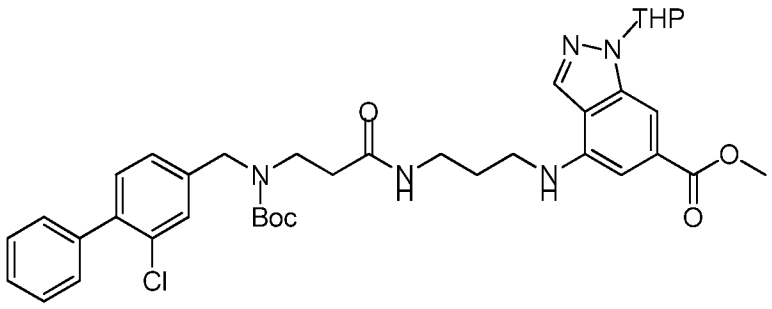
Methyl 4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 1.80



[00383] To a mixture of **compound 1.79** (1.9 g, 5.60 mmol) in DMSO (30 mL) was added ammonium hydroxide (2.07 g, 14.8 mmol), CuI (224 mg, 1.18 mmol), (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid (301 mg, 2.30 mmol) and K_2CO_3 (2.39 g, 17.31 mmol) sequentially at RT under N_2. The reaction mixture was heated to 90 °C and stirred for 16 h. The mixture was diluted with water (40 mL), extracted with EA (30 mL × 3), the combined organic phases were washed (brine, 50 mL × 3), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford **compound 1.80** (1.2 g, 4.36 mmol, 77.8% yield) as a yellow solid.

[00384] **LCMS** (AM3): rt = 0.727 min, (276.1 $[M+H]^+$), 57.3% purity.

Methyl 4-((3-(3-((tert-butoxycarbonyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 1.81



[00385] To a mixture of **compound 1.80** (1.29 g, 2.91 mmol) and **Intermediate H** (1 g, 3.63 mmol) in DCE (30 mL) was added $NaBH(AcO)_3$ (1.54 g, 7.26 mmol) at 25 °C. The mixture was stirred at 25 °C for 16 h. The mixture was concentrated in *vacuo* and the residue was purified (PM71) to afford **compound 1.81** (460 mg, 0.653 mmol, 18% yield) as a white solid.

[00386] LCMS (AM3): rt = 1.096 min, (704.4 $[M+H]^+$), 100% purity.

[00387] The following Intermediates in Table 1 were made with non-critical changes or substitutions to the exemplified procedure for Intermediate H that would be understood by one skilled in the art, wherein R may or may not contain a THP protecting group.

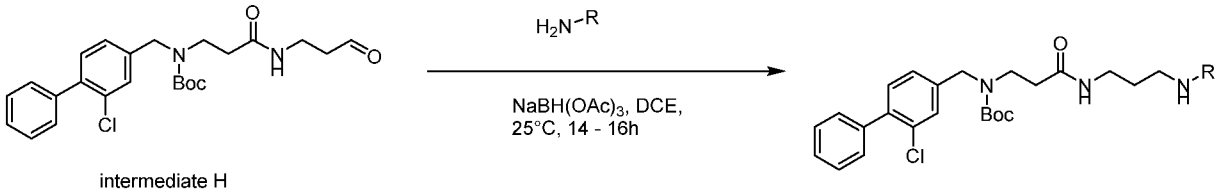
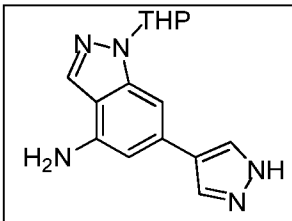
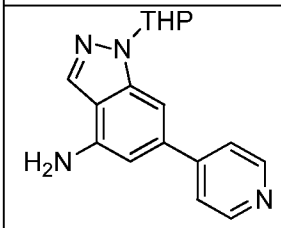


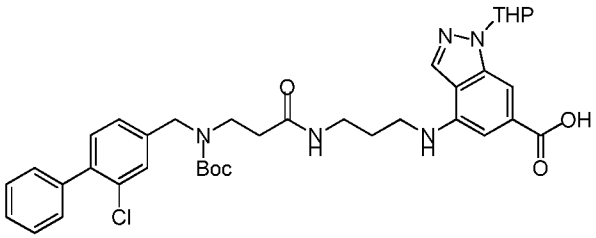
Table 1

Reagent H_2N-R IUPAC name/Intermediate No.	Product Intermediate IUPAC name/Intermediate No.	Analytical

 6-(1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **1.302**	tert-Butyl (3-((3-((6-(1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)carbamate **1.303**	**LCMS** (AM3): rt = 0.970 min, (712.4 $[M+H]^+$), 65.3% purity. **Purification Method** PM94
 6-(Pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **1.322**	tert-Butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate **1.323**	**LCMS** (AM3): rt = 0.946 min, (723.3 $[M+H]^+$), 97.1% purity. **Purification Method** PM98

Synthesis of Intermediate 1.83

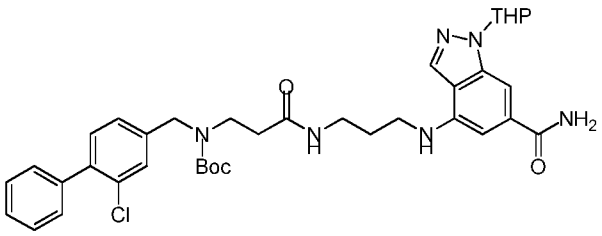
4-((3-(3-((tert-butoxycarbonyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylic acid 1.82



[00388] To a mixture of **compound 1.81** (360 mg, 0.511 mmol) in THF (18 mL), MeOH (0.2 mL) and water (0.2 mL) was added $LiOH.H_2O$ (214.5 mg, 5.11 mmol) at 25 °C. The mixture was stirred at 25 °C for 20 h. The reaction mixture was concentrated in *vacuo* and the residue was purified (PM72) to afford **compound 1.82** (340 mg, 0.493 mmol, 96.4% yield) as a yellow solid.

[00389] LCMS (AM3): rt = 0.987 min, (690.4 $[M+H]^+$), 86.7% purity.

tert-butyl(3-((3-((6-carbamoyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)carbamate 1.83

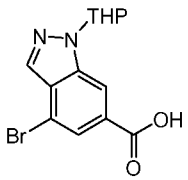


[00390] To a mixture of **compound 1.82** (150 mg, 0.217 mmol) and NH_4Cl (23.25 mg, 0.435 mmol) in THF (6 mL) was added HATU (99.16 mg, 0.261 mmol) and DIPEA (84.26 mg, 0.652 mmol) at 25 °C. The mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (10 mL) and extracted with EA (15 mL × 2). The combined organic phase was washed (brine, 30mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.83** (130 mg) as a yellow oil, which was used directly without further purification.

[00391] LCMS (AM3): rt = 0.957 min, (689.4 $[M+H]^+$), 85% purity.

Synthesis of Intermediate 1.88

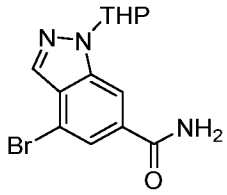
4-Bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylic acid 1.84



[00392] To a solution of **compound 1.79** (1.0 g, 2.95 mmol) in THF (10 mL) and water (10 mL) was added $LiOH.H_2O$ (247 mg, 5.9 mmol) at 30 °C. The resulting mixture was stirred at 30 °C for 2 h. The solvent was removed *in vacuo*, the aqueous phase was acidified with aq. HCl (1 M) to pH = 4, and then extracted with EA (50 mL × 2). The combined organic phases were washed (brine, 50 mL), dried (Na_2SO_4) and concentrated in *vacuo* to afford **compound 1.84** (950 mg) as a white solid.

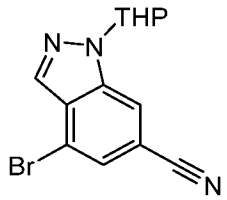
[00393] LCMS (AM3): rt = 0.827 min, (239.9 $[M+2]^+$), 85% purity.

4-Bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxamide 1.85



To a solution of **compound 1.84** (500 mg, 1.54 mmol) in DMF (10 mL) was added EDCI (590 mg, 3.08 mmol), HOBt (416 mg, 3.08 mmol), DIPEA (397 mg, 3.08 mmol) and NH_4Cl (329 mg, 6.15 mmol) sequentially at 30 °C. The resulting mixture was stirred at 30 °C for 15 h. The mixture was diluted with water (50 mL) and extracted with EA (50 mL × 2). The combined organic phases were washed (brine, 50 mL), dried (Na_2SO_4) and concentrated in *vacuo* to afford **compound 1.85** (450 mg) as a colourless oil, which was used directly without further purification.

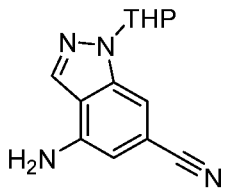
4-Bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carbonitrile 1.86



[00394] To a solution of **compound 1.85** (450 mg, 1.39 mmol) in THF (10 mL) was added Burgess reagent (330.1 mg, 1.39 mmol) at 30 °C. The resulting mixture was stirred at 30 °C for 15 h. The solvent was removed *in vacuo* and the residue dissolved in EA (50 mL). The organic phase was washed (brine, 25 mL), dried (Na_2SO_4) and concentrated in *vacuo*. The residue was purified (PM7) to afford **compound 1.86** (370 mg, 1.21 mmol, 87% yield) as a white solid.

[00395] **^{1}H NMR** (400 MHz, $CHCl_3$-*d*$CHCl_3$-*d*) δ 8.12 (s, 1H), 8.02 (d, *J* = 0.8 Hz, 1H), 7.56 (d, *J* = 0.8 Hz, 1H), 5.78 (dd, *J* = 9.2, 2.8 Hz, 1H), 4.05-3.98 (m, 1H), 3.83-3.75 (m, 1H), 2.53-2.42 (m, 1H), 2.20-2.11 (m, 2H), 1.85-1.70 (m, 3H) ppm.

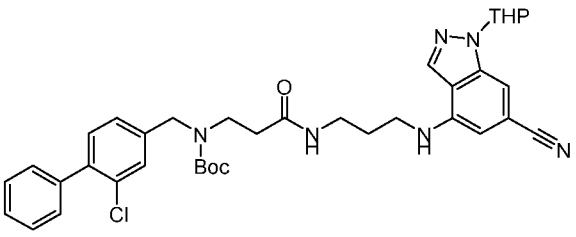
4-Amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carbonitrile 1.87



[00396] To a mixture of **compound 1.86** (320 mg, 1.05 mmol) in DMSO (8 mL) was added aq. NH_3 solution (387 mg, 2.76 mmol), CuI (41.80 mg, 0.219 mmol), (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid (56.19 mg, 0.429 mmol) and K_2CO_3 (433 mg, 3.14 mmol) sequentially at rt. The reaction mixture was heated to 90 °C and stirred for 16 h under N_2 protection. The reaction mixture was diluted with water (30 mL) and extracted with EA (30 mL × 2). The combined organic phases were washed (brine, 50 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.87** (250 mg) as a yellow oil.

[00397] LCMS (AM3): rt = 0.753 min, (265.1 $[M+Na]^+$), 48% purity.

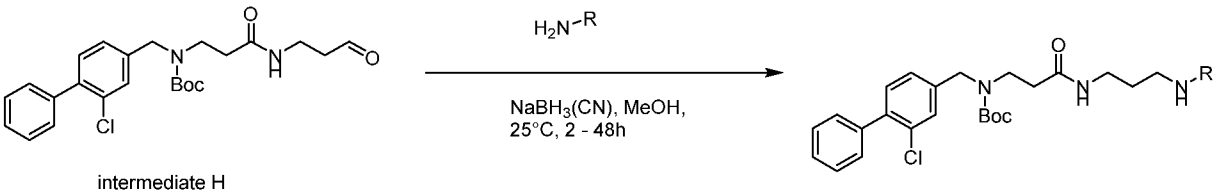
tert-butyl((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 1.88



[00398] A mixture of **compound 1.87** (200 mg, 0.826 mmol) and **Intermediate H** (367 mg, 0.826 μmol in MeOH (10 mL) was stirred at 30 °C for 12 h, then $NaBH_3CN$ (519 mg, 8.26 mmol) was added. The reaction mixture was stirred at 30 °C for 2 h. The reaction mixture was concentrated in *vacuo* and the residue was purified (PM73) to afford **compound 1.88** (200 mg, 0.28 mol, 33.9% yield) as a white solid.

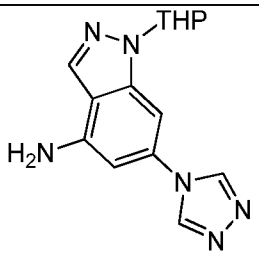
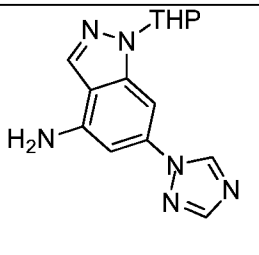
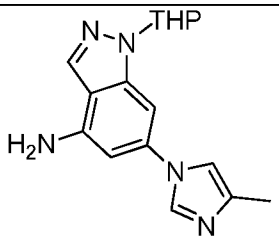
[00399] LCMS (AM2): rt = 1.010 min, (671.3 $[M+H]^+$), 94% purity.

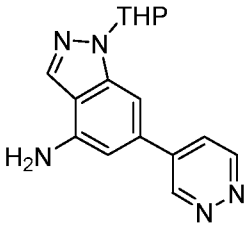
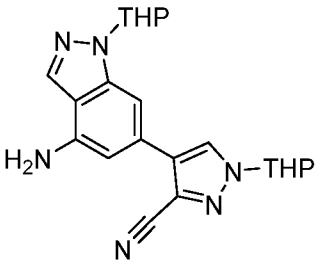
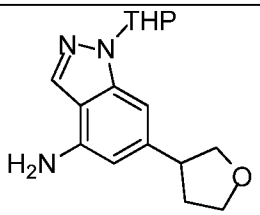
[00400] The following Intermediates in Table 2 were made with non-critical changes or substitutions to the exemplified procedure for Intermediate 1.88 that would be understood by one skilled in the art, wherein R may or may not contain a THP protecting group.

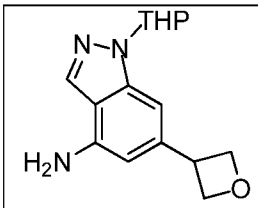
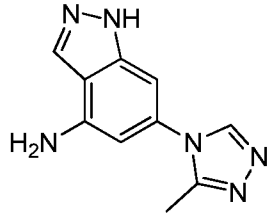
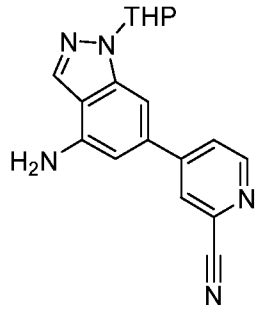
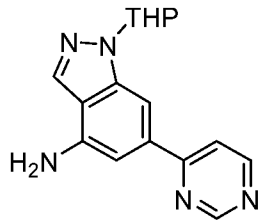


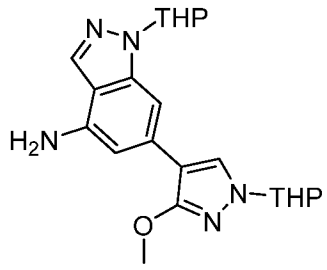
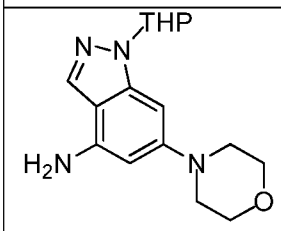
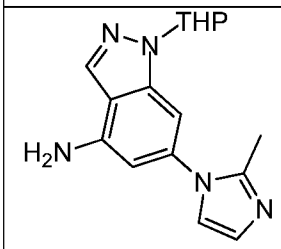
intermediate H

Table 2

Reagent H_2N-R IUPAC name/Intermediate No.	Product Intermediate IUPAC name/Intermediate No.	Analytical
 1-(Tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine **1.273**	tert-Butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate **1.274**	**LCMS** (AM3): rt = 1.037 min, (713.3 $[M+H]^+$), 77.9% purity. **Purification Method** PM74
 1-(Tetrahydro-2H-pyran-2-yl)-6-(1H-1,2,4-triazol-1-yl)-1H-indazol-4-amine **1.294**	tert-Butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((1-(tetrahydro-2H-pyran-2-yl)-6-(1H-1,2,4-triazol-1-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate **1.295**	**LCMS** (AM3): rt = 1.080 min, (713.2 $[M+H]^+$), 98.7% purity. **Purification Method** PM84
 6-(4-methyl-1H-imidazol-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **1.903**	tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(4-methyl-1H-imidazol-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **1.904**	**LCMS** (AM3): rt = 0.935 min, (726.1 $[M+H]^+$), 96.2% purity. **Purification Method** PM114

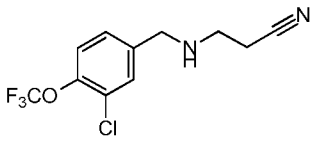
 6-(pyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **1.923**	tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((6-(pyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate **1.924**	**LCMS** (AM3): rt = 1.136 min, (826.2 $[M+H]^+$), 97.1% purity. **Purification Method** PM120
 4-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-3-carbonitrile **1.927**	tert-butyl((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(3-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **1.928**	**LCMS** (AM3): rt = 1.160 min, (821.1 $[M+H]^+$), 97.6% purity. **Purification Method** PM120
 1-(tetrahydro-2H-pyran-2-yl)-(tetrahydrofuran-3-yl)-1H-indazol-4-amine **2.008**	tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((1-(tetrahydro-2H-pyran-2-yl)-6-(tetrahydrofuran-3-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate **2.009**	**LCMS** (AM3): rt = 1.002 min, (716.4 $[M+H]^+$), 95.5% purity. **Purification Method** PM90

 6-(oxetan-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.010**	tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(oxetan-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.011**	**LCMS** (AM3): rt = 1.070 min, (703.6 $[M+H]^+$), 99.5% purity. **Purification Method** PM103
 6-(3-methyl-4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine **2.071**	tert-butyl((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(3-methyl-4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.072**	**LCMS** (AM3): rt =0.913 min, (643.2 $[M+H]^+$),100% purity. **Purification Method** PM152
 4-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)picolinonitrile **2.095**	tert-butyl((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(2-cyanopyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.096**	**LCMS** (AM3): rt = 1.073 min, (748.2 $[M+H]^+$), 96.4% purity **Purification Method** PM123
 6-(pyrimidin-4-yl)-1-(tetrahyd 2H-pyran-2-yl)-1H-indazol-4-amine **2.098**	tert-butyl((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((6-(pyrimidin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate **2.099**	**LCMS** (AM3): rt = 1.065 min, (724.3 $[M+H]^+$), 96.7% purity **Purification Method** PM124

 6-(3-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.100**	tert-butyl((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(3-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.101**	**LCMS** (AM3): rt = 1.131 min, (826.3 $[M+H]^+$), 94.7% purity **Purification Method** PM120
 6-morpholino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.267**	tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((4-(6-morpholino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)butyl)amino)-3-oxopropyl)carbamate **2.268**	**LCMS** (AM3): rt = 0.970 min, (731.5 $[M+H]^+$), 91.4% purity **Purification Method** PM162
 6-(2-methyl-1H-imidazol-1-yl)(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.270**	tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(2-methyl-1H-imidazol-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.271**	**LCMS** (AM3): rt = 0.950 min, (726.3 $[M+H]^+$), 94.1% purity. **Purification Method** PM164

Synthesis of Intermediate 1.225

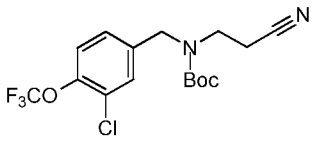
3-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)propanenitrile 1.223



[00401] A mixture of 3-chloro-4-(trifluoromethoxy)benzaldehyde (CAS 83279-39-4, 1 g, 4.45 mmol) and 3-aminopropanenitrile (780.32 mg, 11.13 mmol) in MeOH (20 mL) was stirred at 35 °C for 12 h, then $NaBH(AcO)_3$ (3.78 g, 17.81 mmol) was added. The reaction mixture was stirred at 35 °C for 3 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified (PM61) to afford **compound 1.223** (820 mg, 2.94 mmol, 66.1% yield) as a brown oil.

[00402] LCMS (AM3): rt = 0.717 min, (278.9 $[M+H]^+$), 100% purity.

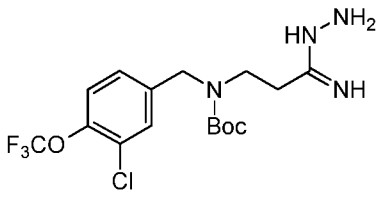
tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(2-cyanoethyl)carbamate 1.224



[00403] To a mixture of **compound 1.223** (820 mg, 2.94 mmol) and TEA (893.31 mg, 8.83 mmol) in THF (10 mL) was added Boc_2O (706.45 mg, 3.24 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 16 h. The mixture was concentrated *in vacuo* and the residue was purified (PM6) to afford **compound 1.224** (1 g, 2.64 mmol, 89.7% yield) as a colourless oil.

[00404] LCMS (AM3): rt = 1.207 min, (323.5 $[M-tBu+2H]^+$), 91.3% purity.

tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(3-hydrazinyl-3-iminopropyl)carbamate 1.225



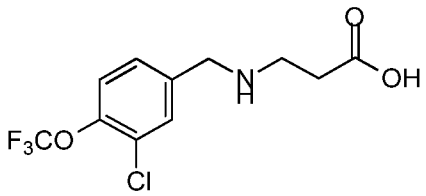
[00405] To a mixture of **compound 1.224** (900 mg, 2.38 mmol) in a methanolic solution of NaOMe (2.45 M, 22.50 mL) was added hydrazine hydrate (1.55 g, 30.86 mmol) at RT. The reaction mixture was heated to 70 °C and stirred for 5 h. The mixture was adjusted to pH 7 by adding an aq. solution of FA (4 N). The mixture was filtered and the filtrate was concentrated

in vacuo to give a residue that was purified (PM68) to afford **compound 1.225** (170 mg, 413.81 μmol, 17.4% yield) as a colourless oil.

[00406] LCMS (AM3): rt = 0.842 min, (411.1 $[M+H]^+$), 79.8% purity.

Synthesis of Intermediate 1.246

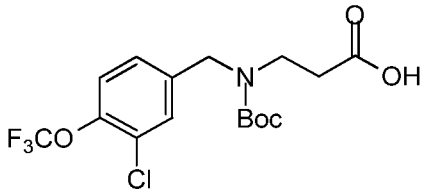
3-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)propanoic acid 1.242



[00407] To a solution of 3-chloro-4-(trifluoromethoxy)benzaldehyde (CAS 83279-39-4, 7 g, 31.17 mmol) in MeOH (50 mL) was added 3-aminopropanoic acid (8.33 g, 93.51 mmol) at 20 °C. After stirring for 24 h at 20 °C, $NaBH(AcO)_3$ (19.82 g, 93.51 mmol) was added. The reaction mixture was stirred at 20 °C for 1 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified (PM67) to afford **compound 1.242** (7 g, 17.00 mmol, 54.5% yield, TFA salt) as a yellow oil.

[00408] LCMS (AM3): rt = 0.703 min, (298.1 $[M+H]^+$), 98.7% purity.

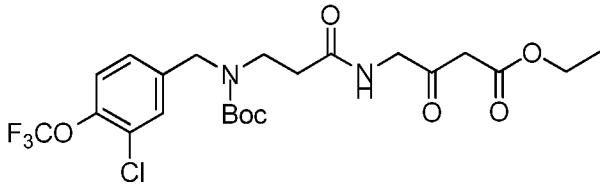
3-((tert-Butoxycarbonyl)(3-chloro-4-(trifluoromethoxy)benzyl)amino)propanoic acid 1.243



[00409] To a solution of **compound 1.242** (7 g, 23.52 mmol) in THF (50 mL) and H_2O (10 mL) was added $NaHCO_3$ (3.95 g, 47.03 mmol) and Boc_2O (7.70 g, 35.28 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was acidified to pH 3 with aq. HCl (1 M) and then extracted with EA (50 mL × 3). The combined organic layers were washed (brine, 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified (PM2) to afford **compound 1.243** (5.55 g, 13.95 mmol, 59.3% yield) as a yellow oil.

[00410] LCMS (AM3): rt = 0.998 min, (420.0 $[M+Na]^+$), 98.4% purity.

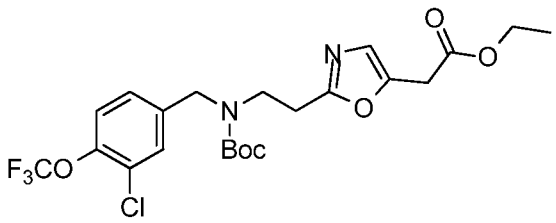
Ethyl 4-(3-((tert-butoxycarbonyl)(3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamido)-3-oxobutanoate 1.244



[00411] To a mixture of **compound 1.243** (5.9 g, 14.83 mmol) and HATU (6.77 g, 17.80 mmol) in DMF (50 mL) was added DIPEA (5.75 g, 44.50 mmol) at 30 °C. After stirring at 30 °C for 30 min, Ethyl 4-amino-3-oxobutanoate hydrochloride (2.69 g, 14.84 mmol, HCl salt) was added and the mixture was stirred at 30 °C for 2 h. The mixture was diluted with H_2O (100 mL) and the aq. phase was extracted with EA (100 mL × 3). The combined organic phases were washed (brine, 200 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM61) to afford **compound 1.244** (3.9 g, 7.43 mmol, 50.1% yield) as a red oil.

[00412] LCMS (AM3): rt = 1.030 min, (525.1 $[M+H]^+$), 74.0% purity.

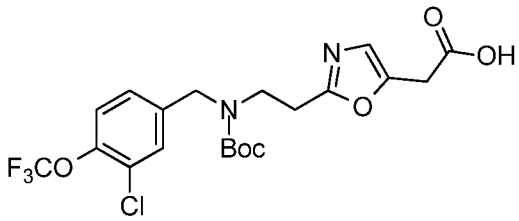
Ethyl 2-(2-(2-((tert-butoxycarbonyl)(3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)oxazol-5-yl)acetate 1.245



[00413] To a mixture of **compound 1.244** (2.8 g, 5.33 mmol) in THF (40 mL) was added Burgess reagent (3.81 g, 16.00 mmol) at 20 °C. The mixture was stirred at 20 °C for 2 h. The mixture was concentrated in *vacuo* and the residue was purified (PM4) to afford **compound 1.245** (1.3 g, 2.56 mmol, 48% yield) as a yellow oil.

[00414] LCMS (AM3): rt = 1.100 min, (507.2 $[M+H]^+$), 94.0% purity.

2-(2-(2-((tert-Butoxycarbonyl)(3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)oxazol-5-yl)acetic acid 1.246

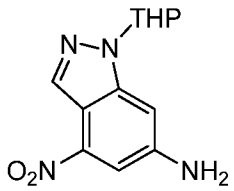


[00415] To a mixture of **compound 1.245** (1.1 g, 2.17 mmol) in THF (20 mL), MeOH (2 mL) and H_2O (2 mL) was added $LiOH.H_2O$ (910.56 mg, 21.70 mmol) at 20 °C. The mixture was stirred at 20 °C for 14 h. The mixture was acidified to pH 6 with aq. HCl (1 N) and the aq. phase was extracted with EA (30 mL × 3). The combined organic phases were washed (brine, 80 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.246** (1.1 g) as a yellow oil, which was used without further purification.

[00416] LCMS (AM3): rt = 1.002 min, (479.4 $[M+H]^+$), 99.2% purity.

Synthesis of Intermediate 1.273

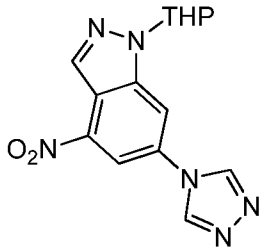
4-Nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-amine 1.271



[00417] To a mixture of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (WO2019027960, 2 g, 6.13 mmol) in DMSO (20 mL) was added ammonium hydroxide (2.27 g, 16.2 mmol), CuI (245 mg, 1.29 mmol), (2S, 4S)-4-hydroxypyrrolidine-2-carboxylic acid (330 mg, 2.51 mmol) and K_2CO_3 (2.54 g, 18.4 mmol) sequentially at rt. The mixture was heated to 90 °C and stirred for 16 h under N_2. The mixture was diluted with water (50 mL) and the aqueous phase was extracted with EA (50 mL × 2). The combined organic phase was washed (brine, 90 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.271** (1.7 g) as a red oil.

[00418] LCMS (AM3): rt = 0.769 min, (263.1 $[M+H]^+$), 69.6% purity.

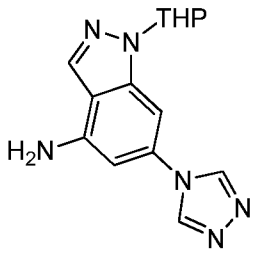
4-Nitro-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazole 1.272



[00419] To a mixture of **compound 1.271** (400 mg, 1.39 mmol), N-formamidoformamide (611 mg, 6.94 mmol) and TEA (983 mg, 9.72 mmol) in pyridine (8 mL) was added dropwise chlorotrimethylsilane (2.26 g, 20.8 mmol) at rt. The mixture was heated to 120 °C and stirred for 16 h. The mixture was concentrated in *vacuo* and the residue was diluted with water (30 mL). The aqueous phase was extracted with EA (30 mL × 3) and the combined organic phases were washed (brine, 80 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM2) to afford **compound 1.272** (100 mg, 0.318 mmol, 22.9% yield) as a yellow solid.

[00420] **^{1}H NMR** (400 MHz, $CHCl_3$-*d*) δ: 8.65 (s, 1H), 8.54 (s, 2H), 8.12 (d, *J* = 2.0 Hz, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 5.79 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.92-3.88 (m, 1H), 3.75-3.67 (m, 1H), 2.47-2.37 (m, 1H), 2.18-2.08 (m, 2H), 1.81-1.65 (m, 3H) ppm.

1-(Tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine 1.273

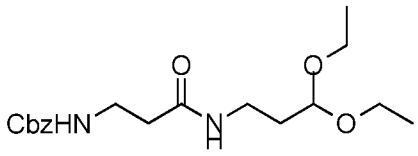


[00421] To a solution of **compound 1.272** (100 mg, 0.318 mmol) in MeOH (10 mL) was added 10% Pd/C (30 mg) under N_2 at 25 °C. The resulting suspension was degassed and purged with H_2 (x3). The mixture was stirred under a H_2 atmosphere (15 psi) at 25 °C for 2 h. The mixture was filtered and the filtrate concentrated in *vacuo* to afford **compound 1.273** (90 mg) as a yellow solid.

[00422] **LCMS** (AM3): rt = 0.640 min, (285.2 $[M+H]^+$), 95.0% purity.

Synthesis of Intermediate 1.280

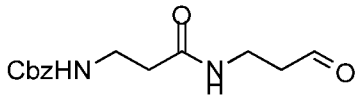
Benzyl (3-((3,3-diethoxypropyl)amino)-3-oxopropyl)carbamate 1.276



[00423] To a mixture of 3-(((benzyloxy)carbonyl)amino)propanoic acid (3 g, 13.44 mmol), HATU (6.13 g, 16.13 mmol), DIPEA (3.47 g, 26.88 mmol, 4.68 mL) in THF (50 mL) was added 3,3-diethoxypropan-1-amine (1.98 g, 13.44 mmol) at 20 °C. The resulting mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into water (50 mL) and extracted with EA (50 mL × 3). The combined organic phases were washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude product was purified (PM2) to afford **compound 1.276** (4.4 g, 12.48 mmol, 92.9% yield) as a yellow oil.

[00424] LCMS (AM3): rt = 0.843 min, (375.2 $[M+Na]^+$), 61.8% purity.

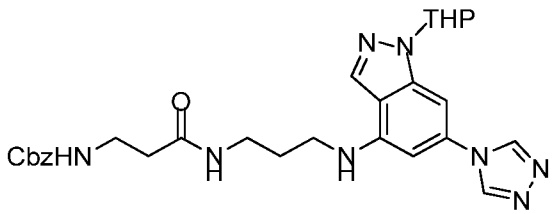
Benzyl (3-oxo-3-((3-oxopropyl)amino)propyl)carbamate 1.277



[00425] A mixture of **compound 1.276** (2 g, 5.67 mmol) in water (8 mL) and AcOH (8 mL) was stirred at 20 °C for 1 h. The reaction mixture was diluted with water (50 mL) and basified with saturated aq. $NaHCO_3$ solution to pH = 8. The mixture was extracted with EA (50 mL × 3) and the combined organic phases were washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give **compound 1.277** (2 g) as a white solid.

[00426] LCMS (AM3): rt = 0.717 min, (279.2 $[M+H]^+$), 93.6% purity.

Benzyl (3-oxo-3-((3-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 1.278

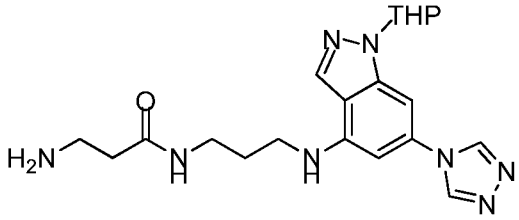


[00427] A mixture of **compound 1.273** (680 mg, 2.39 mmol) and **compound 1.277** (698.9 mg, 2.51 mmol) in DCE (10 mL) was stirred at 30 °C for 12 h, then $NaBH(AcO)_3$ (2.03 g, 9.57 mmol) was added. The mixture was stirred at 30 °C for 4 h. The mixture was concentrated in

vacuo and the residue was purified (PM75) to afford **compound 1.278** (500 mg, 0.915 mmol, 38.3% yield) as a yellow solid.

[00428] LCMS (AM3): rt = 0.832 min, (547.4 $[M+H]^+$), 95.7% purity.

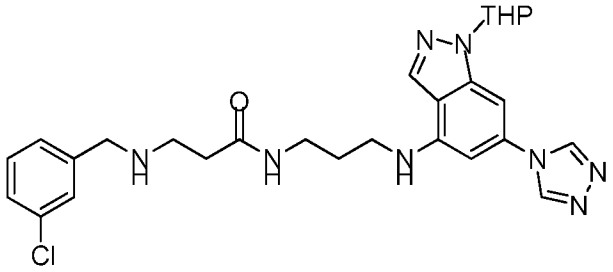
3-Amino-N-(3-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide 1.279



[00429] To a solution of **compound 1.278** (350 mg, 0.640 mmol) in MeOH (30 mL) was added 10% Pd/C (100 mg) under N_2 at 20 °C. The resulting suspension was degassed and purged with H_2 (x3). The mixture was stirred under a H_2 atmosphere (15 psi) at 20 °C for 16 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to afford **compound 1.279** (260 mg) as a white solid.

[00430] LCMS (AM3): rt = 0.543 min, (413.2 $[M+H]^+$), 87.8% purity.

3-((3-Chlorobenzyl)amino)-N-(3-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide 1.280

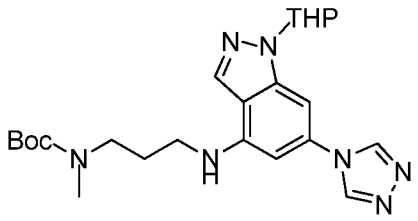


[00431] A mixture of 3-chlorobenzaldehyde (17.04 mg, 0.121 mmol) and **compound 1.279** (50 mg, 0.121 mmol) in MeOH (1 mL) was stirred at 30 °C for 12 h, then $NaBH(AcO)_3$ (103 mg, 0.485 mmol) was added. The mixture was stirred at 30 °C for 14 h. The mixture was concentrated in *vacuo* and the residue was purified (PM76) to afford **compound 1.280** (20 mg, 0.03724 mmol, 30.7% yield) as a white solid.

[00432] LCMS (AM3): rt = 0.782 min, (537.2 $[M+H]^+$), 100% purity.

Synthesis of Intermediate 1.283

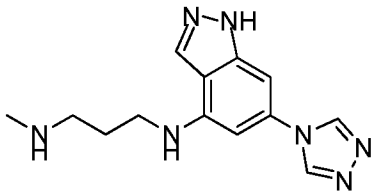
tert-Butyl methyl(3-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)carbamate 1.281



[00433] A solution of **compound 1.273** (150 mg, 527.58 μmol) and tert-butyl methyl(3-oxopropyl)carbamate (98.78 mg, 527.58 μmol) in DCE (6 mL) was stirred at 30 °C for 12 h, then $NaBH(AcO)_3$ (223.63 mg, 1.06 mmol) was added. The mixture was stirred at 30 °C for 1 h. The mixture was concentrated in *vacuo* and the crude product was purified (PM67) to afford **compound 1.281** (61 mg, 131.76 μmol, 25% yield) as a yellow solid.

[00434] LCMS (AM3): rt =0.868 min, (456.2 $[M+H]^+$), 98.5% purity.

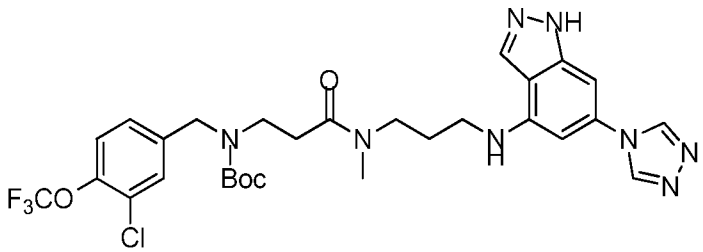
N^1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-N^3-methylpropane-1,3-diamine 1.282



[00435] A solution of **compound 1.281** (125 mg, 274.39 μmol) in aq. HCl (6 M, 5 mL) was stirred at 20 °C for 0.5 h. The mixture was concentrated in *vacuo* to afford **compound 1.282** (105 mg, HCl salt) as a yellow oil.

[00436] LCMS (AM3): rt = 0.297 min, (272.2 $[M+H]^+$), 93.6% purity.

tert-Butyl (3-((3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)(methyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate 1.283

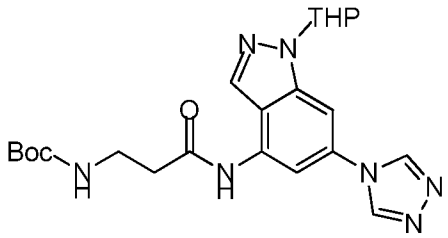


[00437] To a solution of **compound 1.243** (109.85 mg, 276.17 μmol) in DMF (2 mL) was added HATU (126.01 mg, 331.40 μmol) and DIPEA (192.42 μL, 1.10 mmol) at 20 °C. After stirring at 20 °C for 0.5 h, **compound 1.282** (85 mg, 276.17 μmol) was added and the reaction mixture was stirred at 20 °C for 1.5 h. The mixture was poured into water (50 mL) and extracted with EA (50 mL × 2). The combined organic phases were washed (brine, 50 mL), dried (Na_2SO_4) and concentrated in *vacuo*. The crude product was purified (PM67) to afford **compound 1.283** (70 mg, 107.5 μmol, 31.7% yield) as a red solid.

[00438] LCMS (AM3): rt = 0.965 min, (651.2 $[M+H]^+$), 41.1% purity.

Synthesis of Intermediate 1.286

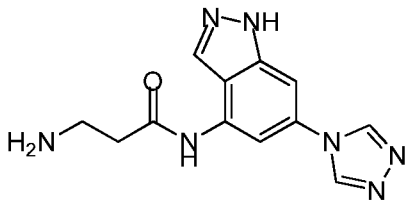
tert-Butyl (3-oxo-3-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)carbamate 1.284



[00439] A mixture of **compound 1.273** (200 mg, 0.703 mmol), 3-((tert-butoxycarbonyl)amino)propanoic acid (133 mg, 0.703 mmol) and EDCI (404 mg, 2.11 mmol) in pyridine (4 mL) was stirred at 80 °C for 4 h. The reaction mixture was concentrated in *vacuo* and the residue was purified (PM67) to afford **compound 1.284** (57 mg, 17.8% yield) as a white solid.

[00440] LCMS (AM3): rt = 0.841 min, (456.2 $[M+H]^+$), 98.0% purity.

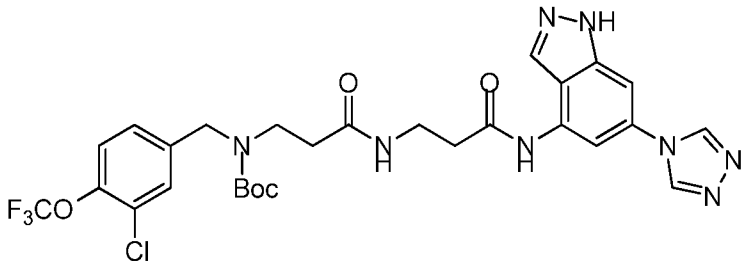
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-aminopropanamide 1.285



[00441] A mixture of **compound 1.284** (100 mg, 0.22 mmol) in a solution of HCl in 1,4-dioxane (4 M, 10 mL) was stirred at RT for 1 h, white solid precipitated. The reaction mixture was filtered and the filter cake was dried *in vacuo* to afford **compound 1.285** (72 mg, HCl salt) as a white solid.

[00442] LCMS (AM3): rt = 0.126 min, (272.1 $[M+H]^+$), 98.4% purity.

tert-Butyl (3-((3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)-3-oxopropyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate 1.286

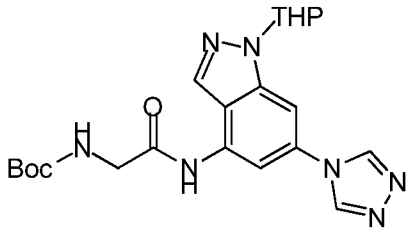


[00443] To a solution of **compound 1.243** (100 mg, 0.251 mmol) in DMF (5 mL) was added HATU (107 mg, 0.281 mmol) and DIPEA (0.122 mL, 0.7 mmol) followed by **compound 1.285** (72 mg, 0.234 mmol, HCl salt), the reaction mixture was stirred at rt for 20 h. The reaction mixture was poured into water (30 mL) and the resulting mixture was extracted with EA (10 mL × 3). The combined organic phases were washed (brine, 30 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM80) to afford **compound 1.286** (35 mg, 23% yield) as a white solid.

[00444] LCMS (AM3): rt = 0.923 min, (651.2 $[M+H]^+$), 100% purity.

Synthesis of Intermediate 1.289

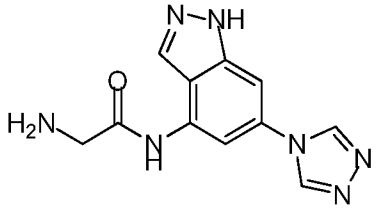
tert-Butyl (2-oxo-2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)carbamate 1.287



[00445] A mixture of **compound 1.273** (200 mg, 0.703 mmol), 2-((tert-butoxycarbonyl)amino)acetic acid (135 mg, 0.771 mmol) and EDCI (400 mg, 2.09 mmol) in pyridine (4 mL) was stirred 85 °C for 18 h. The reaction mixture was concentrated in *vacuo* and the residue was purified (PM67) to afford **compound 1.287** (104 mg, 32.1% yield) as a yellow solid.

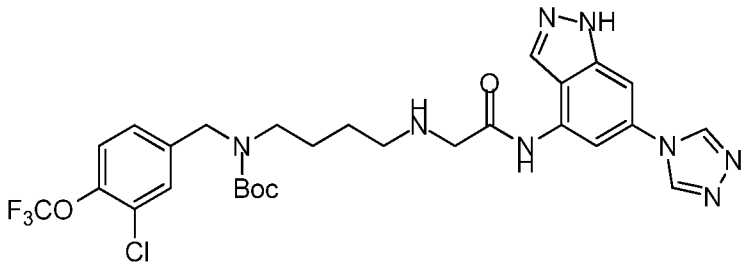
[00446] LCMS (AM3): rt = 0.828 min, (442.3 $[M+H]^+$), 96.6% purity.

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-aminoacetamide 1.288



[00447] A mixture of **compound 1.287** (104 mg, 0.236 mmol) in a solution of HCl in 1,4-dioxane (4 M, 10 mL) was stirred at RT for 14 h, white solid precipitated. The reaction mixture was filtered and the filter cake was dried *in vacuo* to afford **compound 1.288** (62 mg, HCl salt) as a white solid, which was used directly without further purification.

tert-Butyl (4-((2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)-2-oxoethyl)amino)butyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate 1.289

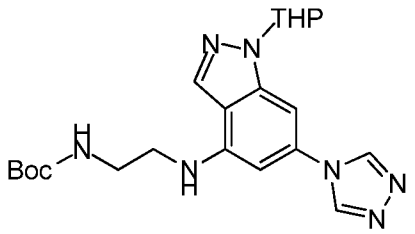


[00448] A mixture of **compound 1.288** (62 mg, 0.211 mmol, HCl salt), **Intermediate I** (90 mg, 0.227 mmol) and NaOAc (35 mg, 0.427 mmol) in MeOH (10 mL) was stirred at rt for 12 h, then $NaBH_3CN$ (53 mg, 0.843 mmol) was added. The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated in *vacuo* and the residue was purified (PM81) to afford **compound 1.289** (50 mg, 37.1% yield) as a white solid.

[00449] LCMS (AM3): rt = 0.879 min, (637.2 $[M+H]^+$), 100% purity.

<u>Synthesis of Intermediate 1.292</u>

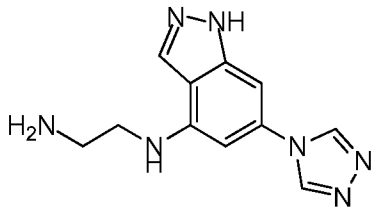
tert-Butyl (2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)carbamate 1.290



[00450] To a solution of **compound 1.287** (450 mg, 1.02 mmol) in THF (20 mL) was added borane tetrahydrofuran complex (1 M, 10 mL) at 0 °C. The reaction mixture was then warmed to rt and stirred for 20 h. The reaction was quenched by addition of aq. NaOH solution (1 N, 20 mL) slowly at 0 °C, then the mixture was heated to 60 °C and stirred for 3 h. The reaction mixture was extracted with EA (20 mL × 3) and the combined organic phases were washed (brine, 60 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM82) to afford **compound 1.290** (120 mg, 27.2% yield) as a brown solid.

[00451] LCMS (AM3): rt = 0.847 min, (428.2 $[M+H]^+$), 98.9% purity.

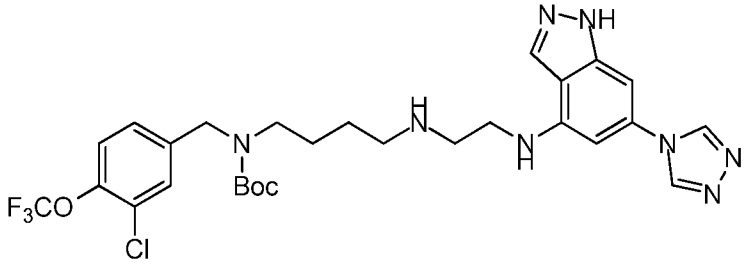
N^1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)ethane-1,2-diamine 1.291



[00452] A mixture of **compound 1.290** (120 mg, 0.281 mmol) in a solution of HCl in MeOH (4 M, 5 mL) was stirred at RT for 1 h. The reaction mixture was concentrated in *vacuo* to afford **compound 1.291** (76 mg, HCl salt) as a brown solid.

[00453] LCMS (AM3): rt = 0.134 min, (244.2 $[M+H]^+$), 100% purity.

tert-Butyl (4-((2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)amino)butyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate 1.292

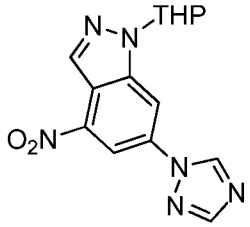


[00454] To a mixture of **compound 1.291** (66 mg, 0.236 mmol, HCl salt), DIPEA (0.488 mmol, 0.085 mL) and **Intermediate I** (100 mg, 0.253 mmol) in MeOH (2 mL) was added $NaBH_3CN$ (60 mg, 0.955 mmol) at RT. The reaction mixture was stirred at rt for 4 h. The reaction mixture was concentrated in *vacuo* and the residue purified (PM83) to afford **compound 1.292** (80 mg, 46% yield, TFA salt) as a white solid.

[00455] **LCMS** (AM3): rt = 0.860 min, (623.2 $[M+H]^+$), 99.5% purity.

Synthesis of Intermediate 1.294

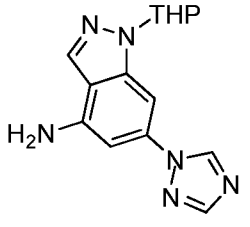
4-Nitro-1-(tetrahydro-2H-pyran-2-yl)-6-(1H-1,2,4-triazol-1-yl)-1H-indazole 1.293



[00456] To a mixture of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (WO2019027960, 1.0 g, 3.06 mmol) and 1,2,4-triazole (423.5 mg, 6.15 mmol) in DMF (25 mL) was added CuI (58.4 mg, 0.305 mmol), Cs_2CO_3 (2.0 g, 6.15 mmol) and (1*R*,2*R*)-N^1,N_2-dimethylcyclohexane-1,2-diamine (87.2 mg, 0.615 mmol) at rt. The mixture was heated to 110 °C and stirred for 16 h under N_2. The mixture was diluted with water (30 mL) and the aqueous phase was extracted with EA (30 mL × 2). The combined organic phases were washed (brine, 50 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM3) to afford **compound 1.293** (160 mg, 0.509 mmol, 16.6% yield) as a yellow solid.

[00457] **^{1}H NMR** (400 MHz, $CHCl_3$-*d*) δ: 8.76 (s, 1H), 8.70 (d, *J* = 0.6 Hz, 1H), 8.50 (d, *J* = 1.6 Hz, 1H), 8.39 (d, *J* = 0.8 Hz, 1H), 8.21 (s, 1H), 5.89 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.03-3.96 (m, 1H), 3.84-3.77 (m, 1H), 2.60-2.52 (m, 1H), 2.24-2.16 (m, 2H), 1.88-1.72 (m, 3H) ppm.

1-(Tetrahydro-2H-pyran-2-yl)-6-(1H-1,2,4-triazol-1-yl)-1H-indazol-4-amine 1.294



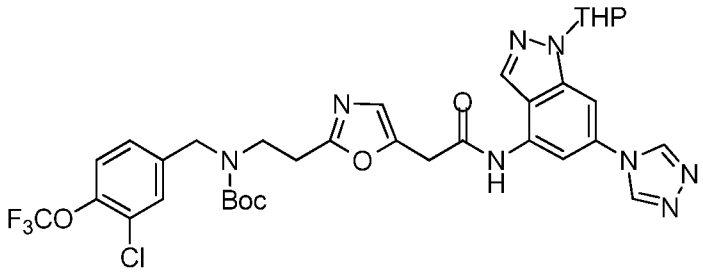
[00458] To a solution of **compound 1.293** (160 mg, 0.509 mmol) in MeOH (10 mL) was added 10% Pd/C (50 mg) under N_2 at 25 °C. The resulting suspension was degassed and purged

with H_2 (x3). The mixture was stirred under H_2 (15 psi) at 25 °C for 4 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to afford **compound 1.294** (140 mg) as a white solid.

[00459] LCMS (AM3): rt = 0.686 min, (285.2 $[M+H]^+$), 93.7% purity.

Synthesis of Intermediate 1.296

tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(2-(5-(2-oxo-2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)oxazol-2-yl)ethyl)carbamate 1.296

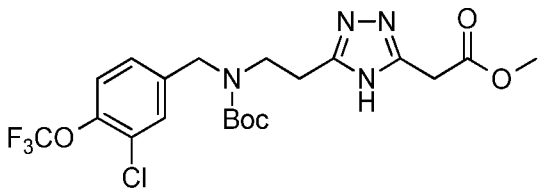


[00460] To a mixture of **compound 1.273** (100 mg, 351.72 μmol), **compound 1.246** (100 mg, 208.84 μmol) and DIPEA (107.96 mg, 835.34 μmol) in THF (2 mL) was added T_3P (50% in EA) (265.79 mg, 417.67 μmol) at 20 °C. The mixture was stirred at 20 °C for 12 h. The mixture was diluted with water (30 mL) and the aq. phase was extracted with EA (30 mL × 3). The combined organic phases were washed (brine, 90 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM86) to afford **compound 1.296** (80 mg, 107.36 μmol, 51.4% yield) as a white solid.

[00461] LCMS (AM3): rt = 0.991 min, (745.2 $[M+H]^+$), 29.1% purity.

Synthesis of Intermediate 1.300

Methyl 2-(5-(2-((tert-butoxycarbonyl)(3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)-4H-1,2,4-triazol-3-yl)acetate 1.297

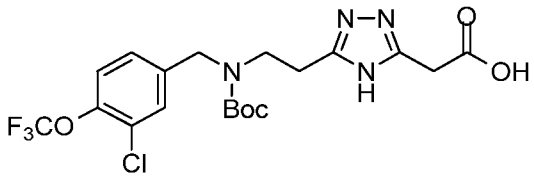


[00462] To a mixture of **compound 1.225** (950 mg, 2.31 mmol) and TEA (701.99 mg, 6.94 mmol) in DMF (10 mL) was added methyl 3-chloro-3-oxo-propanoate (405.33 mg, 2.97 mmol)

at 0 °C. The mixture was warmed to 20 °C and stirred for 1 h, then heated to 110 °C and stirred for 2 h. The mixture was diluted with water (30 mL) and the aq. phase was extracted with EA (30 mL × 3). The combined organic phases were washed (brine, 90 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo.* The residue was purified (PM67) to afford **compound 1.297** (400 mg, 811.56 μmol, 35.1% yield) as a yellow oil.

[00463] LCMS (AM3): rt = 0.965 min, (493.4 $[M+H]^+$), 86.3% purity.

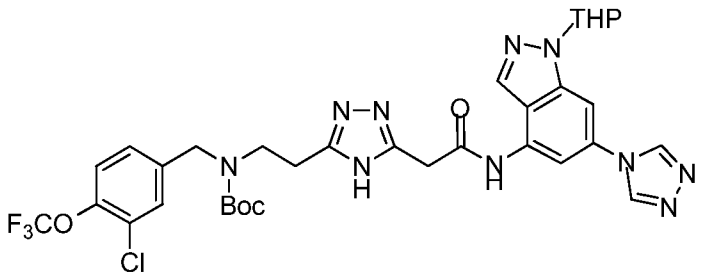
2-(5-(2-((tert-Butoxycarbonyl)(3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)-4H-1,2,4-triazol-3-yl)acetic acid 1.298



[00464] To a mixture of **compound 1.297** (560 mg, 1.14 mmol) in THF (10 mL), MeOH (2 mL) and water (2 mL) was added lithium hydroxide monohydrate (476.79 mg, 11.36 mmol) at 20 °C. The mixture was stirred at 20 °C for 12 h. The mixture was concentrated in *vacuo* to remove the organic solvent and then the aqueous phase was acidified with aq. HCl (1 M) to pH = 4. The mixture was extracted with EA (30 mL × 3) and the combined organic phases were washed (brine, 80 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.298** (540 mg) as a yellow oil.

[00465] LCMS (AM3): rt = 0.920 min, (479.4 $[M+H]^+$), 91.0% purity.

tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(2-(5-(2-oxo-2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)-4H-1,2,4-triazol-3-yl)ethyl)carbamate 1.299

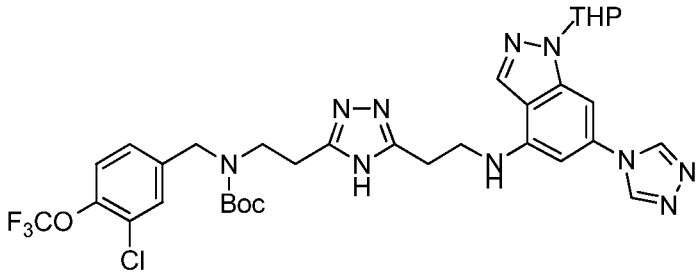


[00466] To a mixture of **compound 1.298** (240 mg, 501.20 μmol), **compound 1.273** (185.25 mg, 651.56 μmol) and DIPEA (259.11 mg, 2.00 mmol) in THF (5 mL) was added T_3P (50% in EA) (856.00 mg, 1.35 mmol) at 30 °C. The mixture was stirred at 30 °C for 3 h. The mixture

was diluted with water (30 mL) and the aqueous phase was extracted with EA (30 mL × 3). The combined organic phases were washed (brine, 90 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo.* The residue was purified (PM92) to afford **compound 1.299** (170 mg, 228.14 μmol, 45.5% yield) as a white solid.

[00467] LCMS (AM3): rt = 0.985 min, (745.2 $[M+H]^+$), 94.3% purity.

tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(2-(5-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)-4H-1,2,4-triazol-3-yl)ethyl)carbamate 1.300

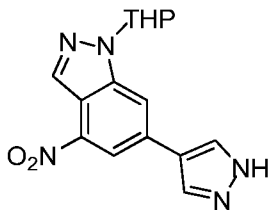


[00468] To a mixture of **compound 1.299** (170 mg, 228.14 μmol) in 2-methyltetrahydrofuran (5 mL) was added borane tetrahydrofuran complex (1 M, 2.28 mL) at 0 °C. The mixture was warmed to 20 °C and stirred for 4 h. The mixture was quenched by addition of MeOH (5 mL) and aq. NaOH (1 N, 5 mL) at 0 °C, and then heated to 60 °C and stirred for 12 h. The aqueous phase was extracted with EA (30 mL × 2) and the combined organic phases were washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM92) to afford **compound 1.300** (50 mg, 68.38 μmol, 29.9% yield) as a brown solid.

[00469] LCMS (AM3): rt = 0.969 min, (731.2 $[M+H]^+$), 96.1% purity.

Synthesis of Intermediate 1.302

4-Nitro-6-(1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 1.301

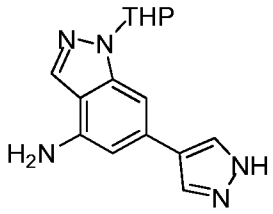


[00470] To a mixture of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (WO2019027960, 670 mg, 2.05 mmol), Cs_2CO_3 (1.34 g, 4.11 mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (725 mg, 2.47 mmol) in 1,4-

dioxane (10 mL) and water (1 mL) was added $Pd(dppf)Cl_2$ (150 mg, 0.205 mmol) at RT. The mixture was heated to 90 °C and stirred for 16 h under N_2. The mixture was concentrated in *vacuo* and the residue was purified (PM3) to afford compound **1.301** (370 mg, 1.18 mmol, 57.5% yield) as a yellow solid.

[00471] LCMS (AM3): rt = 0.788 min, (314.1 $[M+H]^+$), 42.1% purity.

6-(1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 1.302

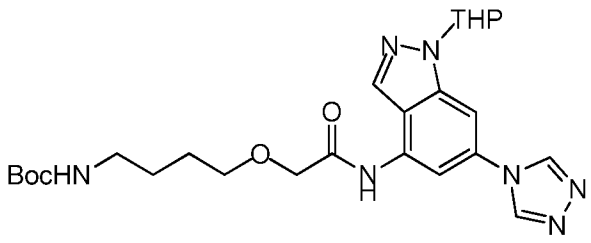


[00472] To a solution of **compound 1.301** (270 mg, 0.862 mmol) in MeOH (10 mL) was added 10% Pd/C (50 mg) under N_2 protection at 25 °C. The resulting suspension was degassed and purged with H_2 (x3). The mixture was stirred under a hydrogen atmosphere (15 psi) at 25 °C for 50 min. The mixture was filtered and the filtrate was concentrated in *vacuo* to afford **compound 1.302** (240 mg) as a yellow solid.

[00473] LCMS (AM3): rt = 0.628 min, (306.1 $[M+Na]^+$), 47.0% purity.

<u>Synthesis of Intermediate 1.306</u>

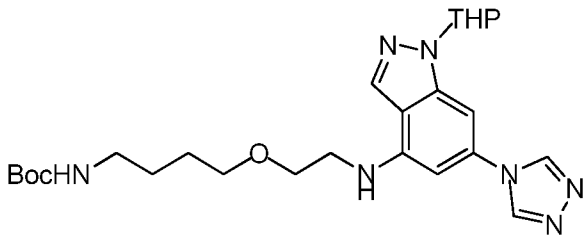
tert-Butyl (4-(2-oxo-2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 1.304



[00474] A mixture of 2-(3-((tert-butoxycarbonyl)amino)propoxy)acetic acid (US2015297738, 2 g, 8.09 mmol), **compound 1.273** (2 g, 7.03 mmol) and EDCI (4.05 g, 21.11 mmol) in pyridine (20 mL) was stirred at 80 °C for 12 h. The reaction mixture was concentrated in *vacuo* and the residue was purified (PM67) to afford **compound 1.304** (1.3 g, 36% yield) as a brown solid.

[00475] LCMS (AM3): rt = 0.875 min, (514.5 $[M+H]^+$), 100% purity.

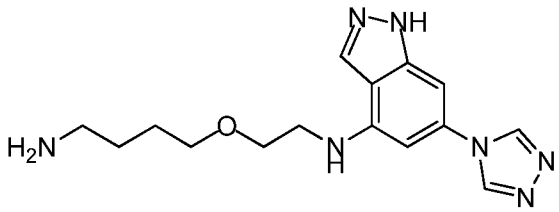
tert-Butyl (4-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 1.305



[00476] To a solution of **compound 1.304** (1.3 g, 2.53 mmol) in THF (25 mL) was added borane tetrahydrofuran complex (1 M, 25 mL) under N_2 at rt. The reaction mixture was stirred at RT for 3 h. The reaction mixture was quenched by slow addition of aq. NaOH solution (1 N, 25 mL), then the resulting mixture was heated to 60 °C and stirred for 4 h. Water (25 mL) was added to the reaction mixture and the mixture was extracted with EA (25 mL × 3). The combined organic phases were washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM95) to afford **compound 1.305** (360 mg, 28.5% yield) as a brown solid.

[00477] LCMS (AM3): rt = 0.902 min, (500.5 $[M+H]^+$), 93.1% purity.

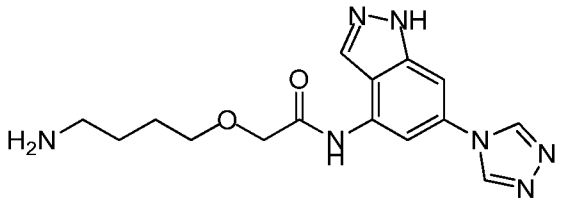
N-(2-(4-aminobutoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine 1.306



[00478] A mixture of **compound 1.305** (360 mg, 0.721 mmol) in a solution of HCl in 1,4-dioxane (4 M, 10 mL) was stirred at RT for 16 h. The reaction mixture was concentrated in *vacuo* to afford **compound 1.306** (270 mg, HCl salt) as a brown solid, which was used directly without further purification.

Synthesis of Intermediate 1.307

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-(4-aminobutoxy)acetamide 1.307

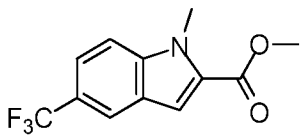


[00479] A mixture of **compound 1.304** (100 mg, 0.195 mmol) in a solution of HCl in 1,4-dioxane (4 M, 10 mL) was stirred at RT for 15 h, yellow solid precipitated. The reaction mixture was filtered and the filter cake was dried *in vacuo* to afford **compound 1.307** (64 mg, 89.9% yield, HCl salt) as a yellow solid.

[00480] LCMS (AM3): rt = 0.167 min, (330.3 $[M+H]^+$), 97.1% purity.

Synthesis of Intermediate 1.311

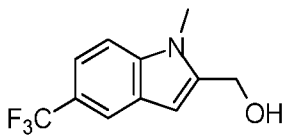
Methyl 1-methyl-5-(trifluoromethyl)-1H-indole-2-carboxylate 1.309



[00481] To a mixture of methyl 5-(trifluoromethyl)-1H-indole-2-carboxylate (CAS 1362860-89-6, 1.5 g, 6.17 mmol) in DMF (10 mL) was added NaH (296.08 mg, 7.40 mmol, 60% dispersion in oil) in one portion at 0 °C under N_2. After being stirred for 0.5 h, iodomethane (1.75 g, 12.34 mmol) was added. The mixture was warmed to 25 °C and stirred for 11.5 h. The mixture was poured into H_2O (50 mL) and the aq. phase was extracted with EA (30 mL × 2). The combined organic phase was washed (brine, 30 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM6) to afford **compound 1.309** (1.2 g, 4.67 mmol, 75.6% yield) as a white solid.

[00482] **^{1}H NMR** (400 MHz, MeOH-d_4) δ: 7.98–7.96 (s, 1H), 7.63–7.58 (m, 1H), 7.56–7.52 (m, 1H), 7.34 (s, 1H), 4.06 (s, 3H), 3.90 (s, 3H) ppm.

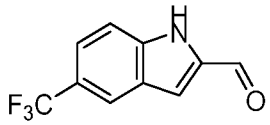
(1-Methyl-5-(trifluoromethyl)-1H-indol-2-yl)methanol 1.310



[00483] To a mixture of **compound 1.309** (1.2 g, 4.67 mmol) in THF (10 mL) was added LAH (177.06 mg, 4.67 mmol) in one portion under N_2 at 25 °C. The mixture was stirred at 25 °C for

0.5 h. The mixture was cooled to 0 °C and diluted with EA (10 mL). The mixture was quenched by addition of H_2O (0.2 mL), 10% NaOH aq. (0.2 mL) and H_2O (0.6 mL), sequentially. The resulting suspension was dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.310** (1g) as a white solid, which was used without further purification.

1-Methyl-5-(trifluoromethyl)-1H-indole-2-carbaldehyde 1.311

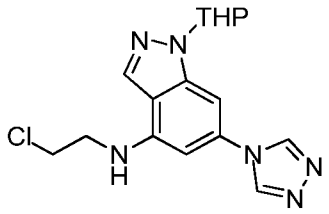


[00484] To a solution of **compound 1.310** (1 g, 4.36 mmol) in DCM (10 mL) was added manganese (IV) oxide (758.65 mg, 8.73 mmol) at 25 °C. The mixture was stirred at 25 °C for 2 h. The mixture was concentrated in *vacuo* and the residue was purified (PM6) to afford **compound 1.311** (300 mg, 1.32 mmol, 30.3% yield) as a yellow solid.

[00485] **^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.92 (s, 1H), 8.09 (s, 1H), 7.70–7.60 (q, 2H), 7.48 (s, 1H), 4.10 (s, 3H) ppm.

Synthesis of Intermediate 1.320

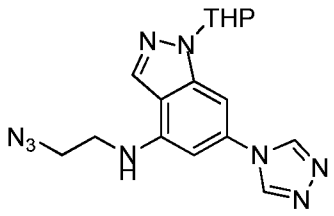
N-(2-chloroethyl)-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine 1.318



[00486] To a solution of 2-chloroacetaldehyde (4.33 mL, 26.91 mmol, 40% aqueous solution) and **compound 1.273** (500 mg, 1.76 mmol) in MeOH (15 mL) was added $NaBH_3CN$ (1.11 g, 17.59 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 2.5 h. The reaction mixture was filtered and concentrated in *vacuo* and the crude product was purified (PM96) to give **compound 1.318** (85 mg, 245.09 μmol, 13.9% yield) as a brown solid.

[00487] **LCMS** (AM3): rt = 0.824 min, (347.1 $[M+H]^+$), 95.5% purity.

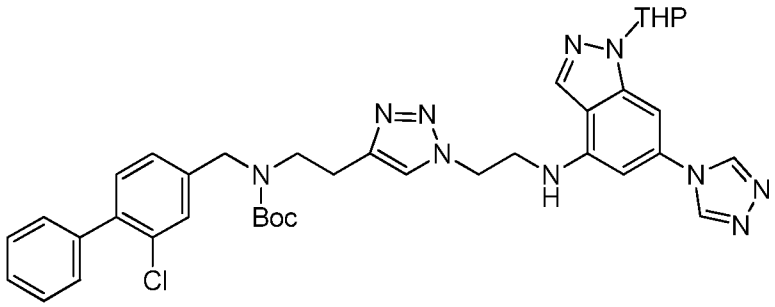
N-(2-azidoethyl)-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine 1.319



[00488] To a solution of **compound 1.318** (85 mg, 245.09 μmol) in DMF (15 mL) was added sodium azide (0.140 g, 2.15 mmol) slowly at rt. The reaction mixture was heated to 50 °C and stirred for 12 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EA (50 mL × 3). The combined organic layer was washed (brine, 50 mL × 5), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.319** (100 mg) as a yellow solid.

[00489] LCMS (AM3): rt = 0.824 min, (354.4[M+H]$^+$), 97.1% purity.

tert-Butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(2-(1-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)-1H-1,2,3-triazol-4-yl)ethyl)carbamate 1.320

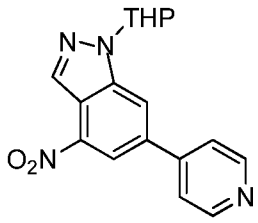


[00490] To a solution of **compound 1.319** (100 mg, 282.98 μmol) and **Intermediate J** (104.67 mg, 282.98 μmol) in DMF (7 mL) and MeOH (1 mL) was added CuI (10.78 mg, 56.60 μmol) at rt. The reaction mixture was heated to 100 °C and stirred for 16 h under N_2. The reaction mixture was diluted with water (30 mL) and extracted with EA (50 mL × 3). The combined organic layer was washed (brine, 80 mL × 4), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.320** (240 mg) as a brown oil.

[00491] LCMS (AM3): rt = 1.030 min, (723.3[M+H]$^+$), 56.6% purity.

Synthesis of Intermediate 1.322

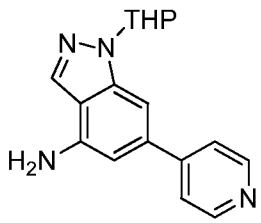
4-Nitro-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 1.321



[00492] To a mixture of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (WO2019027960, 2.5 g, 7.67 mmol), pyridin-4-yl boronic acid (1.88 g, 15.33 mmol) and K_2CO_3 (2.12 g, 15.33 mmol) in 1,4-dioxane (20 mL) and water (2 mL) was added $Pd(dppf)Cl_2.CH_2Cl_2$ (625.98 mg, 766.53 μmol) under N_2 at RT. The mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was concentrated in *vacuo* and the residue purified (PM2) to afford **compound 1.321** (2 g, 5.86 mmol, 76.4% yield) as a yellow gum.

[00493] LCMS (AM3): rt = 0.789 min, (325.2 $[M+H]^+$), 95.4% purity.

6-(Pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 1.322

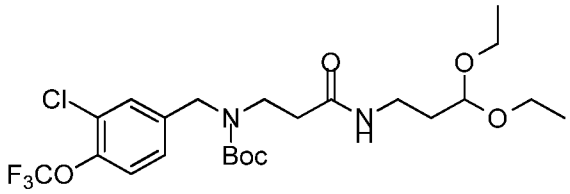


[00494] To a solution of **compound 1.321** (2.0 g, 6.17 mmol) in MeOH (100 mL) was added 10% Pd/C (100 mg, 6.17 mmol) under N_2 protection at 25 °C. The suspension was degassed and purged with H_2 (x3). The mixture was stirred under a H_2 atmosphere (15 psi) at 25 °C for 2 h. The reaction mixture was filtered, the filtrate was concentrated in *vacuo* to afford **compound 1.322** (1.7 g) as a yellow gum.

[00495] LCMS (AM3): rt = 0.568 min, (295.2 $[M+H]^+$), 95.0% purity.

Synthesis of Intermediate 1.326

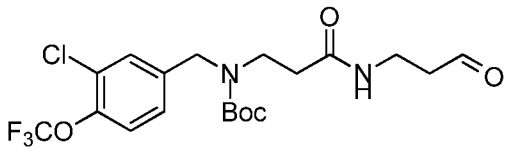
tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(3-((3,3-diethoxypropyl)amino)-3-oxopropyl)carbamate 1.324



[00496] To a solution of **compound 1.243** (1.3 g, 3.27 mmol), 3,3-diethoxypropan-1-amine (577.35 mg, 3.92 mmol) and TEA (1.4 mL, 10.06 mmol) in THF (30 mL) was added T_3P (50% in EA) (6.73 mmol, 4 mL) at 20 °C. The resulting mixture was stirred at 20 °C for 1 h. The residue was poured onto water (100 mL) and extracted with EA (50 mL × 3). The combined organic phases were washed (brine, 50 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM2) to give **compound 1.324** (933 mg, 1.77 mmol, 54.1% yield) as a yellow oil.

[00497] LCMS (AM3): rt = 1.072 min, (549.3 $[M+Na]^+$), 78.2% purity.

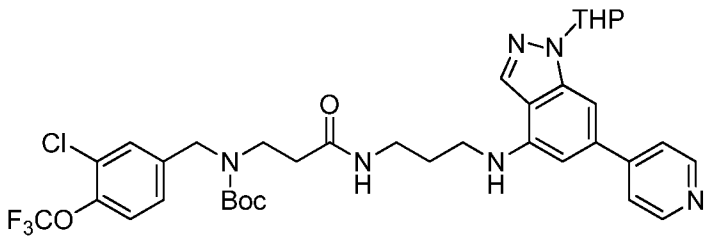
tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(3-oxo-3-((3-oxopropyl)amino)propyl)carbamate 1.325



[00498] A mixture of **compound 1.324** (533 mg, 1.01 mmol) in a solution of AcOH (6 mL, 104.91 mmol), THF (3 mL) and water (3 mL) was stirred at 20 °C for 1 h. The mixture was basified to pH = 8 (sat. $NaHCO_3$ (aq.)) and then extracted with EA (20 mL × 3). The combined organic phases were washed (brine, 30 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.325** (513 mg) as a yellow oil.

[00499] LCMS (AM3): rt =0.975 min, (453.1 $[M+H]^+$), 82.9% purity.

tert-Butyl 3-chloro-4-(trifluoromethoxy)benzyl(3-oxo-3-((3-((6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 1.326



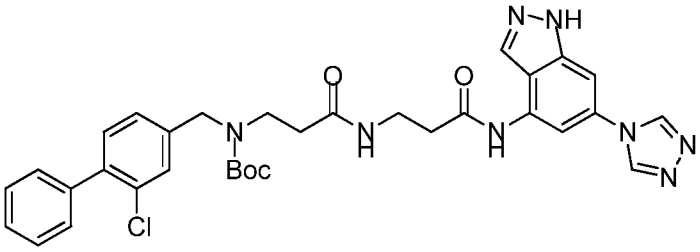
[00500] A solution of **compound 1.322** (100 mg, 339.73 μmol) and **compound 1.325** (230.77 mg, 509.60 μmol) in DCE (5 mL) was stirred at 20 °C for 2 h, then $NaBH(AcO)_3$ (216.01 mg, 1.02 mmol) was added. The mixture was stirred at 20 °C for 12 h. The mixture was

concentrated in *vacuo* and the residue was purified (PM61) to afford **compound 1.326** (240 mg, 299.53 μmol, 88.2% yield, FA salt) as a yellow solid.

[00501] LCMS (AM3): rt = 0.840 min, (731.4 $[M+H]^+$), 97.3% purity.

Synthesis of Intermediate 1.328

tert-Butyl (3-((3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)-3-oxopropyl)amino)-3-oxopropyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)carbamate 1.328

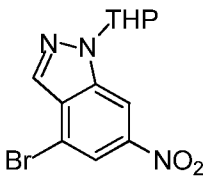


[00502] To a solution of **Intermediate D** (158.09 mg, 405.49 μmol) and **compound 1.285** (110 mg, 405.49 μmol) in pyridine (2 mL) was added EDCI (155 mg, 810.98 μmol) at 30 °C. The mixture was stirred at 30 °C for 1 h. The mixture was concentrated in *vacuo* and the residue was purified (PM61) to afford **compound 1.328** (60 mg, 86.76 μmol, 21.4% yield) as a yellow solid.

[00503] LCMS (AM3): rt = 0.931 min, (643.3 $[M+H]^+$), 87.4% purity.

Synthesis of Intermediate 1.363

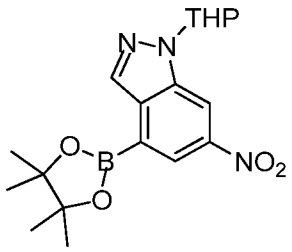
4-Bromo-6-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 1.356



[00504] To a mixture of 4-bromo-6-nitro-1H-indazole (CAS 885518-54-7, 1 g, 4.13 mmol) and 3,4-dihydro-2H-pyran (521.32 mg, 6.20 mmol) in THF (10 mL) was added $TsOH.H_2O$ (65 mg, 341.71 μmol) at rt. The mixture was heated to 50 °C and stirred for 12 h. Sat. $NaHCO_3$ (aq.) solution (20 mL) was added to the mixture and the mixture was extracted with EA (30 mL × 3). The combined organic phase was washed (brine, 80 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM7) to afford **compound 1.356** (1.3 g, 3.99 mmol, 96.5% yield) as a white solid.

[00505] **^{1}H NMR** (400 MHz, $CHCl_3$-*d*) δ: 8.55 (dd, *J* = 1.6, 0.8 Hz, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 8.14 (d, *J* = 0.8 Hz, 1H), 5.82 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.05-4.00 (m, 1H), 3.83-3.77 (m, 1H), 2.56-2.46 (m, 1H), 2.21-2.12 (m, 2H), 1.92-1.68 (m, 3H) ppm.

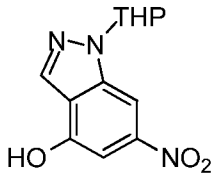
6-Nitro-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole 1.357



[00506] To a mixture of **compound 1.356** (1.3 g, 3.99 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.11 g, 4.38 mmol) in toluene (20 mL) was added KOAc (782.38 mg, 7.97 mmol) and $Pd(dppf)Cl_2$ (291.65 mg, 398.60 μmol) at RT. The mixture was heated to 80 °C and stirred for 16 h under N_2. The mixture was concentrated in *vacuo* and the residue was purified (PM7) to afford c**ompound 1.357** (1.4 g, 3.75 mmol, 94.1% yield) as a colourless oil.

[00507] **^{1}H NMR** (400 MHz, $CHCl_3$-*d*) δ: 8.63 (s, 1H), 8.52-8.51 (d, 2H), 5.83 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.06-4.01 (m, 1H), 3.83-3.77 (m, 1H), 2.58-2.49 (m, 1H), 2.22-2.08 (m, 2H), 1.88-1.67 (m, 3H), 1.42 (s, 12 H) ppm.

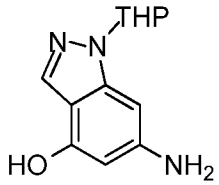
6-Nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-ol 1.358



[00508] To a mixture of **compound 1.357** (500 mg, 1.34 mmol) in EtOH (10 mL) was added hydroxylamine hydrochloride (279.3 mg, 4.02 mmol) and NaOH (202.3 mg, 2.68 mmol) at 35 °C. The mixture was stirred at 35 °C for 19 h. The mixture was adjusted to pH = 6 by adding HCl (aq.) solution (1 N) and diluted with water (40 mL). The aqueous phase was extracted with EA (40 mL × 3). The combined organic phase was washed (brine, 100 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM5) to afford **compound 1.358** (300 mg, 1.14 mmol, 42.5% yield) as a yellow solid.

[00509] **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.28 (s, 1H), 8.28 (s, 1H), 8.14 (s, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 6.01 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.88-3.77 (m, 2H), 2.43-2.32 (m, 1H), 2.05-1.96 (m, 2H), 1.81-1.70 (m, 1H), 1.63-1.52 (m, 2H) ppm.

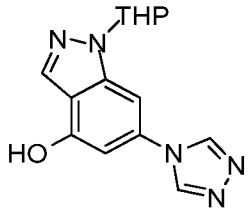
6-Amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-ol 1.359



[00510] To a solution of **compound 1.358** (900 mg, 3.42 mmol) in MeOH (50 mL) was added 10% Pd/C (150 mg) under N_2 protection. The suspension was degassed and purged with H_2 (x3) at 20 °C. The mixture was stirred at 20 °C for 3 h under an H_2 atmosphere (15 psi). The mixture was filtered and the filtrate was concentrated in *vacuo* to afford **compound 1.359** (900 mg) as a brown solid, which was used directly without purification.

[00511] **LCMS** (AM3): rt = 0.619 min, (234.2 $[M+H]^+$), 93.8% purity.

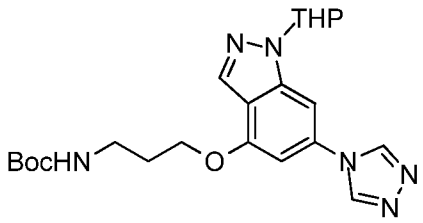
1-(Tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-ol 1.360



[00512] To a mixture of **compound 1.359** (900 mg, 3.86 mmol), N,N'-diformylhydrazine (1.70 g, 19.29 mmol) and TEA (2.73 g, 27.01 mmol) in pyridine (20 mL) was added TMSCl (6.29 g, 57.87 mmol) at rt. The mixture was then heated to 120 °C and stirred for 12 h under N_2 protection. The mixture was concentrated in *vacuo* and the residue was purified (PM67) to afford **compound 1.360** (820 mg, 2.87 mmol, 74.5% yield) as a yellow solid.

[00513] **LCMS** (AM3): rt = 0.742 min, (286.5 $[M+H]^+$), 58.1% purity.

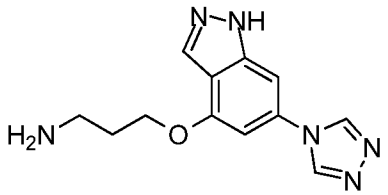
tert-Butyl (3-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propyl)carbamate 1.361



[00514] A mixture of **compound 1.360** (400 mg, 1.40 mmol), tert-butyl (3-bromopropyl)carbamate (500.78 mg, 2.10 mmol) and K_2CO_3 (387.55 mg, 2.80 mmol) in DMF (10 mL) was stirred at 80 °C for 16 h. The mixture was diluted with water (30 mL) and the aqueous phase was extracted with EA (30 mL × 2). The combined organic phases were washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM95) to afford **compound 1.361** (500 mg, 1.13 mmol, 80.6% yield) as a white solid.

[00515] LCMS (AM3): rt = 0.888 min, (443.1 $[M+H]^+$), 100% purity.

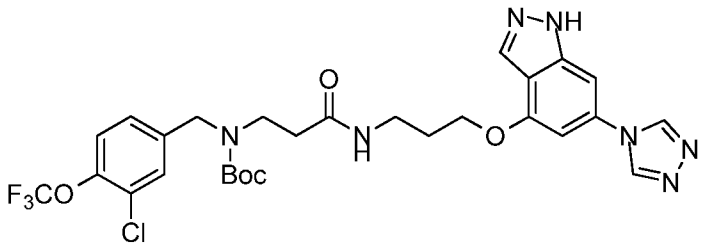
3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propan-1-amine 1.362



[00516] To a mixture of **compound 1.361** (500 mg, 1.13 mmol) in 1,4-dioxane (10 mL) was added a solution of HCl in 1,4-dioxane (4 M, 10 mL) at 20 °C. The mixture was stirred at 20 °C for 3 h. The mixture was concentrated in *vacuo* to afford **compound 1.362** (340 mg, HCl salt) as a white solid, which was used directly without purification.

[00517] LCMS (AM6): rt = 1.209 min, (259.2 $[M+H]^+$), 91.8% purity.

tert-Butyl (3-((3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate 1.363



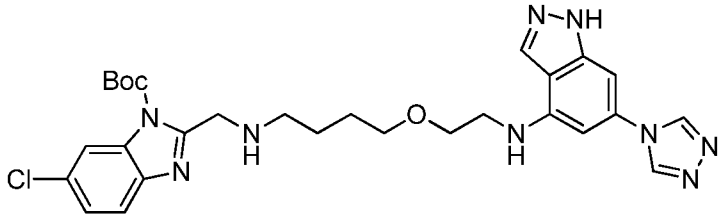
[00518] A mixture of **compound 1.243** (150 mg, 377.10 μmol), HATU (172.06 mg, 452.52 μmol) and DIPEA (194.95 mg, 1.51 mmol) in DMF (3 mL) was stirred at 30 °C for 0.5 h, then

compound 1.362 (100 mg, 339.28 μmol) was added. The mixture was stirred at 30 °C for 2 h. The mixture was diluted with water (30 mL) and extracted with EA (30 mL × 3). The combined organic phase was washed (brine, 90 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.363** (300 mg) as a brown oil which was used without further purification.

[00519] LCMS (AM3): rt = 0.959 min, (638.1 $[M+H]^+$), 45.6% purity.

Synthesis of Intermediate 1.371

tert-Butyl 2-(((4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)amino)methyl)-6-chloro-1H-benzo[d]imidazole-1-carboxylate 1.371

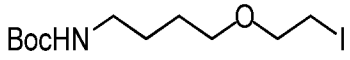


[00520] To a mixture of **compound 1.306** (300 mg, 951.26 μmol) and K_2CO_3 (394.41 mg, 2.85 mmol) in DMF (30 mL) was added 2-chloromethyl-1-tert-butoxycarbonyl-6-chlorobenzimidazole (CAS 305357-46-4, 143.24 mg, 475.63 μmol), then the reaction mixture was heated to 50 °C and stirred for 2 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EA (80 mL). The organic layer was washed (brine, 50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude product was purified (PM99) to afford **compound 1.371** (60 mg, 103.43 μmol, 10.9% yield) as a brown solid.

[00521] LCMS (AM7): rt = 0.899 min, (580.3 $[M+H]^+$), 24.0% purity.

Synthesis of Intermediate 1.374

tert-Butyl (4-(2-iodoethoxy)butyl)carbamate 1.372

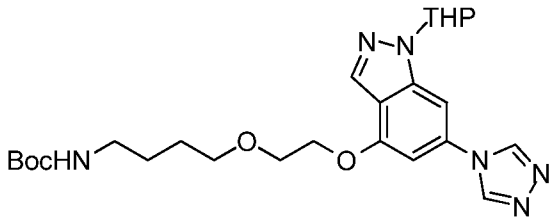


[00522] To a mixture of tert-butyl (4-(2-hydroxyethoxy)butyl)carbamate (WO2022185041, 1.3 g, 5.57 mmol), imidazole (569.03 mg, 8.36 mmol) and PPh_3 (2.19 g, 8.36 mmol) in DCM (10 mL) was added iodine (2.12 g, 8.36 mmol) at 0 °C under N_2. The mixture was warmed to RT and stirred for 12 h. The excess iodine was quenched with sat. Na_2SO_3 (aq.) (30mL) and the mixture was extracted with EA (50 mL × 3). The combined

organic phase was washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM7) to afford **compound 1.372** (1.4 g, 4.08 mmol, 73.2% yield) as a yellow oil.

[00523] **^{1}H NMR** (400 MHz, MeOH-d_4) δ: 3.70 (t, *J* = 6.4 Hz, 2H), 3.52 (t, *J* = 6.0 Hz, 2H), 3.31 (t, *J* = 6.4 Hz, 2H), 3.08 (t, *J* = 6.8 Hz, 2H), 1.65-1.54 (m, 4H), 1.45 (s, 9H) ppm.

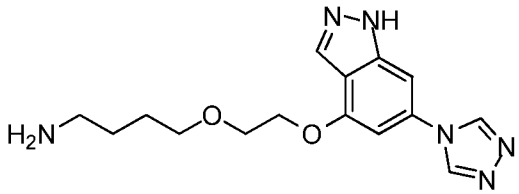
tert-Butyl (4-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butyl)carbamate 1.373



[00524] To a mixture of **compound 1.360** (200 mg, 701.01 μmol) and K_2CO_3 (193.77 mg, 1.40 mmol) in DMF (2 mL) was added **compound 1.372** (360.88 mg, 1.05 mmol), the mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was concentrated in *vacuo* to give a residue which was purified (PM61) to afford **compound 1.373** (300 mg, 545.36 μmol, 77.8% yield) as a brown solid.

[00525] **LCMS** (AM3): rt = 0.730 min, (501.1 $[M+H]^+$),72.6% purity.

4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butan-1-amine 1.374

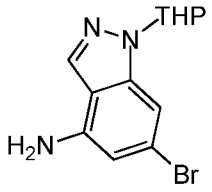


[00526] A mixture of **compound 1.373** (0.3 g, 599.29 μmol) in a solution of HCl in 1,4-dioxane (4 M, 10 mL) was stirred at 20 °C for 2 h. The reaction mixture was concentrated in *vacuo* to afford **compound 1.374** (0.2 g, HCl salt) as a brown solid, which was used directly without purification.

[00527] **LCMS** (AM3): rt = 0.445 min, (316.9 $[M+H]^+$), 85.8% purity.

Synthesis of Intermediate 1.383

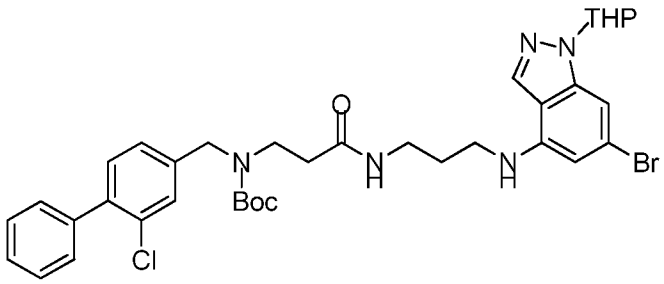
6-Bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 1.381



[00528] To a solution of $NiCl_2.6H_2O$ (400 mg, 1.69 mmol) in MeOH (10 mL) and THF (20 mL) was added $NaBH_4$ (63 mg, 1.69 mmol) at 0 °C. After stirring for 5 min, 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Ref: WO2019027960, 1.1 g, 3.37 mmol) was added, followed by addition of $NaBH_4$ (382 mg, 10.12 mmol). The mixture was stirred at 0 °C for 25 min. The mixture was quenched with water (100 mL) and filtered, and the filtrate was extracted with EA (50 mL × 2). The combined organic phases were washed (brine, 50 mL), dried (Na_2SO_4) and concentrated in *vacuo* to afford **compound 1.381** (990 mg, 3.03 mmol, 89.8% yield) as a yellow oil.

[00529] LCMS (AM3): rt = 0.877 min, (296.0 $[M+H]^+$), 90.6% purity.

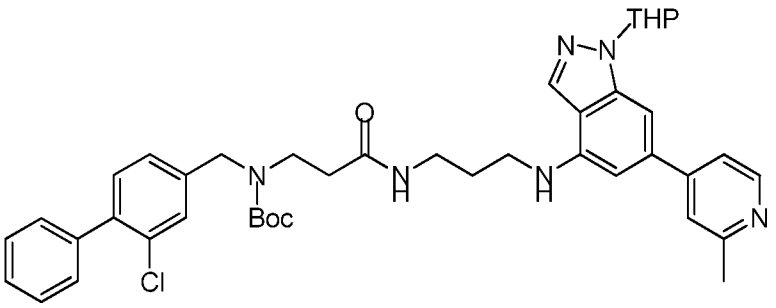
tert-Butyl (3-((3-((6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)carbamate 1.382



[00530] To a solution of **compound 1.381** (200 mg, 0.67 mmol) in MeOH (10 mL) was added **Intermediate H** (360 mg, 0.81 mmol) at 25 °C and the reaction mixture stirred for 11 h. $NaBH_3CN$ (346 mg, 5.52 mmol) was added and the mixture stirred at 25 °C for 1 h. The mixture was concentrated in *vacuo* and the crude product purified (PM69) to afford **compound 1.382** (150 mg, 0.20 mmol, 36.5% yield) as a light-yellow oil.

[00531] LCMS (AM3): rt = 1.114 min, (726.1 $[M+H]^+$), 96.1% purity.

tert-Butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(2-methylpyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 1.383

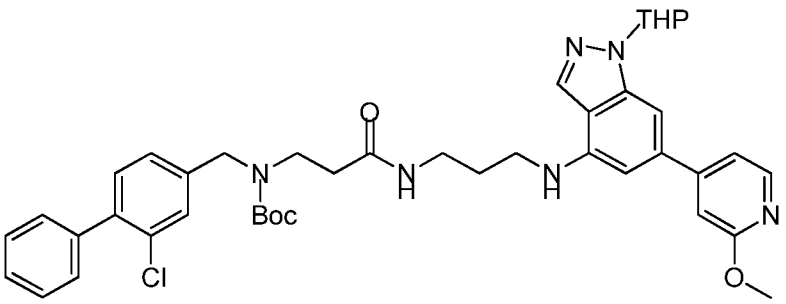


[00532] A mixture of **compound 1.382** (150 mg, 0.206 mmol), K_2CO_3 (57 mg, 0.413 mmol), (2-methylpyridin-4-yl)boronic acid (34 mg, 0.248 mmol) and Brettphos G3 Pd (19 mg, 0.020 mmol) in 1,4-dioxane (2 mL) and H_2O (0.2 mL) was stirred at 90 °C for 0.5 h under microwave irradiation. The mixture was concentrated in *vacuo* and the crude product was purified (PM67) to afford **compound 1.383** (90 mg, 0.121 mmol, 58.3% yield) as a yellow solid.

[00533] LCMS (AM3): rt = 0.947 min, (737.2 $[M+H]^+$), 98.9% purity.

Synthesis of Intermediate 1.384

tert-Butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(2-methoxypyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 1.384

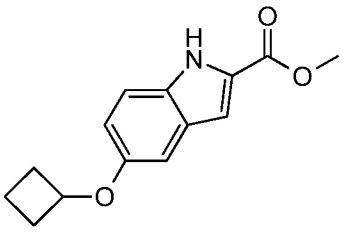


[00534] A solution of **compound 1.382** (150 mg, 0.206 mmol), K_2CO_3 (57 mg, 0.413 mmol), (2-methoxypyridin-4-yl)boronic acid (38 mg, 0.248 mmol) and Brettphos G3 Pd (19 mg, 0.020 mmol) in 1,4-dioxane (2 mL) and H_2O (0.2 mL) was stirred at 90 °C for 0.5 h under microwave irradiation and under N_2. The mixture was concentrated in *vacuo* and purified (PM67) to afford **compound 1.384** (100 mg, 0.118 mmol, 57.4% yield) as a yellow solid.

[00535] LCMS (AM3): rt =1.108 min, (753.3 $[M+H]^+$), 89.5% purity.

Synthesis of Intermediate 1.420

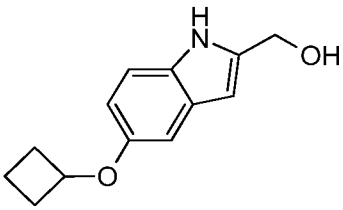
Methyl 5-cyclobutoxy-1H-indole-2-carboxylate 1.418



[00536] A mixture of methyl 5-hydroxy-1H-indole-2-carboxylate (850 mg, 4.45 mmol, *Bioorganic and Medicinal Chemistry Letters*, **2000**, 10 (5), 483–486), bromocyclobutane (1.70 mL, 18.01 mmol) and K_2CO_3 (1.53 g, 11.07 mmol) in DMF (15 mL) was stirred at 80 °C for 20 h. The reaction mixture was poured into H_2O (45 mL), extracted with EA (20 mL × 2), the combined organic phase washed (brine, 40 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo.* The residue was purified (PM8) to afford **compound 1.418** (700 mg, 60.3% yield) as a yellow solid.

[00537] LCMS (AM3): rt = 0.942 min, (246.3 $[M+H]^+$), 93.9% purity.

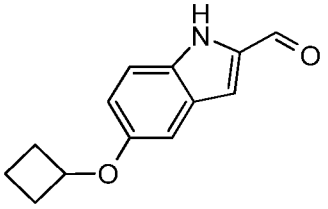
(5-Cyclobutoxy-1H-indol-2-yl)methanol 1.419



[00538] To a mixture of LAH (260 mg, 6.85 mmol) in THF (20 mL) was added **compound 1.418** (650 mg, 2.65 mmol) in THF (5 mL) at 0 °C. The reaction mixture was warmed to RT, stirred for 2 h, then the reaction quenched with H_2O (0.5 mL) followed by aq. 10% NaOH solution (0.5 mL) and H_2O (1 mL). The reaction mixture was stirred for 1 h, then Na_2SO_4 added, the mixture filtered and the filtrate concentrated in *vacuo* to afford **compound 1.419** (470 mg, 81.6% yield) as a white solid, which was used directly without purification.

[00539] LCMS (AM3): rt = 0.840 min, (218.3 $[M+H]^+$), 90.3% purity.

5-Cyclobutoxy-1H-indole-2-carbaldehyde 1.420

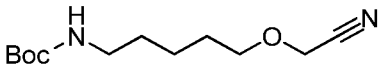


[00540] A mixture of **compound 1.419** (470 mg, 2.16 mmol) and MnO_2 (1.88 g, 21.63 mmol) in DCM (20 mL) was stirred at RT for 12 h. The reaction mixture was filtered and the filtrate was concentrated in *vacuo*. The residue was purified (PM7) to afford **compound 1.420** (370 mg, 58.8% yield) as a brown solid.

[00541] **LCMS** (AM4): rt = 0.846 min, (216.1 $[M+H]^+$), 74.2 % purity.

Synthesis of Intermediate 1.461

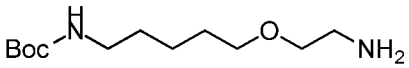
tert-Butyl (5-(cyanomethoxy)pentyl)carbamate 1.460



[00542] To a solution of tert-butyl (5-hydroxypentyl)carbamate (4 g, 19.68 mmol) in DCM (50 mL) was added 2-bromoacetonitrile (4.72 g, 39.36 mmol), TBAI (1.45 g, 3.94 mmol) and Ag_2O (4.56 g, 19.68 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h. The mixture was filtered and concentrated in *vacuo*, and the residue was purified (PM8) to afford **compound 1.460** (280 mg, 1.16 mmol, 5.9% yield) as a colourless oil.

[00543] **^{1}H NMR** (400 MHz, $CHCl_3$-*d*) δ: 4.56 (br s, 1H), 4.23 (s, 2H), 3.57 (t, *J* = 6.4 Hz, 2H), 3.11 (q, *J* = 6.0 Hz, 2H), 1.67–1.60 (quin, 2H), 1.54–1.42 (m, 2H), 1.44 (s, 9H), 1.42–1.35 (m, 2H) ppm.

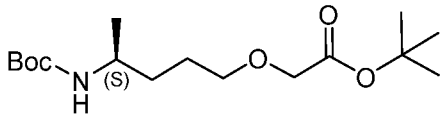
tert-Butyl (5-(2-aminoethoxy)pentyl)carbamate 1.461



[00544] To a solution of **compound 1.460** (400 mg, 1.65 mmol) in MeOH (10 mL) was added Raney Ni (141.43 mg, 1.65 mmol) and ammonium hydroxide (826.46 mg, 6.60 mmol, 28%) under N_2. The suspension was degassed and purged with H_2 (x3). The mixture was hydrogenated under H_2 at 25 °C for 12 h. The catalyst was removed by filtration and the filtrate was concentrated in *vacuo* to give **compound 1.461** (423 mg) as a light yellow oil, which was used without purification.

Synthesis of Intermediate 1.848

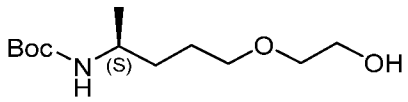
tert-Butyl (S)-2-((4-((tert-butoxycarbonyl)amino)pentyl)oxy)acetate 1.847



To a solution of tert-butyl (S)-(5-hydroxypentan-2-yl)carbamate (5 g, 24.60 mmol, Ref: ACS Medicinal Chemistry Letters, 2021, vol. 12, # 1, p. 121 - 128) and tert-butyl 2-bromoacetate (9.90 g, 50.76 mmol) in NaOH aq. (10 g dissolved in 25 mL water) was added TBAI (500 mg, 1.35 mmol) at 0 °C and stirred at 0 °C for 2 h. The reaction mixture was diluted with H_2O (80 mL) and extracted (MTBE, 80 mL × 2). The combined organic phases were washed (brine, 100 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue which was purified (PM56) to afford **compound 1.847** (7 g, 22.05 mmol, 89.6% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 4.37 (s, 1 H) 3.94 (s, 2 H) 3.64 (s, 1 H) 3.51 (t, *J* = 6.0 Hz, 2 H) 1.70 - 1.61 (m, 2 H) 1.54 - 1.50 (m, 2 H) 1.48 (s, 9 H) 1.43 (s, 9 H) 1.12 (d, *J* = 6.4 Hz, 3 H) ppm.

tert-Butyl (S)-(5-(2-hydroxyethoxy)pentan-2-yl)carbamate 1.848

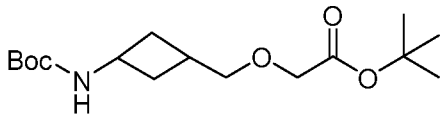


To a mixture of LAH (900.00 mg, 23.71 mmol) in THF (50 mL) at 0 °C was added slowly a solution of **compound 1.847** (6 g, 18.90 mmol) in THF (50 mL). The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched slowly at 0 °C with H_2O (1 mL), NaOH aq.(15% wt., 1 mL) then H_2O (3 mL) and stirred for 0.5 h. Na_2SO_4 (10 g) was added, and the resulting suspension stirred for 0.5 h then filtered. The filter cake was washed with EA (100 mL). The filtrate was concentrated in *vacuo* to give a residue which was purified (PM3) to afford **compound 1.848** (3.5 g, 14.15 mmol, 74.8% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 3.75 - 3.72 (m, 2H), 3.70 - 3.65 (m, 1H), 3.55 - 3.52 (m, 2H), 3.51 - 3.48 (m, 2 H), 1.69 - 1.60 (m, 2H), 1.53 - 1.48 (m, 2H), 1.45 (s, 9H), 1.13 (d, *J* = 6.4 Hz, 3H) ppm.

Synthesis of Intermediate 1.856

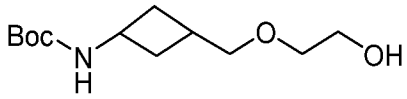
tert-Butyl 2-((3-((tert-butoxycarbonyl)amino)cyclobutyl)methoxy)acetate 1.855



To a solution of tert-butyl (3-(hydroxymethyl)cyclobutyl)carbamate (CAS 167081-37-0, 5 g, 24.84 mmol), tert-butyl 2-bromoacetate (9.69 g, 49.69 mmol) in NaOH aq. (10 g dissolved in 25 mL water) was added TBAI (458.81 mg, 1.24 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then diluted with water (100 mL) and extracted (MTBE, 100 mL × 2). The combined organic phases were washed (brine, 150 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue which was purified (PM56) to afford **compound 1.855** (9.8 g, crude) as colourless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 4.88 - 4.63 (m, 1H), 4.25 - 4.15 (m, 0.5H), 4.08 - 3.96 (m, 0.5H), 3.94 (d, *J* = 6.0 Hz, 2H), 3.54 (d, *J* = 7.2 Hz, 1H), 3.45 (d, *J* = 5.6 Hz, 1H), 2.48 - 2.43 (m, 1H), 2.27 - 2.19 (m, 1.5H), 2.02 - 1.96 (m, 1H), 1.76 - 1.54 (m, 1.5H), 1.48 (s, 9 H) 1.42 (s, 9 H) ppm.

tert-Butyl (3-((2-hydroxyethoxy)methyl)cyclobutyl)carbamate 1.856

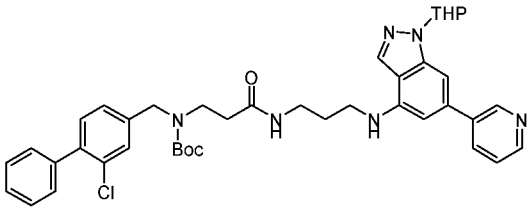


To a solution of **compound 1.855** (3 g, 9.51 mmol) in cooled THF (40 mL) at 0 °C was added LAH (400 mg, 10.54 mmol) slowly. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched slowly with water (0.4 mL). 15% wt. aq. NaOH solution (0.4 mL) and water (1.2 mL) were added at 0 °C and the mixture stirred for 0.5 h. Na_2SO_4 (5 g) was added. The resulting suspension was stirred for 0.5 h, filtered and concentrated in *vacuo* to give a residue which was purified (PM3) to afford **compound 1.856** (1 g, 4.08 mmol, 42.8% yield) as colourless oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ: 4.74 (s, 1H), 4.28 - 4.15 (m, 0.5H), 4.05 -3.95 (m, 0.5H), 3.75 - 3.72 (m, 2H), 3.57 - 3.54 (m, 2H), 3.53 - 3.51 (m, 1H), 3.42 (d, *J* = 5.6 Hz, 1H), 2.49 - 2.41 (m, 1.5H), 2.25 - 2.16 (m, 1.5H), 2.02 - 1.95 (m, 1H), 1.66-1.58 (m, 1H), 1.44 (s, 9H) ppm.

Synthesis of Intermediate 1.888

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((6-(pyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 1.888

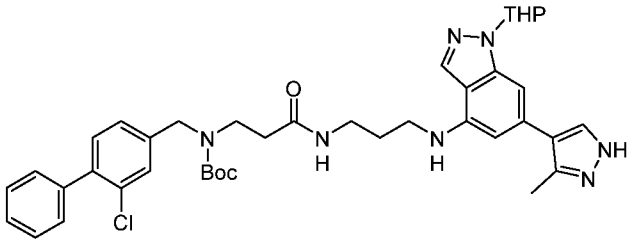


[00545] To a solution of **compound 1.382** (150 mg, 206.86 μmol) in H_2O (0.2 mL) and DME (2 mL) was added K_2CO_3 (57.18 mg, 413.73 μmol), 3-pyridylboronic acid (30.51 mg, 248.24 μmol) and $Pd(PPh_3)_4$ (23.9 mg, 20.69 μmol). The mixture was stirred at 90 °C for 0.5 h under microwave irradiation. The mixture was concentrated in *vacuo* to give a crude residue, which was purified (PM100) to afford **compound 1.888** (100 mg, 121.39 μmol, 58.68% yield) as a yellow solid.

[00546] LCMS (AM3): rt = 0.904 min, (723.2 $[M+H]^+$), 87.81% purity.

Synthesis of Intermediate 1.889

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(3-methyl-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 1.889

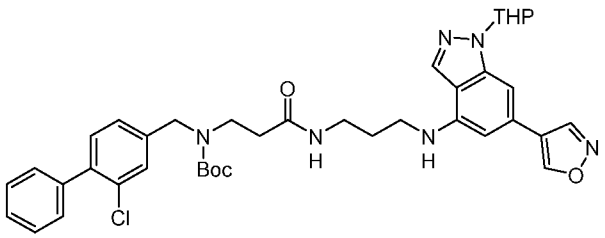


[00547] To a solution of **compound 1.382** (200 mg, 275.82 μmol) in dioxane (2 mL) and H_2O (0.2 mL) was added K_2CO_3 (76.24 mg, 551.64 μmol), 3-methyl-1H-pyrazol-4-yl)boronic acid (41.68 mg, 330.98 μmol) and $Pd(dppf)Cl_2$ (20.18 mg, 27.58 μmol). The mixture was stirred at 90 °C for 0.5 h under microwave irradiation. The solid was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM101) to afford **compound 1.889** (65 mg, 79.38 μmol, 28.78% yield) as a light-yellow oil.

[00548] LCMS (AM3): rt = 0.984 min, (726.2 $[M+H]^+$), 88.7% purity.

Synthesis of Intermediate 1.890

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(isoxazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 1.890

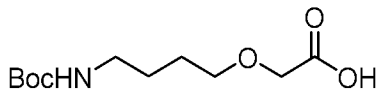


[00549] To a solution of **compound 1.382** (100 mg, 137.91 μmol) in dioxane (2 mL) and H_2O (0.2 mL) was added $Pd(dppf)Cl_2$ (10.09 mg, 13.79 μmol), isoxazol-4-ylboronic acid (18.68 mg, 165.49 μmol) and K_3PO_4 (58.55 mg, 275.82 μmol). The mixture was stirred at 80 °C for 0.5 h under microwave irradiation. The solid was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM110) to afford **compound 1.890** (90 mg, 52.74 μmol, 38.25% yield) as a light-yellow oil.

[00550] LCMS (AM3): rt = 1.095 min, (713.2 $[M+H]^+$), 41.8% purity.

Synthesis of Intermediate 1.895

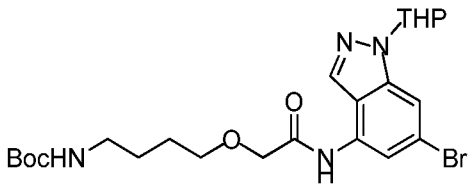
2-(4-((tert-butoxycarbonyl)amino)butoxy)acetic acid 1.891



[00551] To a solution of tert-butyl (4-hydroxybutyl)carbamate (CAS 75178-87-9, 20 g, 105.68 mmol) and 2-bromoacetic acid (13.33 g, 95.96 mmol) in THF (300 mL) at 0°C was added NaH (8.06 g, 201.51 mmol, 60% purity). The mixture was warmed to 25°C and stirred for 16 h. The reaction mixture was poured onto NaOH (aq.) (1 N, 200 mL). The mixture was extracted with DCM (150 mL × 3). The aqueous phase was adjusted to pH=3 (conc. HCl) and the mixture extracted with DCM (300 mL × 3). The combined organic phase was washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.891** (18 g, 72.79 mmol, 75.85% yield) as a yellow oil.

[00552] **^{1}H NMR**: (400 MHz, $CHCl_3$-*d*) δ: 10.88 (s, 1H), 4.08 (s, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 3.13 (s, 2H), 1.89 - 1.52 (m, 4H), 1.42 (s, 9H) ppm

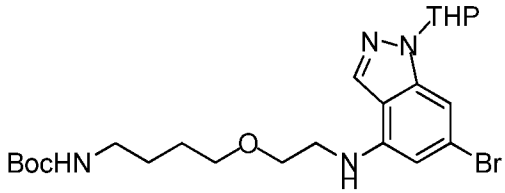
tert-butyl (4-(2-((6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)-2-oxoethoxy)butyl)carbamate 1.892



[00553] To a solution of **compound 1.381** (3.4 g, 11.48 mmol) in pyridine (100 mL) was added EDCI (22.01 g, 114.80 mmol) and **compound 1.891** (3.12 g, 12.63 mmol). The mixture was stirred at 100 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM66) to afford **compound 1.892** (5.5 g, 10.47 mmol, 85.0% yield) as a light-yellow oil.

[00554] **LCMS** (AM3): rt = 0.927 min, (525.2 $[M+H]^+$), 93.3% purity.

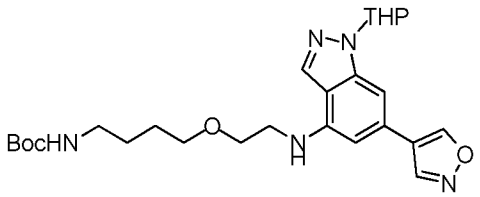
tert-butyl (4-(2-((6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 1.893



[00555] To a solution of **compound 1.892** (5.5 g, 10.47 mmol) in THF (50 mL) at 0°C was added borane; methylsulfanylmethane (10 M, 10.47 mL). The mixture was warmed to 25°C and stirred for 2 h. MeOH (40 mL) was added slowly, the mixture was stirred at 25°C for 1 h, the mixture was concentrated in *vacuo* to give a residue, which was purified (PM200) to afford **compound 1.893** (4 g, 6.34 mmol, 60.67% yield) as a light-red oil.

[00556] **LCMS** (AM3): rt = 1.017 min, (511.2 $[M+H]^+$), 98.3% purity.

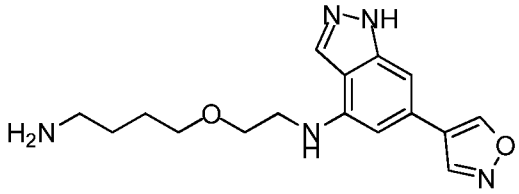
(4-(2-((6-(isoxazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 1.894



[00557] To a solution of **compound 1.893** (2 g, 3.17 mmol) in dioxane (20 mL) and H_2O (2 mL) was added K_3PO_4 (1.34 g, 6.33 mmol), isoxazol-4-ylboronic acid (741.2 mg, 3.80 mmol) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxypalladium;dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (287.13 mg, 0.31 mmol). The mixture was stirred at 60 °C for 3 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM239) to afford **compound 1.894** (1.4 g, 2.8 mmol, 88.4% yield) as a light-yellow oil.

[00558] **LCMS** (AM3): rt = 0.978 min, (500.2 $[M+H]^+$), 100% purity.

N-(2-(4-aminobutoxy)ethyl)-6-(isoxazol-4-yl)-1H-indazol-4-amine 1.895

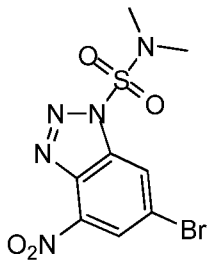


[00559] A solution of **compound 1.894** (700 mg, 1.40 mmol) in HCl/dioxane (4 M, 10 mL) was stirred at 25°C for 2 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM240) to afford **compound 1.895** (130 mg, 0.363 mmol, 25.9% yield, HCl salt) as a light-yellow solid.

LCMS (AM3): rt = 0.678 min, (316.2 $[M+H]^+$), 98.3% purity

Synthesis of Intermediate 1.900

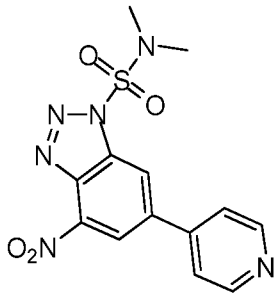
6-bromo-N,N-dimethyl-4-nitro-1H-benzo[d][1,2,3]triazole-1-sulfonamide 1.897



[00560] To a solution of 6-bromo-4-nitro-1H-benzo[d][1,2,3]triazole (WO2016168682, 850 mg, 3.50 mmol) in DCM (20 mL) at 25 °C was added TEA (1.06 g, 10.49 mmol) and dimethylsulfamoyl chloride (602.69 mg, 4.20 mmol) and the mixture stirred for 12 h. The mixture was then concentrated in *vacuo* to give a residue, which was purified (PM46) to afford **compound 1.897** (850 mg, 2.43 mmol, 66.9% yield) as a light yellow solid.

[00561] **LCMS** (AM3): rt =0.931 min, (350.0 $[M+H]^+$), 96.5% purity.

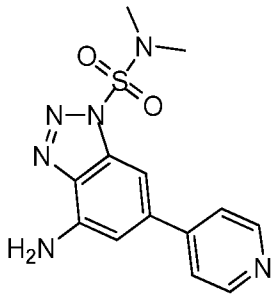
N,N-dimethyl-4-nitro-6-(pyridin-4-yl)-1H-benzo[d][1,2,3]triazole-1-sulfonamide 1.898



[00562] To a solution of **compound 1.897** (850 mg, 2.43 mmol) in dioxane (5 mL) and H_2O (0.5 mL) was added $Pd(dppf)Cl_2$ (177.63 mg, 0.24 mmol), pyridin-4-ylboronic acid (358.06 mg, 2.91 mmol) and K_2CO_3 (671.00 mg, 4.86 mmol) under N_2. The mixture was stirred at 80 °C for 0.5 h under microwave irradiation. The mixture was neutralized to pH=7 with formic acid, then concentrated in *vacuo* to give a residue, which was purified (PM41) to afford **compound 1.898** (170 mg, 0.40 mmol, 16.5% yield) as a light-yellow solid.

[00563] LCMS (AM3): rt = 0.465 min, (348.8 $[M+H]^+$), 82.1% purity.

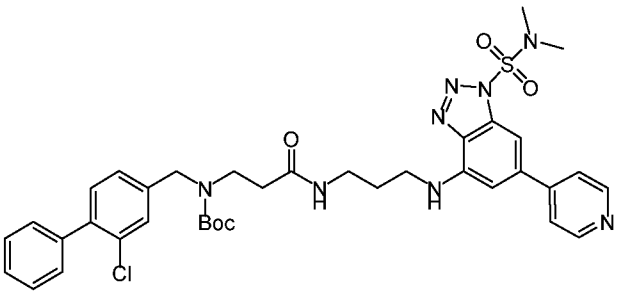
4-amino-N,N-dimethyl-6-(pyridin-4-yl)-1H-benzo[d][1,2,3]triazole-1-sulfonamide 1.899



[00564] To a solution of **compound 1.898** (170 mg, 0.40 mmol) in EtOH (5 mL) and H_2O (1 mL) was added Fe (44.75 mg, 0.80 mmol) and NH_4Cl (214.33 mg, 4.01 mmol). The mixture was stirred at 65 °C for 1 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM38) to afford **compound 1.899** (120 mg, 0.315 mmol, 78.8% yield) as a light-yellow oil.

[00565] LCMS (AM6): rt = 1.047 min, (319.2 $[M+H]^+$), 83.8% purity.

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((1-(N,N-dimethylsulfamoyl)-6-(pyridin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 1.900

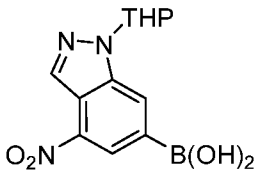


[00566] To a solution of **compound 1.899** (110 mg, 0.289 mmol) in MeOH (5 mL) at 25 °C was added **Intermediate H** (193.25 mg, 0.434 mmol) and the reaction mixture stirred for 11 h. $NaBH_3CN$ (181.96 mg, 2.90 mmol) was added and the mixture stirred for 1 h. The resultant mixture was concentrated in *vacuo* to give a residue, which was purified (PM111) to afford **compound 1.900** (50 mg, 22.2% yield) as a yellow solid.

[00567] LCMS (AM3): rt = 0.816 min, (747.2 $[M+H]^+$), 96.1% purity.

Synthesis of Intermediate 1.903

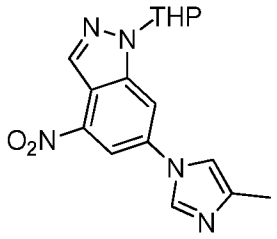
(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)boronic acid 1.901



[00568] To a solution of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (WO2019027960, 1 g, 3.07 mmol) in dioxane (10 mL) was added KOAc (601.83 mg, 6.13 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (778.60 mg, 3.07 mmol) and $Pd(dppf)Cl_2$ (224.35 mg, 0.31 mmol). The mixture was stirred at 90 °C for 25 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM112) to afford **compound 1.901** (0.62 g, 62.1% yield) as a light-yellow solid.

[00569] ^{1}**H NMR**: (400 MHz, MeOH-d_4) δ: 8.65 - 8.54 (m, 3H), 6.06 - 6.00 (m, 1H), 3.94 - 3.89 (m, 1H), 3.83 - 3.76 (m, 1H), 2.48 - 2.42 (m, 1H), 2.08 - 2.02 (m, 2H), 1.79 - 1.75 (m, 1H), 1.64 - 1.64 (m, 2H) ppm.

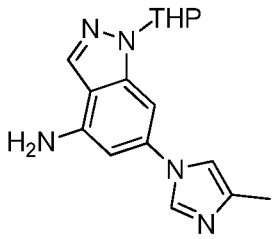
6-(4-methyl-1H-imidazol-1-yl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 1.902



[00570] To a solution of **compound 1.901** (570 mg, 1.75 mmol) in DMF (2 mL) was added TEA (708.63 mg, 7.00 mmol), 4-methyl-1H-imidazole (215.61 mg, 2.63 mmol), 4Å molecular sieves (50 mg, 1.75 mmol) and $Cu(OAc)_2$ (381.59 mg, 2.10 mmol). The mixture was stirred at 65 °C for 12 h under O_2. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM46) to afford **compound 1.902** (200 mg, 30.9% yield) as a red solid.

[00571] LCMS (AM3): rt =0.746 min, (328.1 $[M+H]^+$), 88.7% purity.

6-(4-methyl-1H-imidazol-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 1.903

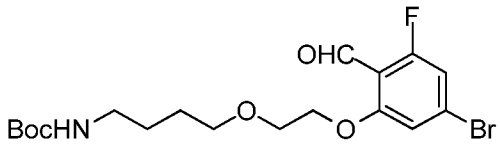


[00572] To a solution of $NiCl_2.6H_2O$ (61.19 mg, 0.257 mmol) in MeOH (10 mL) was added $NaBH_4$ (9.74 mg, 0.257 mmol). After 5 minutes, **compound 1.902** (190 mg, 0.514 mmol) and $NaBH_4$ (58.43 mg, 1.54 mmol) was added. The mixture was stirred at 0 °C for 25 minutes. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM113) to afford **compound 1.903** (180 mg, 92.8% yield) as a red solid.

[00573] LCMS (AM3): rt =0.235 min, (297.9 $[M+H]^+$), 79.0% purity.

Synthesis of Intermediate 1.910

tert-butyl (4-(2-(5-bromo-3-fluoro-2-formylphenoxy)ethoxy)butyl)carbamate 1.906

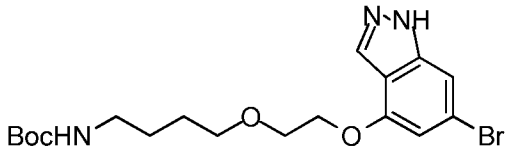


[00574] To a solution of 4-bromo-2-fluoro-6-hydroxybenzaldehyde (CAS 1427438-90-1, 12 g, 54.79 mmol) in DMF (150 mL) was added K_2CO_3 (18.93 g, 136.98 mmol) and **compound**

1.372 (22.57 g, 65.75 mmol). The mixture was stirred at 80 °C for 12 h. The mixture was extracted with EA (1000 mL) and washed with H_2O (200 mL × 3). The organic phase was dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM47) to afford **compound 1.906** (43 g, 89.3% yield) as a light-yellow oil.

[00575] LCMS (AM3): rt = 0.965 min, (455.9 $[M+Na]^+$), 88.5% purity.

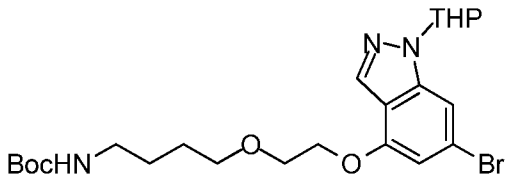
tert-butyl (4-(2-((6-bromo-1H-indazol-4-yl)oxy)ethoxy)butyl)carbamate 1.907



[00576] To a solution of **compound 1.906** (43 g, 87.62 mmol) in ethylene glycol (500 mL) was added $NH_2NH_2.H_2O$ (76.22 g, 1.52 mol). The mixture was stirred at 100 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM43) to afford **compound 1.907** (27 g, 67.0% yield) as a light-yellow oil.

[00577] LCMS (AM3): rt = 0.934 min, (428.1 $[M+H]^+$), 96.5% purity.

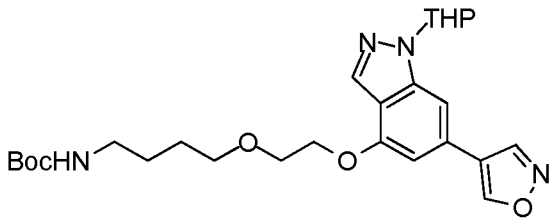
tert-butyl (4-(2-((6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)ethoxy)butyl)carbamate 1.908



[00578] To a solution of **compound 1.907** (27 g, 63.04 mmol) in THF (100 mL) was added $TsOH.H_2O$ (1.20 g, 6.30 mmol) and DHP (53.02 g, 630.37 mmol). The mixture was stirred at 60 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM115) to afford **compound 1.908** (9.8 g, 50.9% yield) as a yellow oil.

[00579] LCMS (AM3): rt = 0.882 min, (512.1 $[M+H]^+$), 84.0% purity.

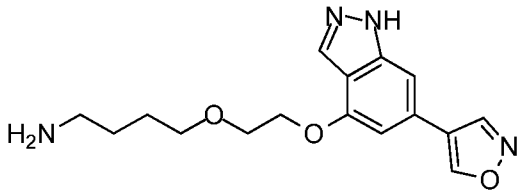
tert-butyl (4-(2-((6-(isoxazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)ethoxy)butyl)carbamate 1.909



[00580] To a solution of **compound 1.908** (9.8 g, 16.06 mmol) in H_2O (48 mL) and DMF (100 mL) was added KF (2.80 g, 48.19 mmol), 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-oxazole (CAS 928664-98-6, 3.76 g, 19.28 mmol) and $Pd(dppf)Cl_2$ (1.18 g, 1.61 mmol). The mixture was stirred at 60 °C for 2 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM43) to afford **compound 1.909** (4.4 g, 54.7% yield) as a light-yellow oil.

[00581] LCMS (AM3): rt = 0.985 min, (501.2 $[M+H]^+$), 100% purity.

[00582] 4-(2-((6-(isoxazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butan-1-amine 1.910

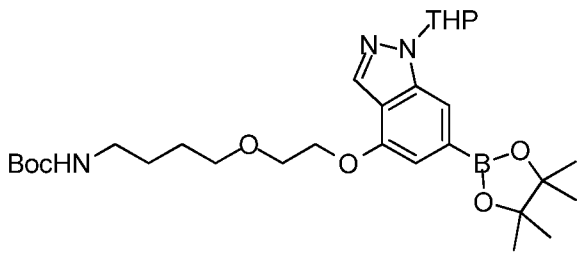


[00583] To a solution of **compound 1.909** (4.4 g, 8.79 mmol) in dioxane (20 mL) was added HCl/dioxane (4 M, 50 mL) at 0 °C. The mixture was stirred at 25°C for 2 h, then concentrated in *vacuo* to give a residue, which was purified (PM116) to afford **compound 1.910** (2.7 g, 82.4% yield, HCl salt) as a red solid.

[00584] LCMS (AM3): rt = 0.668 min, (317.0 $[M+H]^+$), 84.9% purity.

Synthesis of Intermediate 1.913

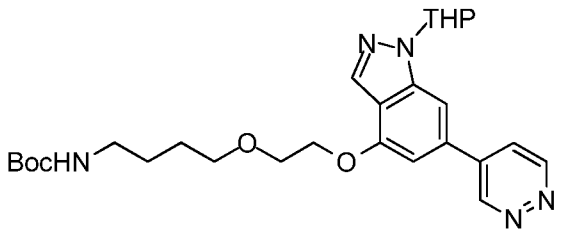
tert-butyl (4-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-4-yl)oxy)ethoxy)butyl)carbamate 1.911



[00585] To a solution of **compound 1.908** (6.5 g, 10.78 mmol) in dioxane (50 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.29 g, 12.94 mmol), KOAc (2.12 g, 21.56 mmol) and $Pd(dppf)Cl_2$ (788.92 mg, 1.08 mmol). The mixture was stirred at 85 °C for 12 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM40) to afford **compound 1.911** (6.5 g, 92.6% yield) as a yellow oil.

[00586] LCMS (AM3): rt = 0.908, 0.988 min, (560.4 $[M+H]^+$), 80.2% purity.

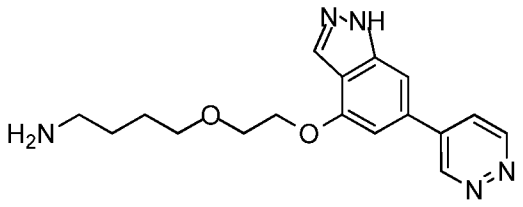
tert-butyl (4-(2-((6-(pyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)ethoxy)butyl)carbamate 1.912



[00587] To a solution of **compound 1.911** (6.50 g, 10.00 mmol) in dioxane (100 mL) and H_2O (10 mL) under N_2 was added $Pd(dppf)Cl_2$ (664.92 mg, 0.91 mmol), 4-bromopyridazine (2.18 g, 9.09 mmol, HBr salt) and K_2CO_3 (3.77 g, 27.26 mmol). The mixture was stirred at 80 °C for 12 h. The mixture was concentrated in *vacuo* to give a crude residue, which was purified (PM117) to afford **compound 1.912** (2.9 g, 44.3% yield) as a yellow solid.

[00588] LCMS (AM3): rt = 0.889 min, (512.1 $[M+H]^+$), 71.1% purity.

4-(2-((6-(pyridazin-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butan-1-amine 1.913

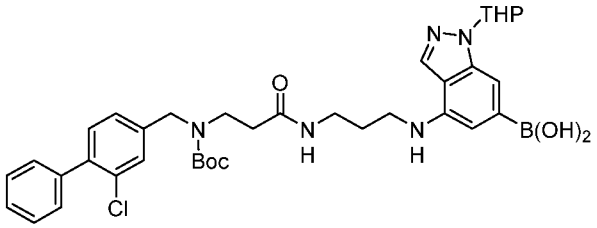


[00589] To a solution of **compound 1.912** (2.85 g, 3.96 mmol) in MeOH (10 mL) was added HCl/MeOH (4 M, 50 mL). The mixture was stirred at 25 °C for 2 h. The mixture was concentrated in *vacuo* to give a residue, which was recrystallized with EA (100 mL) at 25 °C to afford **compound 1.913** (1.8 g, 96.6% yield, HCl salt) as a yellow solid.

[00590] LCMS (AM3): rt = 0.611 min, (328.0 $[M+H]^+$), 85.0% purity.

Synthesis of Intermediate 1.915

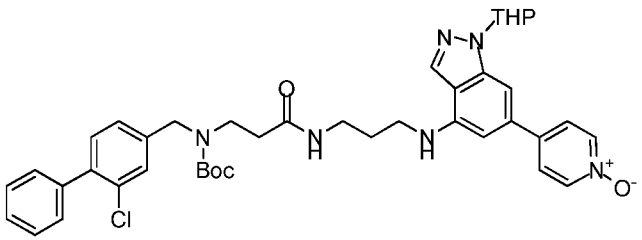
(4-((3-(3-((tert-butoxycarbonyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)boronic acid 1.914



[00591] To a solution of **compound 1.382** (1.45 g, 2.00 mmol) in dioxane (10 mL) under N_2 was added KOAc (392.51 mg, 4.00 mmol), $Pd(dppf)Cl_2$ (146.32 mg, 0.2 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (609.36 mg, 2.40 mmol). The mixture was stirred at 85 °C for 12 h. The solid was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM118) to afford **compound 1.914** (900 mg, 1.24 mmol, 61.77% yield) as a dark brown solid.

[00592] LCMS (AM3): rt =1.004 min, (690.4 $[M+H]^+$), 94.7% purity.

4-(4-((3-(3-((tert-butoxycarbonyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)pyridine 1-oxide 1.915

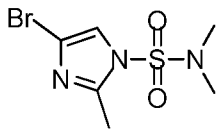


[00593] To a solution of **compound 1.914** (200 mg, 0.29 mmol) in H_2O (0.5 mL) and DME (5 mL) under N_2 was added K_2CO_3 (80.12 mg, 0.58 mmol), 4-chloropyridine 1-oxide (45.06 mg, 0.32 mmol) and $Pd(PPh_3)_4$ (33.49 mg, 0.029 mmol). The mixture was stirred at 80 °C for 12 h. The resultant mixture was then concentrated in *vacuo* to give a residue, which was purified (PM90) to afford **compound 1.915** (0.15 g, 61.6% yield) as a yellow solid.

[00594] LCMS (AM3): rt =1.023 min, (739.4 $[M+H]^+$), 88.4% purity.

Synthesis of Intermediate 1.918

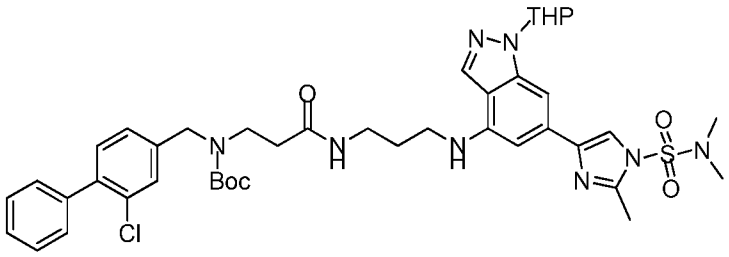
4-bromo-N, N, 2-trimethyl-1H-imidazole-1-sulfonamide 1.917



[00595] To a solution of 4-Bromo-2-methyl-1H-imidazole, (CAS 16265-11-5, 350 mg, 2.17 mmol) in DCM (10 mL) at 25 °C was added TEA (879.91 mg, 8.70 mmol) and dimethylsulfamoyl chloride (468.24 mg, 3.26 mmol) and the mixture stirred for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM64) to afford **compound 1.917** (200 mg, 31.9% yield) as a light-yellow oil.

[00596] LCMS (AM1): rt = 0.698 min, (270.2 $[M+H]^+$), 93.4% purity.

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(1-(N,N-dimethylsulfamoyl)-2-methyl-1H-imidazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 1.918

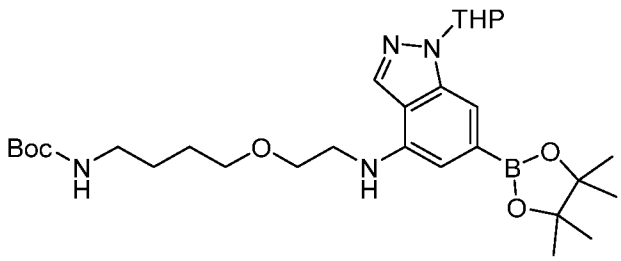


[00597] To a solution of **compound 1.914** (250 mg, 0.36 mmol) in H_2O (0.5 mL) and DME under N_2 (5 mL) was added K_2CO_3 (125.18 mg, 0.91 mmol), **compound 1.917** (145.72 mg, 0.54 mmol) and $Pd(PPh_3)_4$ (41.87 mg, 0.036 mmol). The mixture was stirred at 80 °C for 12 hrs. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM119) to afford **compound 1.918** (100 mg, 32.7% yield) as a light-yellow oil.

[00598] LCMS (AM1): rt =0.960 min, (833.0 $[M+H]^+$), 98.9% purity.

<u>Synthesis of Intermediate 1.921</u>

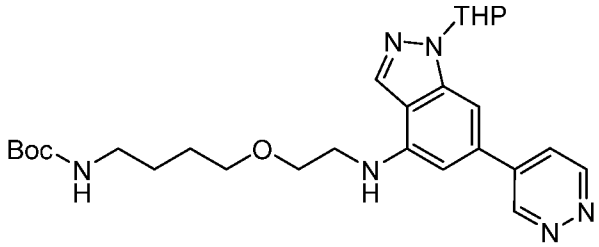
tert-butyl(4-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 1.919



[00599] To a solution of **compound 1.893** (2.8 g, 5.47 mmol) in dioxane (40 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.09 g, 8.21 mmol), $Pd(dppf)Cl_2$ (400.58 mg, 547.46 μmol) and KOAc (1.07 g, 10.95 mmol). The reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM2) to afford **compound 1.919** (3.2 g, crude) as a yellow oil.

[00600] LCMS (AM3): rt = 1.095 min, (559.4 $[M+H]^+$), 75.9% purity.

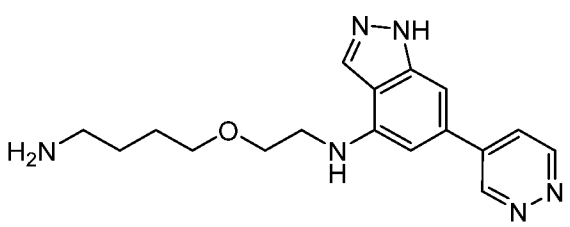
tert-butyl (4-(2-((6-(pyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 1.920



[00601] To a solution of **compound 1.919** (3.1 g, 5.55 mmol) in dioxane (15 mL) and H_2O (1.5 mL) was added K_2CO_3 (1.53 g, 11.10 mmol), 4-bromopyridazine (1.63 g, 8.33 mmol, HCl salt) and $Pd(dppf)Cl_2$ (406.13 mg, 555.04 μmol). The reaction mixture was stirred at 80 °C for 12 h under N_2. The reaction mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM2) to afford **compound 1.920** (2.6 g, 5.09 mmol, 91.74% yield) as a yellow oil.

[00602] LCMS (AM3): rt = 0.904 min, (511.1 $[M+H]^+$), 100% purity.

N-(2-(4-aminobutoxy)ethyl)-6-(pyridazin-4-yl)-1H-indazol-4-amine 1.921

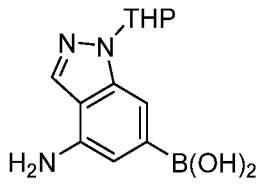


[00603] To a solution of **compound 1.920** (2.6 g, 5.09 mmol) in dioxane (10 mL) was added HCl/dioxane (4 M, 10 mL) slowly. The reaction mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated in *vacuo* to afford **compound 1.921** (2.2 g, crude, HCl salt) as a red solid.

[00604] **LCMS** (AM3): rt = 0.761 min, (326.9 $[M+H]^+$), 93.4% purity.

Synthesis of Intermediate 1.923

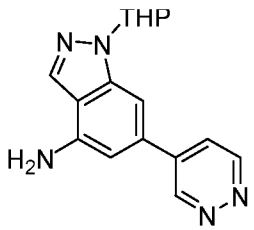
(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)boronic acid 1.922



[00605] A solution of **compound 1.901** (3.5 g, 9.02 mmol) in MeOH (10 mL) was added Pd/C (500 mg, 9.02 mmol, 10% purity) under N_2. The suspension was degassed and purged with H_2 (x3). The mixture was stirred at 25°C for 12 h under H_2 (15 psi). The mixture was filtered and concentrated in *vacuo* to afford **compound 1.922** (3 g, crude) as a brown oil, which was used for the next step without further purification.

[00606] **LCMS** (AM3): rt = 0.508 min, (260.4 $[M+H]^+$), 42.07% purity

6-(pyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 1.923

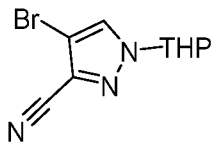


[00607] To a mixture of **compound 1.922** (200 mg, 766.04 μmol) and 4-bromopyridazine (240.03 mg, 919.24 μmol) in dioxane (2 mL) and H_2O (0.2 mL) was added K_2CO_3 (211.75 mg, 1.53 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (62.56 mg, 76.60 μmol) in one portion under N_2. The mixture was stirred at 90 °C for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM38) and then by prep-TLC (PM2) to afford **compound 1.923** (200 mg, 457.90 μmol, 59.77% yield) as a yellow oil.

[00608] **LCMS** (AM3): rt = 0.873 min, (398.6 $[M+H]^+$), 86.0% purity.

Synthesis of Intermediate 1.927

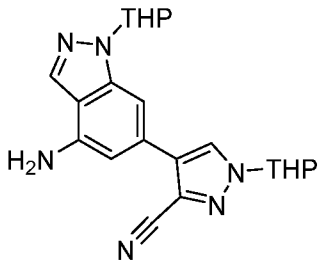
4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-3-carbonitrile 1.926



[00609] To a mixture of 4-Bromo-1H-pyrazole-5-carbonitrile (CAS 288246-16-2, 500 mg, 2.91 mmol) and DHP (366.82 mg, 4.36 mmol) in THF (10 mL) was added $TsOH.H_2O$ (276.51 mg, 1.45 mmol) under N_2. The mixture was stirred at 60 °C for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM49) to afford **compound 1.926** (600 mg, 2.34 mmol, 80.59% yield) as a colourless oil.

[00610] **^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.13 (s, 1H), 5.50 - 5.47 (m, 1H), 4.00 - 3.97 (m, 1H), 3.73 - 3.70 (m, 1H), 2.09 - 2.06 (m, 2H), 2.04 - 2.03 (m, 1H), 1.67 - 1.65 (m, 2H), 1.63 - 1.62 (m, 1H) ppm.

4-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-3-carbonitrile 1.927

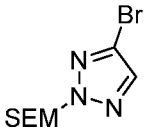


[00611] To a mixture of **compound 1.926** (200 mg, 766.04 µmol) and **compound 1.922** (235.42 mg, 919.24 µmol) in dioxane (2 mL) and H_2O (0.2 mL) was added K_2CO_3 (211.75 mg, 1.53 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (62.56 mg, 76.60 µmol) in one portion under N_2. The mixture was stirred at 90 °C for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM38) to afford **compound 1.927** (170 mg, 350.87 umol, 45.80% yield) as a yellow oil.

[00612] **LCMS** (AM3): rt = 0.913 min, (393.5 $[M+H]^+$), 81.3% purity.

Synthesis of Intermediate 1.931

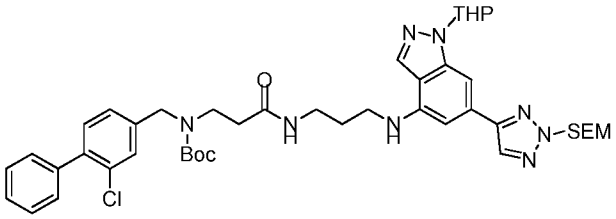
4-bromo-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazole 1.929



[00613] To a mixture of 5-Bromo-1H-1,2,3-triazole (CAS 40964-56-5, 450 mg, 3.04 mmol) in THF (5 mL) was added NaH (182.46 mg, 4.56 mmol, 60% purity) at 0 °C and stirred for 0.5 h, then SEM-Cl (608.47 mg, 3.65 mmol) was added and the mixture was stirred at 30 °C for 0.5 h. The mixture was quenched with water (20 mL) and the aqueous phase was extracted with EA (20 mL × 2). The combined organic phase was washed (brine, 30 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM50) to afford **compound 1.929** (550 mg, 1.98 mmol, 65.00% yield) as a colourless oil.

[00614] **^{1}H NMR** (400MHz, $CHCl_3$-*d*) δ 7.72 (d, *J* = 17.6 Hz, 1H), 5.69 (d, *J* = 15.6 Hz, 2H), 3.69 - 3.53 (m, 2H), 0.95 - 0.89 (m, 2H), -0.01 (d, *J* = 4.4 Hz, 9H) ppm.

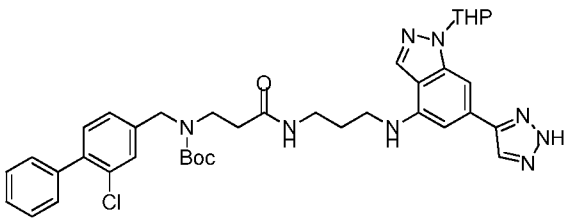
tert-butyl((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((1-(tetrahydro-2H-pyran-2-yl)-6-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,3-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 1.930



[00615] To a mixture of **compound 1.929** (120.96 mg, 434.76 μmol) and **compound 1.914** (150 mg, 217.38 μmol) in DME (3 mL) and H_2O (0.3 mL) was added K_2CO_3 (60.09 mg, 434.76 μmol) and $Pd(PPh_3)_4$ (25.12 mg, 21.74 μmol). The mixture was stirred at 90 °C for 16 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified by prep-TLC (EA) to afford **compound 1.930** (110 mg, 130.40 μmol, 59.99% yield) as a purple oil.

[00616] **LCMS** (AM3): rt =1.165 min, (843.4 $[M+H]^+$), 59% purity.

tert-butyl((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((1-(tetrahydro-2H-pyran-2-yl)-6-(2H-1,2,3-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 1.931

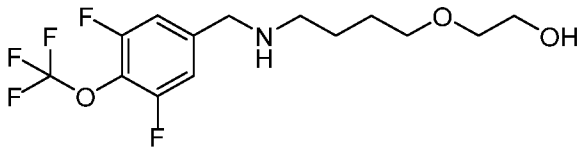


[00617] A mixture of **compound 1.930** (160 mg, 189.68 μmol) and TBAF (1 M, 5 mL) was stirred at 70 °C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM121) to afford **compound 1.931** (90 mg, 126.18 μmol, 66.52% yield) as a yellow solid.

[00618] LCMS (AM3): rt =1.080 min, (713.3 $[M+H]^+$),93% purity.

Synthesis of Intermediate 1.941

2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethan-1-ol 1.939

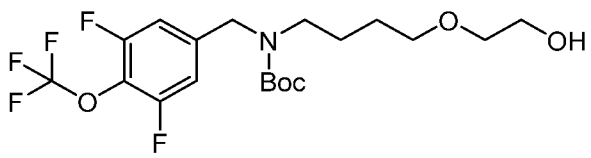


[00619] To a mixture of 3,5-Difluoro-4-(trifluoromethoxy)benzaldehyde (WO2022185041, 12.8 g, 42.46 mmol, 75% purity) and 2-(4-aminobutoxy)ethan-1-ol (CAS 1019567-93-1 , 8.64 g, 50.93 mmol, HCl salt) in MeOH (120 mL) was added DIPEA (7.13 g, 55.20 mmol) at 20°C and the mixture stirred for 12 h, $NaBH_3CN$ (8.00 g, 127.38 mmol) was added portionwise. The resulting mixture was stirred for 3 h. The reaction mixture was diluted with H_2O (50 mL) and filtered. The filtrate was concentrated in *vacuo* to give a residue, which was purified (PM241) to afford **compound 1.939** (11.9 g, 24.98 mmol, 58.83% yield, 96% purity, TFA salt) as a yellow oil.

[00620] **LCMS** (AM16): rt = 0.678 min, (344.2 $[M+H]^+$), 96.2% purity.

[00621] **^{1}H NMR** (400MHz, MeOH-d_4) δ 7.44 - 7.36 (m, 2H), 4.26 (s, 2H), 3.70 - 3.66 (m, 2H), 3.57 - 3.52 (m, 4H), 3.12 (t, J = 7.2 Hz, 2H), 1.89 - 1.79 (m, 2H), 1.77 - 1.67 (m, 2H) ppm.

tert-butyl (3,5-difluoro-4-(trifluoromethoxy)benzyl)(4-(2-hydroxyethoxy)butyl)carbamate 1.940

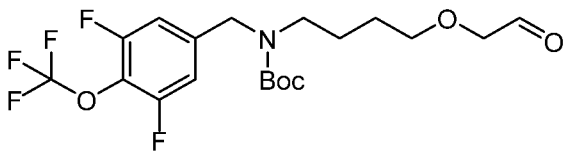


[00622] To a solution of **compound 1.939** (11.9 g, 26.02 mmol, TFA salt) in THF (150 mL) and H_2O (50 mL) was added $NaHCO_3$ (6.56 g, 78.06 mmol) followed by Boc_2O (6.81 g, 31.23 mmol). The mixture was stirred at 20°C for 12 h. The reaction mixture was poured onto H_2O (200 mL) and extracted with EA (150 mL × 3). The combined organic phase was washed (brine, 100 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM45) to afford **compound 1.940** (9.6 g, 20.18 mmol, 77.54% yield, 93.2% purity) as a colourless oil.

[00623] **LCMS** (AM11): rt = 0.492 min, (466.0 $[M+Na]^+$), 93.2% purity.

[00624] **^{1}H NMR** (400MHz, $CHCl_3$-*d*) δ 6.93 - 6.84 (m, 2H), 4.39 (s, 2H), 3.78 - 3.70 (m, 2H), 3.55 - 3.45 (m, 4H), 3.32 - 3.16 (m, 2H), 1.58 - 1.34 (m, 13H) ppm.

tert-butyl (3,5-difluoro-4-(trifluoromethoxy)benzyl)(4-(2-oxoethoxy)butyl)carbamate 1.941

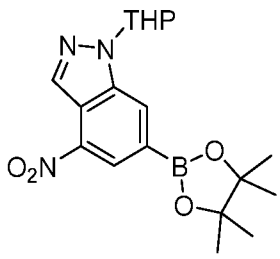


[00625] To a solution of oxalyl dichloride (2.86 g, 22.55 mmol) in DCM (40 mL) was added a solution of DMSO (2.64 g, 33.83 mmol) in DCM (10 mL) at -70°C under N_2. The mixture was cooled to -70°C for 0.5 hr, a solution of **compound 1.940** (5 g, 11.28 mmol) in DCM (30 mL) was added dropwise at -70°C, after 0.5 hr TEA (6.85 g, 67.66 mmol) was added to the mixture at -70°C, the mixture was warmed to 20°C and stirred for 10 minutes. The reaction mixture was filtered and the filtrate was purified (PM43) to afford **compound 1.941** (4.95 g, 11.21 mmol, 99.45% yield) as a yellow oil.

[00626] **^{1}H NMR** (400MHz, DMSO-d_6) δ 9.57 (s, 1H), 7.25 - 7.16 (m, 2H), 4.40 (s, 2H), 3.48 - 3.35 (m, 2H), 3.25 - 3.15 (m, 2H), 1.55 - 1.44 (m, 4H), 1.43 - 1.27 (m, 9H) ppm.

Synthesis of Intermediate 1.945

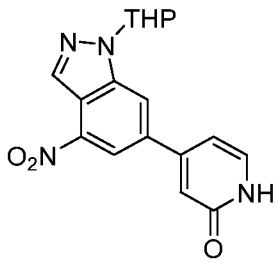
4-nitro-1-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole 1.943



[00627] To a solution of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (WO2019027960, 3 g, 9.20 mmol) in dioxane (45 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.80 g, 11.04 mmol) followed by KOAc (1.81 g, 18.40 mmol) and $Pd(dppf)Cl_2$ (673.05 mg, 919.83 µmol). The mixture was degassed and purged with N_2 (x3), then the mixture was stirred at 90°C for 3 h. The reaction mixture was cooled to 20°C, diluted with DCM (100 mL) and filtered. The filter cake was washed with DCM (60 mL × 2) and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM36) to afford **compound 1.943** (3.09 g, 8.28 mmol, 90.08% yield) as an off-white solid.

[00628] **^{1}H NMR** (400 MHz, $CHCl_3$-*d*) δ 8.66 (s, 1H), 8.55 (s, 1H), 8.37 (s, 1H), 5.87 (dd, *J* = 9.2, 2.8 Hz, 1 H), 4.03 - 4.00 (m,1H), 3.86 - 3.75 (m,1H), 2.65 - 2.53 (m, 1H),2.3 - 2.16 (m, 1H), 2.15 - 2.05 (m, 1H), 1.79 - 1.73 (m, 3H), 1.40 (s, 12H) ppm.

4-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)pyridin-2(1H)-one 1.944

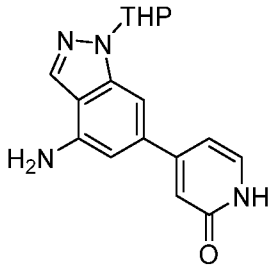


[00629] To a mixture of **compound 1.943** (2 g, 5.36 mmol) in dioxane (30 mL) and H_2O (3 mL) was added 4-bromopyridin-2(1H)-one (1.12 g, 6.43 mmol) and K_2CO_3 (1.48 g, 10.72 mmol) followed by $Pd_2(dba)_3$ (490.72 mg, 535.89 µmol) at 20 °C. The mixture was degassed and purged with N_2 (x3), then the mixture stirred at 90 °C for 12 h. The mixture was filtered and washed with EA (10 mL × 3), then the filtrate was concentrated in *vacuo* to give a residue, which was triturated with EA (20 mL) at 20 °C for 5 minutes, then the filter cake was concentrated in *vacuo* to afford **compound 1.944** (900 mg, 2.43 mmol, 45.40% yield) as a yellow solid.

[00630] **LCMS** (AM11): rt = 0.363 min, (341.0 $[M+H]^+$), 92.07% purity.

[00631] **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.60 (s, 1H), 8.38 (d, *J* = 1.6 Hz, 1H), 7.60 (d, *J* = 6.8 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.71 (dd, *J* = 5.6, 1.6 Hz, 1H), 6.24 - 6.18 (m, 1H), 3.89 - 3.82 (m, 2H), 2.07 (s, 2H), 2.06 - 2.00 (m, 2H), 1.63 - 1.58 (m, 2H) ppm.

4-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)pyridin-2(1H)-one 1.945

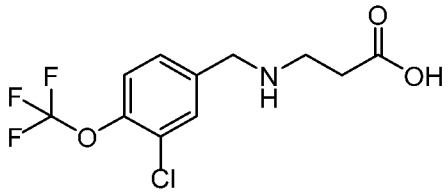


[00632] To a mixture of **compound 1.944** (800 mg, 2.35 mmol) in EtOH (20 mL) and H_2O (5 mL) was added NH_4Cl (1.26 g, 23.51 mmol) and Fe (1.05 g, 18.81 mmol) at 20 °C. The mixture was degassed and purged with N_2 (x3) and the mixture heated to 70 °C and stirred for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM136) to afford **compound 1.945** (280 mg, 902.21 µmol, 34.12% yield) as a yellow gum.

[00633] **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.43 (d, *J* = 6.8 Hz, 1H), 7.09 (s, 1H), 6.53 (d, *J* = 1.6 Hz, 1H), 6.49 - 6.46 (m, 1H), 6.46 - 6.44 (m, 1H), 5.99 (s, 2H), 5.81 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.91 - 3.84 (m, 1H), 3.80 - 3.70 (m, 1H), 3.40 - 3.35 (m, 2H), 2.08 - 2.00 (m, 1H), 1.95 - 1.87 (m, 1H), 1.62 - 1.52 (m, 2H) ppm.

Synthesis of Intermediate 1.951

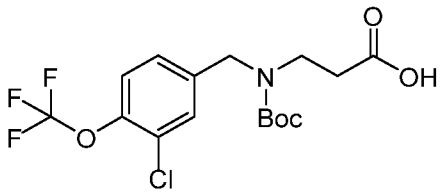
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanoic acid 1.947



[00634] To a mixture of 3-chloro-4-(trifluoromethoxy)benzaldehyde (CAS 83279-39-4, 12.5 g, 55.66 mmol) in MeOH (150 mL) was added 3-aminopropanoic acid (14.88 g, 166.99 mmol). The mixture stirred at 20 °C for 12 h, then $NaBH_3CN$ (7.00 g, 111.33 mmol) was added in portions at 0 °C. The mixture was stirred at 20 °C for 2 h. The reaction mixture was filtered and the filter cake washed with MeOH (30 mL × 3). The filtrate was concentrated in *vacuo* to give a residue, which was purified (PM137) to afford **compound 1.947** (18 g, 43.20 mmol, 68.68% yield, TFA salt) as a yellow oil.

[00635] **LCMS** (AM11): rt = 0.310 min, (298.0 $[M+H]^+$), 98.89% purity.

3-((tert-butoxycarbonyl)(3-chloro-4-(trifluoromethoxy)benzyl)amino)propanoic acid 1.948

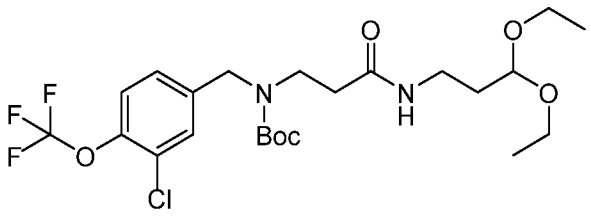


[00636] To a solution of **compound 1.947** (18 g, 43.72 mmol, TFA salt) in THF (150 mL), MeOH (70 mL) and H_2O (70 mL) was added $NaHCO_3$ (14.69 g, 174.89 mmol) followed by Boc_2O (9.54 g, 43.72 mmol) at 20 °C. The mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated in *vacuo*, diluted with water (150 mL), acidified to pH = 5 by HCl (aq.) (1 M) and extracted with EA (150 mL × 3). The combined organic phase was washed (brine, 150 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.948** (16 g, 40.22 mmol, 92.00% yield) as a yellow oil.

[00637] LCMS (AM12): rt = 0.588 min, (420.2 $[M+Na]^+$), 96.89% purity.

[00638] ^{1}H NMR (400MHz, $CHCl_3$-*d*) δ 7.34 (s, 1H), 7.31 – 7.27 (m, 1H), 7.19 – 7.11 (m, 1H), 4.45 (s, 2H), 3.49 (br s, 2H), 2.64 (br s, 2H), 1.48 (s, 9H) ppm.

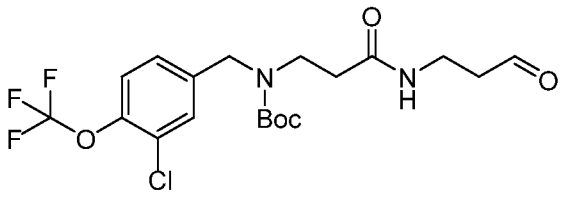
tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-((3,3-diethoxypropyl)amino)-3-oxopropyl)carbamate 1.949



[00639] To a solution of **compound 1.948** (8 g, 17.36 mmol, 86.3% purity) and 3,3-diethoxypropan-1-amine (2.81 g, 19.09 mmol) in THF (120 mL) was added DIPEA (8.97 g, 69.43 mmol) followed by T_3P (12.15 g, 19.09 mmol, 50% purity) dropwise at 0°C. The mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H_2O (200mL) and extracted with EA (150 mL × 3). The combined organic phase was washed by brine (150 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM42) to afford **compound 1.949** (7.1 g, 12.50 mmol, 72.04% yield) as a yellow oil.

[00640] ^{1}H NMR ($CHCl_3$-*d*, 400MHz) δ 7.35 (s, 1H), 7.29 - 7.09 (m, 2H), 6.43 - 6.10 (m, 1H), 4.56 (t, *J* = 5.2 Hz, 1H), 4.43 (s, 2H), 3.63 - 3.73 (m, 2H), 3.55 - 3.48 (m, 4H), 3.37 - 3.32 (m, 2H), 2.51 - 2.30 (m, 2H), 1.87 - 1.78 (m, 4H), 1.45 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 6H) ppm.

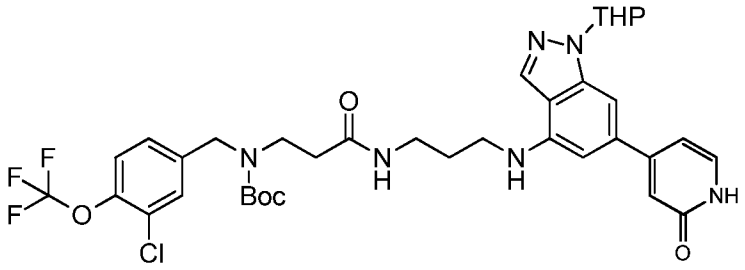
tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-oxo-3-((3-oxopropyl)amino)propyl)carbamate 1.950



[00641] A one neck flask charged with **compound 1.949** (2 g, 3.80 mmol) was cooled to 0°C. To this cooled mixture was added AcOH (20 mL) and H_2O (4 mL). The mixture was stirred at 20°C for 1 h. The reaction mixture was added into sat. $NaHCO_3$ (aq.) (120 mL) at 0°C and extracted with EA (60 mL × 3). The combined organic phase was washed by brine (50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 1.950** (1.4 g, 3.09 mmol, 81.46% yield) as a yellow oil.

[00642] **^{1}H NMR** (400MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.18 - 7.99 (m, 1H), 7.60 - 7.50 (m, 1H), 7.47 (s, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 4.37 (s, 2H), 3.49 - 3.35 (m, 2H), 3.32 -3.25 (m, 2H), 2.64 - 2.53 (m, 2H), 2.39 - 2.24 (m, 2H), 1.50 - 1.25 (m, 9H) ppm.

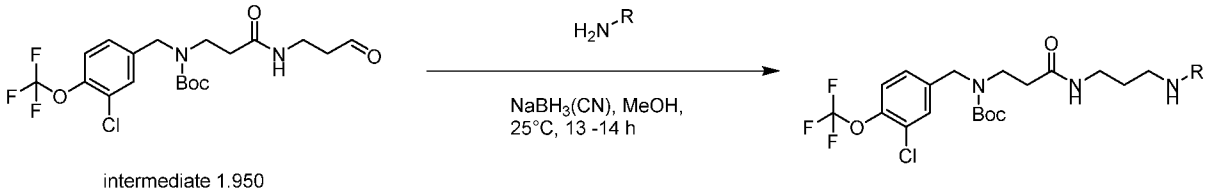
tert-butyl 3-chloro-4-(trifluoromethoxy)benzyl(3-oxo-3-((3-((6-(2-oxo-1,2-dihydropyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 1.951



[00643] To a solution of **compound 1.950** (132.65 mg, 292.92 µmol) in MeOH (2 mL) was added **compound 1.945** (100 mg, 322.22 µmol). The reaction was stirred at 20 °C for 12 h, then $NaBH_3CN$ (55.22 mg, 878.77 µmol) added and the reaction stirred for 20 °C for 2 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM138) to afford **compound 1.951** (48 mg, 64.24 µmol, 21.93% yield) as a yellow solid.

[00644] **LCMS** (AM12): rt = 0.629 min, (747.2 $[M+H]^+$).

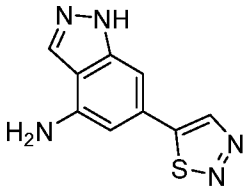
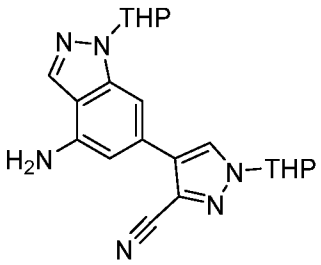
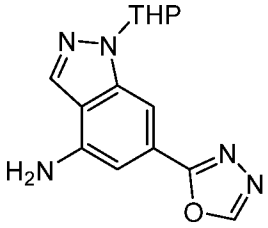
[00645] The following Intermediates in Table 3 were made with non-critical changes or substitutions to the exemplified procedure for Intermediate 1.950 that would be understood by one skilled in the art, wherein R may or may not contain a THP protecting group.

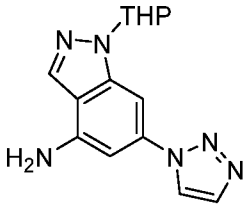
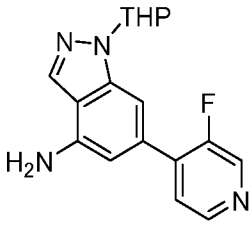


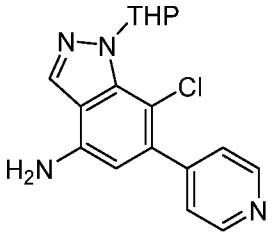
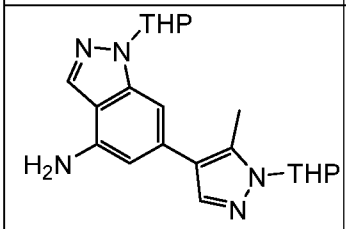
intermediate 1.950

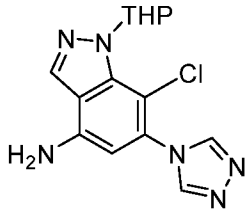
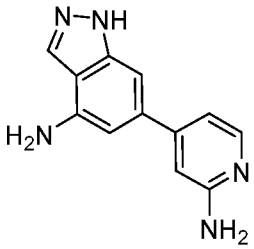
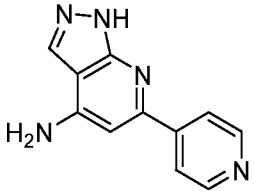
Table 3

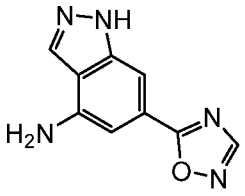
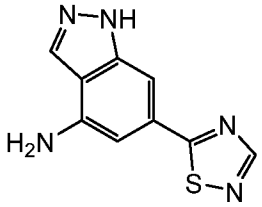
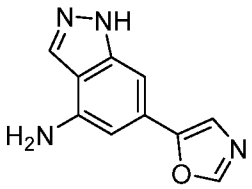
Reagent H_2N-R IUPAC name/Intermediate No.	Product Intermediate IUPAC name/Intermediate No.	Analytical

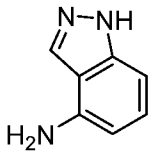
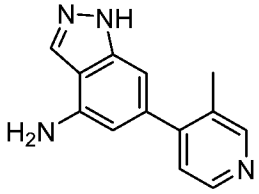
 6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-amine **1.995**	tert-butyl(3-((3-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate **1.999**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.13 (s, 1H), 8.20 (d, *J* = 0.8 Hz, 1H), 7.47 - 7.40 (m, 1H), 7.36 - 7.33 (m, 2H), 7.13 (s, 1H), 6.40 (s, 1H), 4.41 (s, 2H), 3.56 - 3.51 (m, 2H), 3.38 - 3.35 (m, 2H), 2.47 - 2.45 (m, 2H), 1.97 - 1.93 (m, 2H), 1.47 - 1.36 (m, 9H) ppm. **LCMS** (AM11): rt = 0.491 min, (654.4 $[M+H]^+$), 55% purity. **Purification Method** PM141
 4-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-3-carbonitrile **1.927**	tert-butyl N-[[3-chloro-4-(trifluoromethoxy)phenyl]methyl]-N-[3-[3-[[6-(5-cyano-1-tetrahydropyran-2-yl-pyrazol-4-yl)-1-tetrahydropyran-2-yl-indazol-4-yl]amino]propylamino]-3-oxo-propyl]carbamate **2.226**	**^{1}H NMR** (400 MHz, $CHCl_3$-*d*) δ 8.04 (s, 1H), 7.98 (s, 1H), 7.33 (s, 1H), 7.26 - 7.24 (m, 1H), 7.16 - 7.045 (m, 2H), 6.51 (s, 1H), 5.67 (dd, *J* = 7.2 Hz, 1H), 5.49 (dd, *J* = 7.2 Hz, 1H), 4.40 (s, 2H), 4.12 - 4.01 (m, 2H), 3.80 - 3.74 (m, 2H), 3.56 - 3.46 (m, 2H), 3.44 - 3.36 (m, 4H), 2.60 - 2.42 (m, 3H), 2.22 - 2.11 (m, 3H), 2.10 - 2.03 (m, 2H), 1.97 - 1.85 (m, 2H), 1.85 - 1.66 (m, 6H), 1.43 (s, 9H) ppm. **LCMS** (AM16): rt = 0.886 min, (829.4 $[M+H]^+$), 97.36% purity. **Purification Method** PM130
 6-(1,3,4-oxadiazol-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.231**	tert-butyl (3-((3-((6-(1,3,4-oxadiazol-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate **2.233**	**LCMS** (AM16): rt = 0.804 min, (722.2 $[M+H]^+$), 91.00% purity. **Purification Method** PM131

 1-(tetrahydro-2H-pyran-2-yl)-6-(1H-1,2,3-triazol-1-yl)-1H-indazol-4-amine **2.235**	tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-oxo-3-((3-((1-(tetrahydro-2H-pyran-2-yl)-6-(1H-1,2,3-triazol-1-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate **2.236**	**^{1}H NMR** (400 MHz, $CHCl_3$-*d*) δ 8.14 (s, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 7.85 (d, *J* = 1.2 Hz, 1H), 7.32 (s, 1H), 7.30 - 7.28 (m, 1H), 7.16 (s, 1H), 7.14 - 7.09 (m, 1H), 6.62 (s, 1H), 5.68 (dd, *J* = 9.3 Hz, 2.8 Hz, 1H), 4.40 (s, 2H), 4.07 - 3.99 (m, 1H), 3.80 - 3.70 (m, 1H), 3.54 (t, *J* = 6.0 Hz, 2H), 3.46 - 3.36 (m, 4H), 2.61 - 2.42 (m, 3H), 2.20 - 2.12 (m, 1H), 2.11 - 2.02 (m, 1H), 1.94 - 1.83 (m, 2H), 1.81 - 1.71 (m, 2H), 1.70 - 1.64 (m, 1H), 1.44 (s, 9H) ppm **LCMS** (AM16): rt = 0.797 min, (721.3 $[M+H]^+$), 96.6% purity. **Purification Method** PM132
 6-(3-fluoropyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.238**	tert-butyl 3-chloro-4-(trifluoromethoxy)benzyl(3-((3-((6-(3-fluoropyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.239**	**LCMS** (AM11): rt = 0.523 min, (749.2 $[M+H]^+$), 48.87% purity. **Purification Method** PM133

 7-chloro-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.024**	tert-butyl(3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((7-chloro-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.249**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.58 (dd, J = 4.4 Hz, 1.6 Hz, 2H), 8.26 (s, 1H), 7.50 (dd, J = 4.4 Hz, 2.0 Hz, 2H), 7.39 - 7.33 (m, 2H), 7.19 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.47 - 6.41 (m, 1H), 6.15 (s, 1H), 4.38 (s, 2H), 4.01 - 3.94 (m, 1H), 3.82 - 3.71 (m, 1H), 3.52 - 3.48 (m, 2H), 3.30 - 3.23 (m, 2H), 2.45 - 2.38 (m, 2H), 2.15 - 2.05 (m, 2H), 1.93 - 1.85 (m, 2H), 1.83 - 1.56 (m, 4H), 1.51 - 1.32 (m, 11H) ppm. **LCMS** (AM16): rt = 0.868 min, (765.2 $[M+H]^+$), 96.48% purity. **Purification Method** PM158
 6-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.251**	tert-butyl(3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((6-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.252**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.13 (s, 1H), 7.93 (s, 1H), 7.37 - 7.29 (m, 2H), 7.18 - 7.12 (m, 1H), 8.86 (s, 1H), 8.27 (s, 1H), 5.70 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 5.36 - 5.26 (m, 1H), 4.38 (s, 2H), 4.09 - 3.97 (m, 2H), 3.84 - 3.71 (m, 2H), 3.53 - 3.47 (m, 2H), 2.58 - 2.42 (m, 4H), 2.42 - 2.36 (m, 3H), 2.21 - 1.93 (m, 4H), 1.80 - 1.59 (m, 6H), 1.50 - 1.27 (m, 11H) ppm. **LCMS** (AM16): rt = 0.849 min, (818.4 $[M+H]^+$), 93.9% purity. **Purification Method** PM159

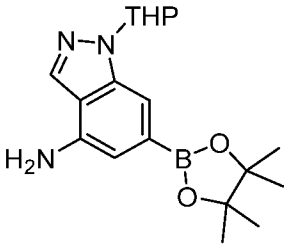
 7-chloro-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine **2.321**	tert-butyl (3-((3-((7-chloro-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate **2.322**	**LCMS** (AM14): rt = 0.694 min, (755.3 $[M+H]^+$), 100% purity. **Purification Method** PM172
 6-(2-aminopyridin-4-yl)-1H-indazol-4-amine **2.306**	tert-butyl (3-((3-((6-(2-aminopyridin-4-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate **2.323**	**LCMS** (AM11): rt = 0.447 min, (662.5 $[M+H]^+$), 98.5% purity. **Purification Method** PM173
 6-(pyridin-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine **2.313**	tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-oxo-3-((3-((6-(pyridin-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)amino)propyl)amino)propyl)carbamate **2.324**	**LCMS** (AM12): rt = 0.517 min, (648.1 $[M+H]^+$), 80.48% purity. **Purification Method** PM174

 6-(1,2,4-oxadiazol-5-yl)-1H-indazol-4-amine **2.335**	tert-butyl (3-((3-((6-(1,2,4-oxadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate **2.336**	**LCMS** (AM12): rt = 0.619 min, (638.4 $[M+H]^+$), 82.50% purity. **Purification Method** PM176
 6-(1,2,4-thiadiazol-5-yl)-1H-indazol-4-amine **2.373**	tert-butyl (3-((3-((6-(1,2,4-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate **2.374**	**LCMS** (AM11): rt = 0.525 min, (676.5 $[M+Na]^+$), 75.49% purity. **Purification Method** PM144
 6-(oxazol-5-yl)-1H-indazol-4-amine **2.388**	tert-butyl 3-chloro-4-(trifluoromethoxy)benzyl(3-((3-((6-(oxazol-5-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.389**	**LCMS** (AM11): rt = 0.596 min, (637.5 $[M+H]^+$), 89.3% purity **Purification Method** PM192

 1H-indazol-4-amine	tert-butyl (3-((3-((1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate **2.390**	**LCMS** (AM16): rt = 0.802 min, (570.2, $[M+H]^+$), 93.9% purity. **Purification Method** PM1131
 6-(3-methylpyridin-4-yl)-1H-indazol-4-amine **2.392**	tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((6-(3-methylpyridin-4-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.393**	**LCMS** (AM11): rt = 0.417 min, (661.5, $[M+H]^+$), 92.0% purity. **Purification Method** PM1194

Synthesis of Intermediate 1.953

1-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-4-amine 1.952

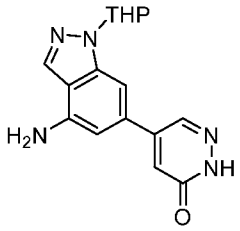


[00646] To a solution of **compound 1.381** (1.71 g, 5.77 mmol) in dioxane (30 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.76 g, 6.93 mmol) followed by KOAc (1.13 g, 11.55 mmol) and $Pd(dppf)Cl_2$ (422.48 mg, 577.39 µmol). The mixture was degassed and purged with N_2 (x3), then the mixture heated to 90°C and stirred for 3 h. The reaction mixture was cooled to 20°C, diluted with EA (90mL) and filtered. The filter cake was washed with EA (40mL × 2) and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM39) to afford **compound 1.952** (1.96 g, 3.78 mmol, 65.46% yield) as a brown oil.

[00647] **LCMS** (AM11): rt = 0.444 min, (344.1 $[M+H]^+$), 66.19% purity.

[00648] **^{1}H NMR** (400 MHz, $CHCl_3$-*d*) δ 8.00 (s, 1 H), 7.43 (s, 1 H), 6.80 (s, 1 H), 5.73 (dd, *J* = 10.0 Hz, 2.4 Hz, 1 H), 4.10 - 4.05 (m, 1 H), 3.81 - 3.70 (m, 1 H), 3.67 (br s, 2 H), 2.61 - 2.57 (m, 1 H), 2.16 - 2.10 (m, 1 H), 2.05 - 1.92 (m, 1 H), 1.81 - 1.71 (m, 2 H), 1.67 - 1.58 (m, 1 H), 1.37 (s, 12 H) ppm.

5-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)pyridazin-3(2H)-one 1.953

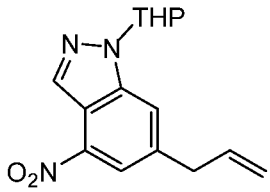


[00649] To a solution of **compound 1.952** (500 mg, 1.46 mmol) in dioxane (5 mL) and H_2O (1 mL) was added 5-chloropyridazin-3(*2H*)-one (190.15 mg, 1.46 mmol), K_2CO_3 (604.00 mg, 4.37 mmol) and Pd(dppf)Cl_2 (106.59 mg, 145.68 µmol). The mixture was stirred at 100 °C for 16 h under N_2. The reaction mixture was poured onto H_2O (10 mL) and extracted with EA (10 mL × 3). The combined organic phase was washed (brine, 10 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was triturated with EA (5 mL) at 20 °C for 10 minutes, filtered and the filter cake was dried under vacuum, to afford **compound 1.953** (176 mg, 463.55 µmol, 31.82% yield) as a brown solid.

[00650] **LCMS** (AM16): rt = 0.436 min, (312.2 $[M+H]^+$), 82.51% purity.

Synthesis of Intermediate 1.995

6-allyl-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 1.991



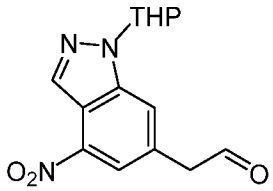
[00651] To a mixture of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (WO2019027960, 1 g, 3.07 mmol) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (772.85 mg, 4.60 mmol) in dioxane (12 mL) and H_2O (3 mL) under N_2 was added K_2CO_3 (1.27 g, 9.20 mmol) followed by Pd(dppf)Cl_2 (224.35 mg, 306.61 µmol). The mixture was heated to 80 °C and stirred for 2 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM139) to afford **compound 1.991** (800 mg, 2.45 mmol, 79.92% yield) as a brown oil.

[00652] **LCMS** (AM14): rt = 0.684 min, (288.2 $[M+H]^+$), 88.08% purity.

[00653] **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.14 (s, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 6.13 - 6.03 (m, 1H), 6.00 (dd, *J* = 9.6, 2.4 Hz, 1H), 5.24 - 5.15 (m, 2H), 3.88 (br s, 1H),

3.83 - 3.74 (m, 1H), 3.68 (d, *J* = 6.8 Hz, 2H), 2.46 - 2.37 (m, 1H), 1.81 - 1.71 (m, 1H), 1.64 - 1.59 (m, 2H) ppm.

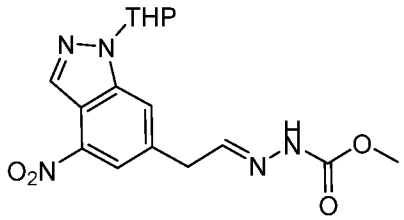
2-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)acetaldehyde 1.992



[00654] To a solution of **compound 1.991** (466 mg, 1.14 mmol, 70% purity) in THF (20 mL) and H_2O (10 mL) at 0 °C was added K_2OsO_4•$2H_2O$ (83.67 mg, 227.07 µmol) and $NaIO_4$ (728.52 mg, 3.41 mmol) portionwise and the mixture stirred at 0 °C for 1 h. The mixture was poured into water (100 mL) and extracted with EA (80 mL × 3). The combined organic phase was washed with Na_2SO_3 aqueous solution (40 mL × 2) and brine (40 mL × 4), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM38) to afford **compound 1.992** (644 mg, 2.23 mmol, 32.68% yield) as a yellow solid.

[00655] **^{1}H NMR** (400 MHz, $CHCl_3$-*d*) δ 9.93 - 9.86 (m, 1H), 8.63 (s, 1H), 8.04 (s, 1H), 7.85 (s, 1H), 5.81 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.01 (d, *J* = 1.2 Hz, 2H), 4.00 - 3.93 (m, 1H), 3.82 - 3.74 (m, 1H), 2.60 - 2.49 (m, 1H), 2.24 - 2.13 (m, 2H), 1.81 - 1.70 (m, 3H) ppm.

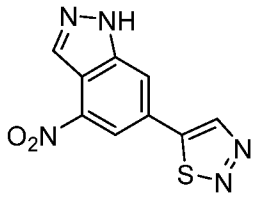
methyl 2-(2-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)ethylidene)hydrazine-1-carboxylate 1.993



[00656] To a solution of **compound 1.992** (644 mg, 2.23 mmol) and ethyl N-aminocarbamate (254.94 mg, 2.45 mmol) in EtOH (15 mL) was added HOAc (133.68 mg, 2.23 mmol) at 20 °C, then the mixture was heated to 50 °C and stirred for 0.5 h. The mixture was concentrated in *vacuo* to afford **compound 1.993** (800 mg, 2.13 mmol, 95.73% yield) as a yellow solid.

[00657] **LCMS** (AM11): rt = 0.413 min, (291.8 $[M+H]^+$), 81.95% purity.

5-(4-nitro-1H-indazol-6-yl)-1,2,3-thiadiazole 1.994

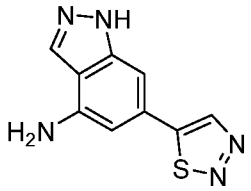


[00658] A solution of **compound 1.993** (800 mg, 2.13 mmol) in $SOCl_2$ (10 mL) was stirred at 80 °C for 0.5 h. The reaction mixture was concentrated in *vacuo* to give a residue. Saturated $NaHCO_3$ aq. solution (40 mL) was added and the mixture extracted with EA (40 mL × 2). The combined organic phase was washed (brine, 20 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM140) to afford **compound 1.994** (200 mg, 760.17 µmol, 35.67% yield) as a yellow solid.

[00659] **LCMS** (AM12): rt = 0.419 min, (247.9 $[M+H]^+$), 93.97% purity.

[00660] **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.23 (br s, 1H), 9.68 (s, 1H), 8.62 (s, 1H), 8.55 - 8.46 (m, 2H) ppm.

6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-amine 1.995



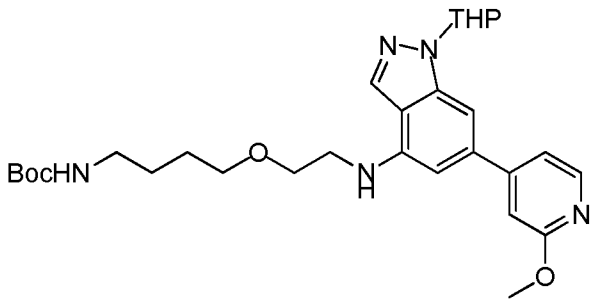
[00661] To a mixture of **compound 1.994** (70 mg, 283.13 µmol) in EA (2 mL) was added $SnCl_2•2H_2O$ (191.66 mg, 849.40 µmol). The mixture was heated to 70 °C and stirred for 0.5 h. The reaction mixture was poured into water (20 mL) and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 20 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was triturated with EA (2 mL) at 20 °C for 5 min. The filter cake was dried *in vacuo* to afford **compound 1.995** (60 mg, 207.13 µmol, 73.16% yield) as a yellow solid.

[00662] **LCMS** (AM11): rt = 0.275 min, (218.0 $[M+H]^+$), 75.30% purity.

[00663] **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 9.32 (s, 1H), 8.17 (s, 1H), 7.10 (s, 1H), 6.44 (s, 1H), 6.12 (s, 2H) ppm.

Synthesis of Intermediate 2.001

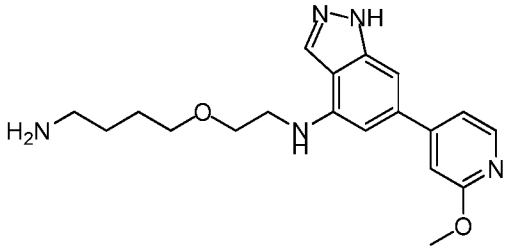
tert-butyl (4-(2-((6-(2-methoxypyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 2.000



To a solution of **compound 1.893** (0.68 g, 1.10 mmol) in dioxane (5 mL) and H_2O (0.5 mL) was added K_2CO_3 (305.40 mg, 2.21 mmol), 2-methoxypyridin-4-yl)boronic acid (311.68 mg, 1.33 mmol) and Brettphos Pd G3 (100.16 mg, 0.11 mmol), the mixture was stirred at 80 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM239) to afford **compound 2.000** (550 mg, 84.5% yield) as a light-yellow solid.

LCMS (AM3): rt = 0.846 min, (540.2 $[M+H]^+$), 91.6% purity.

N-(2-(4-aminobutoxy)ethyl)-6-(2-methoxypyridin-4-yl)-1H-indazol-4-amine 2.001

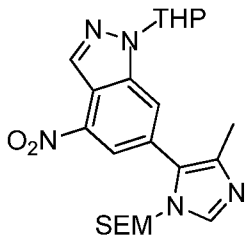


To a solution of **compound 2.000** (500 mg, 0.92 mmol) in DCM (10 mL) was added TFA (15.40 g, 135.06 mmol), the mixture was stirred at RT for 0.5 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM106). H_2O (30 mL) was added and the mixture adjusted to pH= 7-8 (sat. $NaHCO_3$ (aq.)) and extracted with EA (50 mL × 2). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.001** (230 mg, 64.6% yield) as light-yellow oil.

LCMS (AM3): rt = 0.603 min, (356.2 $[M+H]^+$), 92.5% purity

Synthesis of Intermediate 2.006

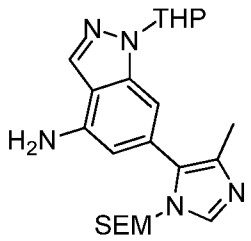
6-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.003



To a solution of **compound 1.943** (0.5 g, 1.34 mmol) in dioxane (10 mL) and H_2O (1 mL) was added K_2CO_3 (370.32 mg, 2.68 mmol), 4-bromo-5-methyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-imidazole (CAS 1222175-06-5, 468.25 mg, 1.61 mmol) and Brettphos G3 (121.45 mg, 0.13 mmol). The mixture was stirred at 80 °C for 12 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM142) to afford **compound 2.003** (280 mg, 43.2% yield) as light-yellow oil.

LCMS (AM3): rt =0.835 min, (458.3 $[M+H]^+$), 94.7% purity.

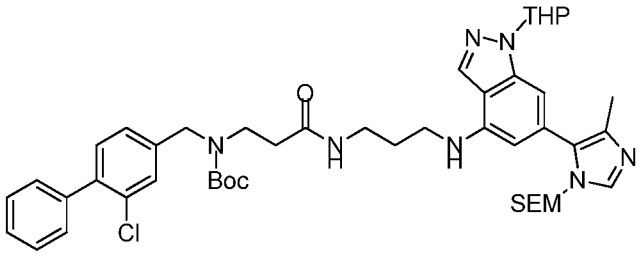
6-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.004



To a solution of **compound 2.003** (260 mg, 0.57 mmol) in THF (10 mL) was added Pd/C (260 mg, 0.056 mmol, 10% purity) under N_2. The suspension was degassed and purged with H_2 (x3). The mixture was stirred at 25 °C for 12 h under H_2 (15 Psi). The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM144) to afford **compound 2.004** (210 mg, 73.6% yield) as a light-yellow oil.

LCMS (AM3): rt = 0.854 min, (428.3 $[M+H]^+$), 85.2% purity.

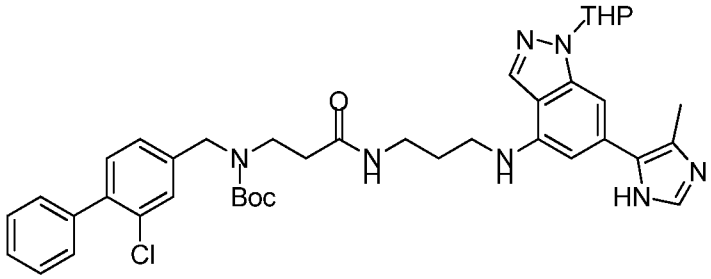
tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-5-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.005



To a solution of **compound 2.004** (200 mg, 0.39 mmol) in MeOH (10 mL) was added **Intermediate H** (265.96 mg, 0.59 mmol). After 11 h, $NaBH_3CN$ (250.42 mg, 3.98 mmol) was added. The mixture was stirred at 25 °C for 1 h. The resultant mixture was then concentrated in *vacuo* to give a residue, which was purified (PM145) to afford **compound 2.005** (160 mg, 41.3% yield) as a light-yellow oil.

LCMS (AM3): rt = 0.921 min, (856.2 $[M+H]^+$), 88.2% purity.

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(4-methyl-1H-imidazol-5-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.006

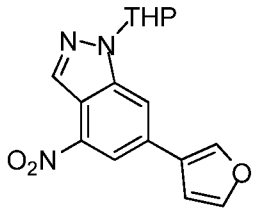


Compound 2.005 (150 mg, 0.15 mmol) was dissolved in THF (5 mL) and TBAF (1 M, 1.54 mL) was added. The mixture was stirred at 70 °C for 1 h. The resultant mixture was concentrated in *vacuo* to give a residue, which was purified (PM146) to afford **compound 2.006** (50 mg, 38.2% yield) as a light-yellow oil.

LCMS (AM3): rt = 0.842 min, (726.2 $[M+H]^+$), 85.8% purity.

Synthesis of Intermediate 2.008

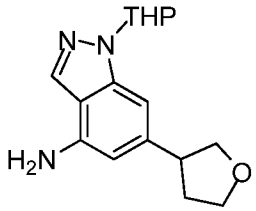
6-(furan-3-yl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.007



To a solution of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (WO2019027960, 400 mg, 1.23 mmol) in dioxane (10 mL) and H_2O (1 mL) was added K_3PO_4 (520.67 mg, 2.45 mmol), furan-3-ylboronic acid (164.67 mg, 1.47 mmol) and $Pd(dppf)Cl_2$ (89.74 mg, 0.122 mmol). The mixture was stirred at 80 °C for 12 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM46) to afford **compound 2.007** (320 mg, 83.2% yield) as a yellow solid.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 8.54 (s, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 8.21 (s, 1 H), 7.68 (s, 1H), 7.05 (s, 1H), 6.02 (dd, *J* = 9.2, 2.8 Hz, 1H), 4.02 - 3.99 (m, 2H), 3.93 - 3.89 (m, 2H), 2.58 - 2.55 (m, 2H), 2.17 - 2.16 (m, 1H), 2.13 - 2.12 (m, 1H), 1.88 - 1.86 (m, 1H), 1.75 - 1.71 (m, 2H) ppm

1-(tetrahydro-2H-pyran-2-yl)-6-(tetrahydrofuran-3-yl)-1H-indazol-4-amine 2.008

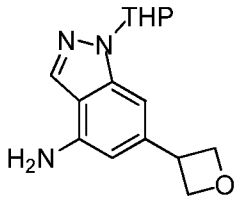


To a solution of **compound 2.007** (320 mg, 1.02 mmol) in MeOH (10 mL) was added Pd/C (0.3 g, 0.102 mmol, 10% purity) under N_2. The suspension was degassed and purged with H_2 (x3). The mixture was stirred at 25 °C for 12 h under H_2 (15 psi). The mixture was neutralized to pH = 7 with formic acid. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM39) to afford **compound 2.008** (260 mg, 84.7% yield) as a red oil.

LCMS (AM3): rt =0.768 min, (288.1 $[M+H]^+$), 95.7% purity.

Synthesis of Intermediate 2.010

6-(oxetan-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.010



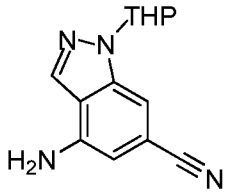
To a 8 mL vial equipped with a stir bar was added **compound 1.381** (500 mg, 1.69 mmol), 3-bromooxetane (300.62 mg, 2.19 mmol), $NiCl_2$.dtbbpy (3.36 mg, 0.008 mmol), bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridyl]phenyl]iridium(1+);4-tertbutyl-

2-(4-tert-butyl-2-pyridyl) pyridine; hexafluorophosphate (18.94 mg, 0.017 mmol), bis(trimethylsilyl)silyl-trimethyl-silane (419.80 mg, 1.69 mmol) and Na_2CO_3 (357.87 mg, 3.38 mmol) and DME (10 mL). The vial was purged with N_2 and sealed. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away) with cooling fan to keep the reaction temperature at 25 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM102) to afford **compound 2.010** (180 mg, 18.7% yield) as a black-brown oil.

LCMS (AM3): rt = 0.768 min, (274.1 $[M+H]^+$), 48.0% purity.

Synthesis of Intermediate 2.014

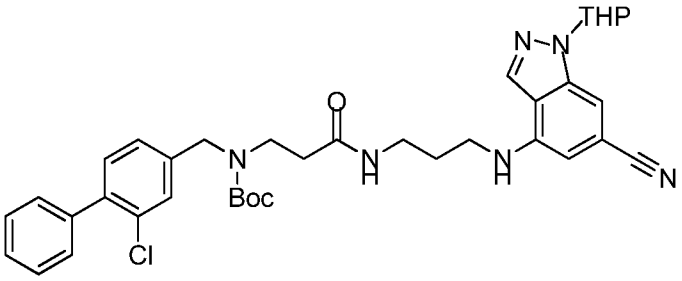
4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carbonitrile 2.012



To a solution of **compound 1.381** (1 g, 3.38 mmol) in DMF (10 mL) was added $Pd(PPh_3)_4$ (390.18 mg, 0.34 mmol) and $Zn(CN)_2$ (1.19 g, 10.13 mmol). The mixture was stirred at 100 °C for 12 h under N_2. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM44) to afford **compound 2.012** (730 mg, 74.7% yield) as a light-yellow oil.

LCMS (AM3): rt = 0.637 min, (242.9 $[M+H]^+$), 83.8% purity.

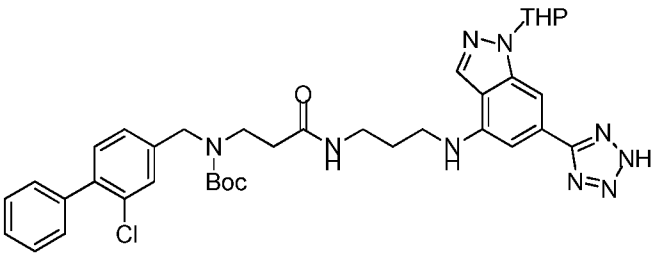
tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.013



To a solution of **compound 2.012** (400 mg, 1.38 mmol) in MeOH (1 mL) was added **Intermediate H** (1.09 g, 2.08 mmol). 1 h later, $NaBH_3CN$ (869.45 mg, 13.84 mmol) was added. The mixture was stirred at 25 °C for 11 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM90) to afford **compound 2.013** (520 mg, 54.9% yield) as black-brown oil.

LCMS (AM3): rt = 1.137 min, (671.4 $[M+H]^+$), 98.2% purity.

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((1-(tetrahydro-2H-pyran-2-yl)-6-(2H-tetrazol-5-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 2.014

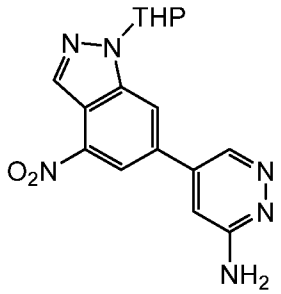


To a solution of **compound 2.013** (470 mg, 0.70 mmol) in DMF (4 mL) was added NaN_3 (910.41 mg, 14.0 mmol) and NH_4Cl (749.10 mg, 14.0 mmol). The mixture was stirred at 100 °C for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM104) to afford **compound 2.014** (200 mg, 0.27 mmol, 38.4% yield) as a yellow solid.

LCMS (AM3): rt = 1.042 min, (714.3 $[M+H]^+$), 96.2% purity.

Synthesis of Intermediate 2.016

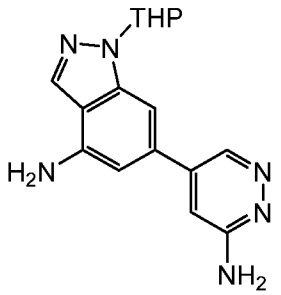
5-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)pyridazin-3-amine 2.015



To a solution of **compound 1.943** (100 mg, 267.95 µmol) in dioxane (1 mL) and H_2O (0.1 mL) was added 5-chloropyridazin-3-amine (34.71 mg, 267.95 µmol), K_2CO_3 (111.10 mg, 803.84 µmol) and $Pd(dppf)Cl_2$ (19.61 mg, 26.79 µmol) at 20°C. The reaction mixture was degassed and purged with nitrogen for 3 times and stirred at 80 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM23) to afford **compound 2.015** (90 mg, 264.44 µmol, 98.69% yield) as a yellow solid.

LCMS (AM3): rt = 0.780 min, (340.8 $[M+H]^+$), 57.26% purity.

6-(6-aminopyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.016

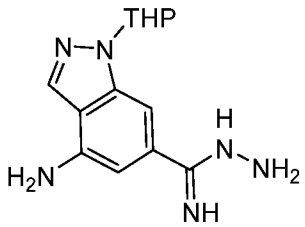


To a solution of **compound 2.015** (90 mg, 264.44 µmol) in EtOH (1 mL) and H_2O (0.2 mL) was added Fe (73.84 mg, 1.32 mmol) and NH_4Cl (70.73 mg, 1.32 mmol) at 25°C. The mixture was stirred at 80°C for 2 h. The mixture was filtered and the filter cake was washed with EtOH (10 mL × 3). The combined filtrate was concentrated in *vacuo* to afford **compound 2.016** (100 mg, crude) as a yellow solid.

LCMS (AM3): rt = 0.385 min, (311.2 $[M+H]^+$), 92.27% purity

Synthesis of Intermediate 2.021

4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboximidhydrazide 2.018

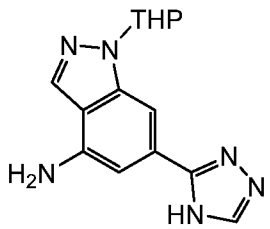


To a mixture of **compound 2.012** (800 mg, 3.30 mmol) in NaOMe (2.45 M, 10 mL) was added $NH_2NH_2.H_2O$ (3.52 g, 70.27 mmol, 3.42 mL). The mixture was stirred at 80°C for 12 hours. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM105) to afford **compound 2.018** (700 mg, 2.14 mmol, 64.90% yield, 98.068% purity, FA salt) as an off-white solid.

LCMS (AM5): rt = 0.631 min, (275.2 $[M+H]^+$), 98.068% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 2H), 8.13 (s, 1H), 7.09 (s, 1H), 6.58 (s, 1H), 5.91 (br. s, 2H), 5.67 - 5.64 (m, 1H), 3.88 - 3.80 (m, 1H), 3.71 - 3.68 (m, 1H), 2.03 - 2.00 (m, 1H), 1.90 - 1.87 (m, 1H), 1.72 - 1.70 (m, 1H), 1.57 - 1.56 (m, 3H) ppm.

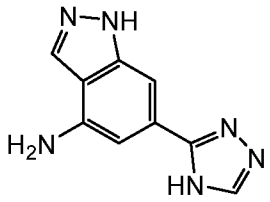
1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-3-yl)-1H-indazol-4-amine 2.019



A solution of **compound 2.018** (700 mg, 2.19 mmol, FA salt) and trimethoxymethane (1.16 g, 10.93 mmol, 1.20 mL) in EtOH (10 mL) was stirred at 80°C for 5 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM106) to afford **compound 2.019** (200 mg, 703.44 μmol, 32.19% yield) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.23 (s, 1H), 8.21 (s, 1H), 7.47 (s, 1H), 7.00 (s, 1H), 6.06 (s, 1H), 5.77 (dd, J = 10.0, 2.0 Hz, 1H), 3.98 - 3.95 (m, 1H), 3.82 - 3.77 (m, 1H), 2.48 - 2.45 (m, 1H), 2.11 - 2.07 (m, 1H), 2.02 - 1.96 (m, 1H), 1.84 - 1.82 (m, 1H), 1.65 - 1.64 (m, 2H) ppm.

6-(4H-1,2,4-triazol-3-yl)-1H-indazol-4-amine 2.020

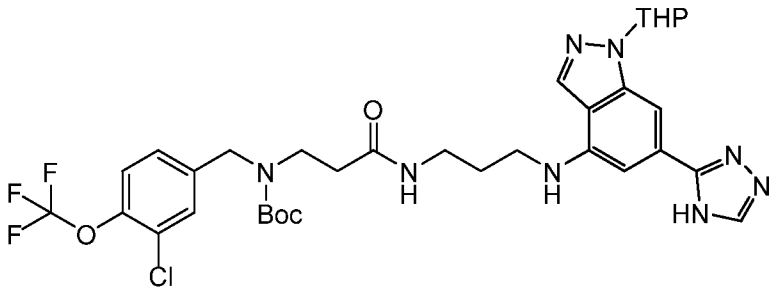


To a solution of **compound 2.019** (20 mg, 70.34 μmol) in DCM (0.5 mL) was added TFA (770.00 mg, 6.75 mmol, 0.5 mL) dropwise. The reaction was stirred at 25°C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM107) to afford **compound 2.020** (3.55 mg, 17.73 μmol, 25.21% yield) as an off-white solid.

LCMS (AM5): rt = 0.372 min, (201.1 $[M+H]^+$), 100.00% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*): *δ* 8.30 (s, 1H), 8.13 (s, 1H), 7.44 (s, 1H), 6.92 (s, 1H) ppm.

tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-oxo-3-((3-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-3-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 2.021

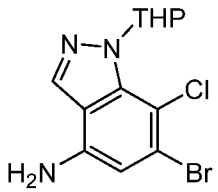


To a solution of **compound 2.020** (70 mg, 164.94 μmol, 66.994% purity) and **compound 1.325** (74.69 mg, 164.94 μmol) in MeOH (1 mL) was added $MgSO_4$ (99.27 mg, 824.70 μmol) and AcOH (9.90 mg, 164.94 umol, 9.43 μL). The reaction was stirred at 20°C for 12 h. $NaBH_3CN$ (36.28 mg, 577.29 μmol) was added and the mixture was stirred at 20°C for 2 h. The mixture was filtered and the filter cake was washed with methanol (10 mL × 3). The combined filtrate was concentrated in *vacuo* to give a residue, which was purified (PM91) to afford **compound 2.021** (70 mg, 82.26 μmol, 49.87% yield) as an off-white solid.

LCMS (AM7): rt = 0.909 min, (721.2 $[M+H]^+$), 84.751% purity.

Synthesis of Intermediate 2.026

6-bromo-7-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.023

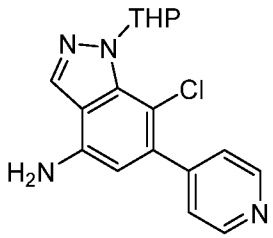


To a solution of **compound 1.381** (3.08 g, 10.40 mmol) in DMF (30 mL) was added NCS (1.53 g, 11.44 mmol) at 0°C. The resulting mixture was stirred at 0°C for 1 h. Water (100 mL) was added and the mixture was extracted with EA (150 mL × 3). The combined organic phase was washed (brine, 100 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM39) to afford **compound 2.023** (1 g, 2.90 mmol, 27.89% yield) as a brown oil.

LCMS (AM3): rt = 0.915 min, (354.0 $[M+Na]^+$), 95.90% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) *δ* 7.93 (s, 1H), 6.66 (s, 1H), 6.39 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.04 - 4.02 (m, 1H), 3.82 - 3.74 (m, 1H), 2.66 - 2.57 (m, 1H), 2.17 - 2.10 (m, 2H), 1.79 - 1.60 (m, 3H) ppm.

7-chloro-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.024

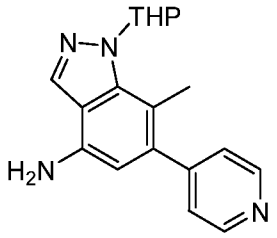


To a solution of **compound 2.023** (1 g, 3.02 mmol) and pyridin-4-yl boronic acid (371.79 mg, 3.02 mmol) in dioxane (10 mL) and H_2O (1 mL) was added K_2CO_3 (836.07 mg, 6.05 mmol) and $Pd(dppf)Cl_2$ (221.32 mg, 302.47 μmol) at 20°C under N_2. The mixture was heated to 90°C and stirred for 16 h. Water (30 mL) was added and the mixture was extracted with EA (50 mL × 3). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM30) to afford **compound 2.024** (300 mg, 886.08 μmol, 29.29% yield) as a yellow solid.

LCMS (AM3): rt = 0.710 min, (329.1 $[M+H]^+$), 97.113% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*): δ 8.68 (d, *J* = 6.0 Hz, 2H), 8.03 (s, 1H), 7.36 (d, *J* = 4.4 Hz, 2H), 6.46 (dd, *J* = 10.4, 2.0 Hz, 1H), 6.31 (s, 1H), 4.20 (br. s, 2H), 4.08 - 4.04 (m, 1H), 3.80 - 3.77 (m, 1H), 2.68 - 2.66 (m, 1H), 2.16 - 2.13 (m, 2H), 1.79 - 1.74 (m, 2H), 1.63 - 1.60 (m, 1H) ppm.

7-methyl-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.025

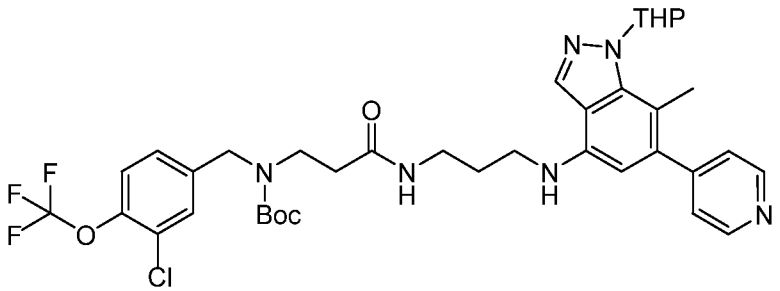


To a solution of **compound 2.024** (240 mg, 729.94 μmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.83 g, 7.30 mmol, 2.04 mL, 50% purity in THF) in DMF (5 mL) was added K_2CO_3 (302.65 mg, 2.19 mmol) and $Pd(dppf)Cl_2$ (53.41 mg, 72.99 μmol) under N_2 at 20°C. The mixture was stirred at 100°C for 16 h. The mixture was cooled to 20°C. 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (458.16 mg, 3.65 mmol, 510.20 μL, 50% purity in THF), K_2CO_3 (201.76 mg, 1.46 mmol) and $Pd(dppf)Cl_2$ (53.41 mg, 72.99 μmol) was added. The mixture was stirred at 100°C for 16 h. Water (30 mL) was added and the mixture was extracted with EA (40 mL × 3). The combined organic phase was washed (brine, 50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM37) to afford **compound 2.025** (220 mg, 661.52 μmol, 90.63% yield) as a yellow solid.

LCMS (AM3): rt = 0.651 min, (309.2$[M+H]^+$), 90.630% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*): δ 8.66 - 8.65 (m, 2H), 8.00 (s, 1H), 7.28 - 7.27 (m, 2H), 6.25 (s, 1H), 5.91 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.06 - 4.03 (m, 1H), 3.74 - 3.71 (m, 1H), 2.76 - 2.74 (m, 1H), 2.48 (s, 3H), 2.21 - 2.15 (m, 2H), 1.78 - 1.72 (m, 3H) ppm.

tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((7-methyl-6-(pyridin-4-yl)-1- (tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.026



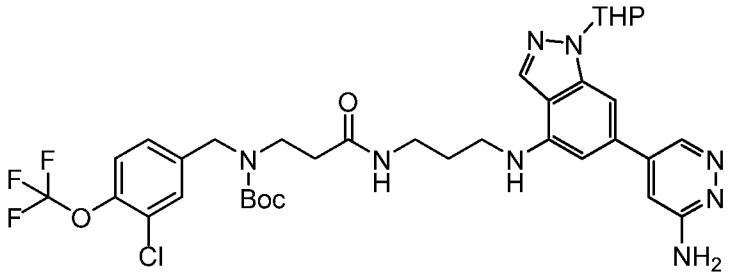
A solution of **compound 1.325** (88.11 mg, 194.57 μmol) and **compound 2.025** (50 mg, 162.14 μmol) in MeOH (0.5 mL) was stirred at 20°C for 12 h. To the mixture was added $NaBH_3CN$ (30.57 mg, 486.42 μmol) and the reaction was stirred at 20°C for 2 h. The

mixture was concentrated in *vacuo* to give a residue, which was purified (PM147) to afford **compound 2.026** (50 mg, 58.21 μmol, 35.90% yield) as a yellow oil.

LCMS (AM7): rt = 1.105 min, (745.3 $[M+H]^+$), 86.753% purity.

Synthesis of Intermediate 2.027

tert-butyl (3-((3-((6-(6-aminopyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl) amino)propyl)amino)-3-oxopropyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate 2.027

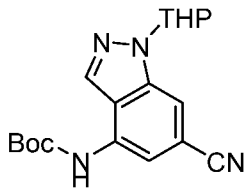


A solution of **compound 2.016** (50 mg, 122.83 μmol, 76.244% purity) and **compound 1.325** (66.75 mg, 147.40 μmol) in MeOH (0.5 mL) was stirred at 30°C for 12 h. To the mixture was added $NaBH_3CN$ (23.16 mg, 368.50 μmol) and the mixture was stirred at 30°C for 2 h. Water (1 mL) was added and the mixture was purified (PM148) to afford **compound 2.027** (40 mg, 46.52 μmol, 37.87% yield, 86.895% purity) as a yellow solid.

LCMS (AM7): rt = 1.057 min, (747.1 $[M+H]^+$), 86.895% purity.

Synthesis of Intermediate 2.038

tert-butyl (6-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)carbamate 2.034

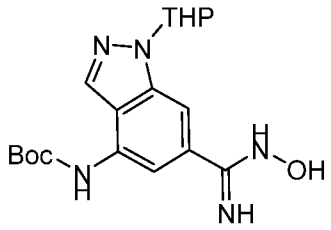


To a solution of **compound 2.012** (800 mg, 3.30 mmol) and DMAP (40.34 mg, 330.20 μmol) in DCM (1 mL) was added $(Boc)_2O$ (1.08 g, 4.95 mmol, 1.14 mL) at 0°C. The mixture was stirred at 20°C for 1 h. The reaction mixture was concentrated in *vacuo* to remove solvent. Water (10 mL) was added and extracted with EA (30 mL × 3). The combined organic layers were washed (brine, 50 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which

was purified (PM35) to afford **compound 2.034** (600 mg, 1.70 mmol, 45.86% yield) as a yellow oil.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.20 - 8.19 (m, 1H), 8.02 - 7.98 (m, 1H), 7.38 (d, J = 0.8 Hz, 1H), 5.77 - 5.75 (m, 1H), 4.02 - 3.98 (m, 1H), 3.80 - 3.75 (m, 1H), 2.47 - 2.44 (m, 1H), 2.14 - 2.11 (m, 2H), 1.78 - 1.71 (m, 3H), 1.39 (s, 9H) ppm.

tert-butyl (6-(N-hydroxycarbamimidoyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl) carbamate 2.035

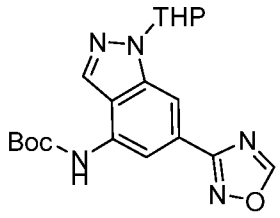


To a solution of $NH_2OH.HCl$ (25.37 mg, 365.08 μmol) and KOAc (35.83 mg, 365.08 μmol) in EtOH (1 mL) and H_2O (0.2 mL) was added **compound 2.034** (100 mg, 292.06 μmol) at 20°C. The mixture was stirred at 70°C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM143) to afford **compound 2.035** (50 mg, 97.66 μmol, 26.75% yield, FA salt) as an off-white solid.

LCMS (AM3): rt = 0.772 min, (375.9 $[M+H]^+$), 82.318% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.99 (s, 1H), 7.63 (s, 1H), 5.78 - 5.76 (m, 1H), 3.91 - 3.89 (m, 1H), 3.76 - 3.73 (m, 1H), 2.43 - 2.39 (m, 1H), 2.05 - 2.02 (m, 1H), 1.94 - 1.91 (m, 1H), 1.58 - 1.56 (m, 3H), 1.51 (s, 9H) ppm.

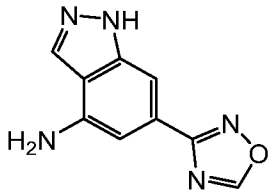
tert-butyl (6-(1,2,4-oxadiazol-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)carbamate 2.036



A solution of **compound 2.035** (50 mg, 118.64 μmol, FA salt) and trimethoxymethane (100.72 mg, 949.11 μmol, 104.05 μL) in EtOH (2 mL) was stirred at 80°C for 5 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM38) to afford **compound 2.036** (20 mg, 47.60 μmol, 40.12% yield) as a colourless oil.

LCMS (AM3): rt = 0.856 min, (386.3 $[M+H]^+$), 91.72% purity.

6-(1,2,4-oxadiazol-3-yl)-1H-indazol-4-amine 2.037

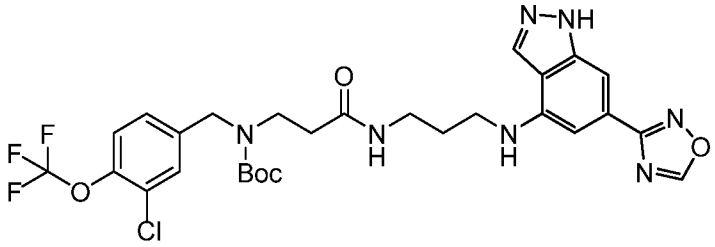


To a solution of **compound 2.036** (20 mg, 51.89 μmol) in DCM (0.5 mL) was added TFA (770.00 mg, 6.75 mmol, 0.5 mL). The mixture was stirred at 20°C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was adjusted to pH = 8 with DIPEA and then purified (PM86) to afford **compound 2.037** (3.41 mg, 16.81 μmol, 32.39% yield) as a yellow solid.

LCMS (AM3): rt = 0.275 min, (202.0 $[M+H]^+$), 99.16% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 9.23 (s, 1H), 8.15 (s, 1H), 7.56 (s, 1H), 7.03 (s, 1H) ppm.

tert-butyl (3-((3-((6-(1,2,4-oxadiazol-3-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl) (3-chloro-4-(trifluoromethoxy)benzyl)carbamate 2.038

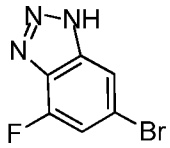


A solution of **compound 2.037** (50 mg, 185.31 μmol, 74.564% purity) and **compound 1.325** (83.92 mg, 185.31 μmol) in MeOH (0.5 mL) was stirred at 30°C for 12 h. To the mixture was added $NaBH_3CN$ (34.94 mg, 555.94 μmol) and the mixture was stirred at 30°C for 2 h. The mixture was diluted with MeOH (1 mL) and purified (PM149) to afford **compound 2.038** (50 mg, 68.37 μmol, 36.90% yield) as a yellow oil

LCMS (AM7): rt = 1.052 min, (638.0 $[M+H]^+$), 87.25% purity.

Synthesis of Intermediate 2.045

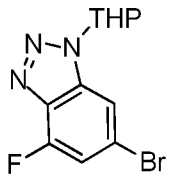
6-bromo-4-fluoro-1H-benzo[d][1,2,3]triazole 2.040



To a solution of 5-Bromo-3-fluorobenzene-1,2-diamine (CAS 517920-69-3, 9.3 g, 45.36 mmol) in AcOH (35 mL) and H_2O (100 mL) was added a solution of $NaNO_2$ (3.44 g, 49.90 mmol) at 20 °C, then the mixture was stirred at 65 °C for 1 h. The reaction mixture was adjusted to pH = 8~9 by saturated $NaHCO_3$ solution and extracted with EA (150 mL × 2). The combined organic layers were washed (brine, 100 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.040** (9.7 g, 44.91 mmol, 99.00% yield) as a black-brown solid, which was used for the next step directly without further purification.

LCMS (AM3): rt = 0.794 min, (218.1 $[M+H]^+$), 100% purity

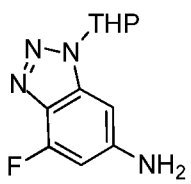
6-bromo-4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazole 2.041



To a solution of DHP (18.89 g, 224.55 mmol, 20.53 mL) and **compound 2.040** (9.7 g, 44.91 mmol) in DCM (150 mL) was added TsOH (773.36 mg, 4.49 mmol). The mixture was stirred at 20°C for 20 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM59) to afford **compound 2.041** (11.4 g, 37.98 mmol, 84.58% yield) as a light-yellow solid.

^{1}H NMR (400 MHz, DMSO) δ 8.12 (s, 1H), 7.61 (d, *J* = 10.0 Hz, 1H), 6.21 - 6.17 (m, 1H), 2.50 - 2.43 (m, 2H), 2.20 - 2.02 (m, 2H), 1.69 - 1.65 (m, 2H), 1.65 - 1.61 (m, 2H).

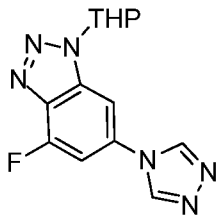
4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-6-amine 2.042



To a solution of **compound 2.041** (5.7 g, 18.99 mmol) in DMSO (75 mL) was added $NH_3.H_2O$ (7.99 g, 56.98 mmol, 8.78 mL, 25% purity), K_2CO_3 (7.87 g, 56.98 mmol), CuI (723.40 mg, 3.80 mmol) and (2R,4R)-4-hydroxypyrrolidine-2-carboxylic acid (996.17 mg, 7.60 mmol). The reaction mixture was stirred at 90°C for 12 h under N_2. The reaction mixture was diluted with H_2O (60 mL) and extracted with EA (80 mL × 2). The combined organic layer was washed (brine, 100 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM25) to afford **compound 2.042** (2.5 g, 10.58 mmol, 55.72% yield) as a yellow oil.

LCMS (AM3): rt = 0.720 min, (237.1 $[M+H]^+$), 75.30% purity

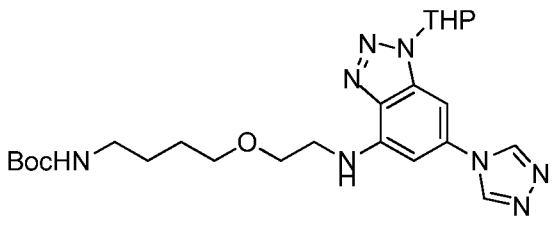
4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazole 2.043



To a solution of N'-formylformohydrazide (4.66 g, 52.91 mmol) and **compound 2.042** (2.5 g, 10.58 mmol) in pyridine (20 mL) was added TEA (7.50 g, 74.08 mmol, 10.31 mL) and TMSCl (17.24 g,158.73 mmol, 20.15 mL). The mixture was stirred at 120 °C for 16 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL × 2). The combined organic layers were washed (brine, 50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM23) to afford **compound 2.043** (1.35 g, 4.68 mmol, 44.25% yield) as a light-yellow solid

LCMS (AM3): rt = 0.794 min, (289.2 $[M+H]^+$), 93.9% purity

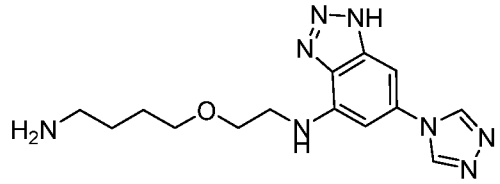
tert-butyl (4-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)ethoxy)butyl)carbamate 2.044



To a solution of **compound 1.461** (1.45 g, 6.24 mmol) and **compound 2.043** (0.9 g, 3.12 mmol) in NMP (10 mL) was added DIPEA (806.98 mg, 6.24 mmol, 1.09mL), then the mixture was stirred at 130 °C for 18 h. The reaction mixture was diluted with water (50 mL) and extracted with EA (75 mL × 2). The combined organic layers were washed (brine, 50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM23) to afford **compound 2.044** (1.50g, 3.00 mmol, 95.98% yield) as a light-yellow oil.

LCMS (AM3): rt = 0.865 min, (501.2 $[M+H]^+$), 75.58% purity

N-(2-(4-aminobutoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine 2.045

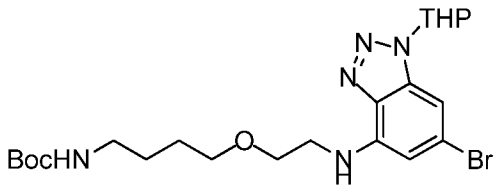


To a solution of **compound 2.044** (1.82 g, 3.64 mmol) in EA (7.5 mL) was added HCl/EA (4 M, 7.46 mL). The mixture was stirred at 0~5 °C for 2 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was triturated with EA at 20 °C for 15 min and filtered. The filter cake was dried *in vacuo* to afford **compound 2.045** (1.55 g, 3.64 mmol, 100.00% yield, HCl salt) as a yellow solid.

LCMS (AM3): rt = 0.250 min, (317.2 $[M+H]^+$), 96.98% purity

Synthesis of Intermediate 2.064

tert-butyl (4-(2-((6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)ethoxy)butyl)carbamate 2.062

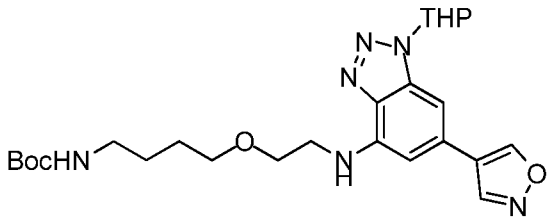


To a solution of tert-Butyl (4-(2-aminoethoxy)butyl)carbamate (CAS 2830620-37-4, 899.86 mg, 3.87 mmol) and **compound 2.041** (775 mg, 2.58 mmol) in NMP (10 mL) was added DIPEA (667.47 mg, 5.16 mmol, 899.56 μL). The mixture was stirred at 140 °C for 18 h. The reaction mixture was diluted with water (50 mL) and extracted with EA (50 mL × 2). The combined organic layers were washed (brine, 30 mL × 2), dried (Na_2SO_4), filtered and

concentrated in *vacuo* to give a residue, which was purified (PM55) to afford **compound 2.062** (640 mg, 1.25 mmol, 48.37% yield) as a light-yellow oil.

LCMS (AM3): rt = 1.066 min, (512.2 $[M+H]^+$), 88.9% purity

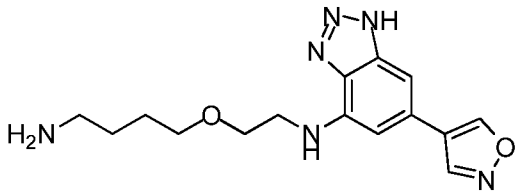
tert-butyl (4-(2-((6-(isoxazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)ethoxy)butyl)carbamate 2.063



To a mixture of **compound 2.062** (640 mg, 1.25 mmol) and isoxazol-4-ylboronic acid (292.28 mg, 1.50 mmol) in DMF (9 mL) and H_2O (3.75 mL) was added KF (217.69 mg, 3.75 mmol, 87.78 μL) and $Pd(dppf)Cl_2$ (91.39 mg, 124.89 μmol). The mixture was stirred at 60 °C for 2.5 h under N_2. The reaction mixture was diluted with water (50 mL) and extracted with EA (75 mL × 2). The combined organic layers were washed (brine, 50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM35) to afford **compound 2.063** (370 mg, 739.13 μmol, 59.18% yield) as a brown oil.

LCMS (AM3): rt = 0.947 min, (501.2 $[M+H]^+$), 100% purity

N-(2-(4-aminobutoxy)ethyl)-6-(isoxazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine 2.064

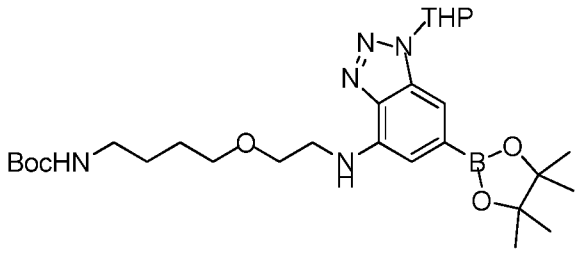


To a solution of **compound 2.063** (720 mg, 1.44 mmol) in EA (5 mL) was added HCl/EA (4 M, 5 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was filtered and the filter cake was dried *in vacuo* to afford **compound 2.064** (320 mg, 822.03 μmol, 57.15% yield, HCl salt) as a yellow solid.

LCMS (AM3): rt = 0.666 min, (317.2 $[M+H]^+$), 93.82% purity

Synthesis of Intermediate 2.067

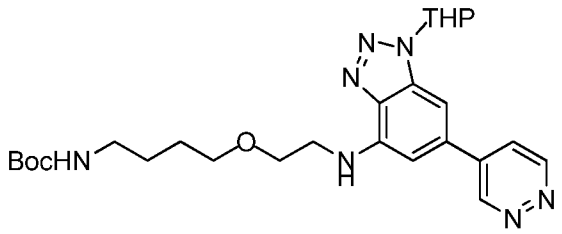
tert-butyl(4-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)ethoxy)butyl)carbamate 2.065



To a mixture of **compound 2.062** (1.5 g, 2.93 mmol) and B_2pin_2 (891.98 mg, 3.51mmol) in 1,4-dioxane (15 mL) was added KOAc (574.55 mg, 5.85 mmol) and $Pd(dppf)Cl_2$ (214.18 mg, 292.72 μmol), then the mixture was stirred at 85 °C for 16 h under N_2. The reaction mixture was diluted with water (30 mL) and extracted with EA (50 mL × 2). The combined organic layers were washed (brine, 300 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM55) to afford **compound 2.065** (1.2 g, 2.14 mmol, 73.27% yield) as a brown oil.

LCMS (AM3): rt = 1.102 min, (560.6 $[M+H]^+$), 77.5% purity

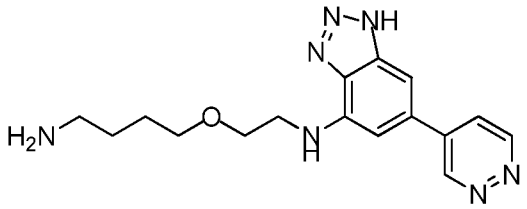
tert-butyl(4-(2-((6-(pyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)ethoxy)butyl)carbamate 2.066



To a mixture of **compound 2.065** (1.15 g, 2.06 mmol) and 4-bromopyridazine (450 mg, 1.88 mmol, HBr salt) in 1,4-dioxane (13.5 mL) and H_2O (1.5 mL) was added K_2CO_3 (777.77 mg, 5.63 mmol) and $Pd(dppf)Cl_2$ (137.26 mg, 187.58umol), then the mixture was stirred at 85 °C for 16 h under N_2. The reaction mixture was diluted with water (50 mL) and extracted with EA (75 mL × 2). The combined organic layers were washed (brine, 50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM23) to afford **compound 2.066** (710mg, 1.39 mmol, 73.98% yield) as a brown oil

LCMS (AM3): rt = 0.950 min, (512.4 $[M+H]^+$), 93.32% purity

N-(2-(4-aminobutoxy)ethyl)-6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine 2.067

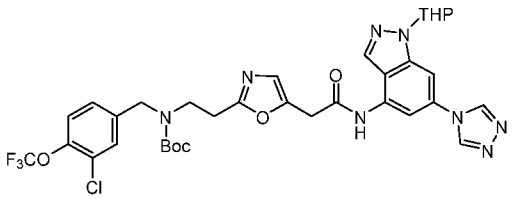


To a solution of **compound 2.066** (788 mg, 1.54 mmol) in EA (5 mL) was added HCl/EA (4 M, 5 mL) at 0~5 °C, then the mixture was stirred at 0-5 °C for 2 h. The mixture was filtered and filter cake was dried *in vacuo* to afford **compound 2.067** (670 mg, 1.53 mmol, 99.60% yield, HCl salt) as a brown solid.

LMS (AM3): rt = 0.662 min, (328.1 $[M+H]^+$), 86.3% purity

Synthesis of Intermediate 2.069

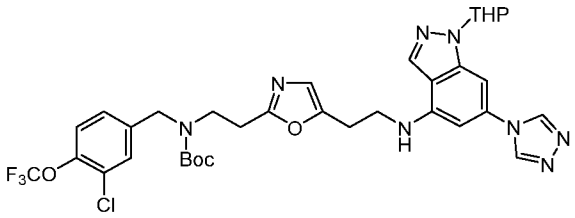
tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(2-(5-(2-oxo-2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)oxazol-2-yl)ethyl)carbamate 2.068



To a mixture of **compound 1.246** (178.13 mg, 0.626 mmol) and **compound 1.273** (300 mg, 0.626 mmol) in THF (5 mL) were added DIPEA (242.91 mg, 1.88 mmol) and T3P (598.03 mg, 0.939 mmol). The mixture was stirred at 20 °C for 12 h. The mixture was diluted with water (30 mL) and extracted with EA (30 mL × 3). The combined organic phase was washed (brine, 90 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM150) to afford **compound 2.068** (80 mg, 107.36 μmol, 17.14% yield) as a white solid.

LCMS (AM3): rt = 1.027 min, (745.3 $[M+H]^+$),100% purity.

tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(2-(5-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)oxazol-2-yl)ethyl)carbamate 2.069

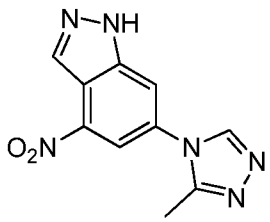


To a mixture of **compound 2.068** (80 mg, 107.36 μmol) in THF (2 mL) was added BH_3-Me_2S (10 M, 0.05 mL) at 0 °C. The mixture was stirred at 20 °C for 36 h. The mixture was quenched with MeOH (5 mL) and followed by NaOH (1N, 5 mL). The mixture was stirred at 60 °C for 4 h, then the mixture was extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified (PM151) to afford **compound 2.069** (50 mg, 68.38 μmol, 63.70% yield) as a grey solid.

LCMS (AM3): rt = 0.862 min, (731.1 $[M+H]^+$),94.9% purity.

Synthesis of Intermediate 2.071

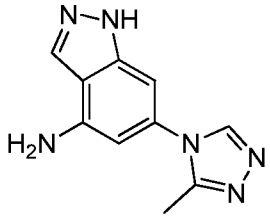
6-(3-methyl-4H-1,2,4-triazol-4-yl)-4-nitro-1H-indazole 2.070



To a mixture of **compound 1.271** (203.38 mg, 2.75 mmol) in ACN (3 mL) was added DMF-DMA (327.14 mg, 2.75 mmol). The mixture was stirred at 50 °C for 0.5 h, then acetohydrazide (600 mg, 2.29 mmol) and HOAc (6.30 g, 104.91 mmol) were added. The mixture was stirred at 120 °C for 16 h. The mixture was adjusted to pH = 8 by saturated Na_2CO_3 solution and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM22) to afford **compound 2.070** (120 mg, 491.38 μmol, 21.48% yield) as a yellow solid.

LCMS (AM3): rt =0.485 min, (244.8 $[M+H]^+$), 90.5% purity.

6-(3-methyl-4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine 2.071

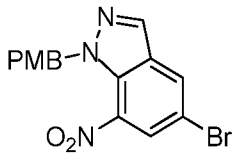


To a solution of **compound 2.070** (120 mg, 491.38 μmol) in MeOH (5 mL) was added Pd/C (30 mg, 10% purity) under N_2. The suspension was degassed and purged with H_2 (x3). The mixture was stirred at 30°C for 4 h under H_2 (15 psi). The catalyst was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.071** (100 mg, crude) as a white solid, which was used directly for the next step.

LCMS (AM5): rt =0.265 min, (215.2 $[M+H]^+$), 85.16% purity.

Synthesis of Intermediate 2.081

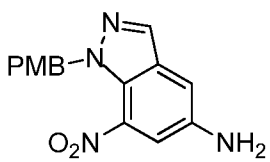
5-bromo-1-(4-methoxybenzyl)-7-nitro-1H-indazole 2.074



To a mixture of 5-Bromo-7-nitro-1H-indazole (CAS 316810-82-9, 2 g, 8.26 mmol) and K_2CO_3 (1.71 g, 12.40 mmol) in DMF (20 mL) was added PMB-Cl (1.55 g, 9.92 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (20 mL) and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 50 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM51) to afford **compound 2.074** (2 g, 5.52 mmol, 66.83% yield) as a yellow solid.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.54 (d, J = 1.6 Hz, 1H), 8.48 (s, 1H), 8.23 (d, J = 1.6 Hz, 1H), 6.89 - 6.77 (m, 4H), 5.68 (s, 2H), 3.67 (s, 3H) ppm

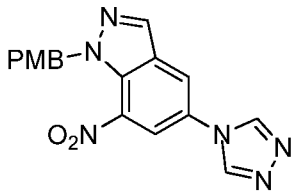
1-(4-methoxybenzyl)-7-nitro-1H-indazol-5-amine 2.075



To a mixture of **compound 2.074** (2 g, 5.52 mmol) in DMSO (20 mL) were added $NH_3.H_2O$ (9.10 g, 64.91 mmol, 10 mL, 25% purity), CuI (220.86 mg, 1.16 mmol), (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid (296.89 mg, 2.26 mmol) and K_2CO_3 (2.29 g, 16.57 mmol). The mixture was stirred at 90 °C for 16 h under N_2. The mixture was diluted with water (40 mL) and extracted with EA (40 mL × 3). The combined organic phase was washed (brine, 100 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM38) to afford **compound 2.075** (500 mg, 1.59 mmol, 28.84% yield) as a yellow oil.

LCMS (AM3): rt = 0.849 min, (299.2 $[M+H]^+$),95% purity.

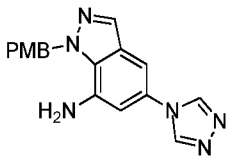
1-(4-methoxybenzyl)-7-nitro-5-(4H-1,2,4-triazol-4-yl)-1H-indazole 2.076



To a mixture of N'-formylformohydrazide (738.07 mg, 8.38 mmol), **compound 2.075** (500 mg, 1.68 mmol) and Et_3N (1.19 g, 11.73 mmol) in pyridine (7 mL) was added TMSCl (2.73 g, 25.14 mmol). The mixture was stirred at 120 °C for 12 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM90) to afford **compound 2.076** (380 mg, 1.08 mmol, 64.71% yield) as a yellow solid.

LCMS (AM3): rt = 0.862 min, (351.2 $[M+H]^+$), 99.6% purity.

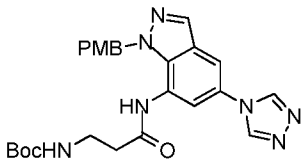
1-(4-methoxybenzyl)-5-(4H-1,2,4-triazol-4-yl)-1H-indazol-7-amine 2.077



To a solution of **compound 2.076** (380 mg, 1.08 mmol) in MeOH (5 mL) was added Pd/C (50 mg, 1.08 mmol, 10% purity) under N_2. The suspension was degassed and purged with H_2 (x3). The mixture was stirred at 30°C for 16 h under H_2 (15psi). The catalyst was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.077** (350 mg, crude) as a white solid.

LCMS (AM3): rt = 0.703 min, (321.2 $[M+H]^+$), 98% purity.

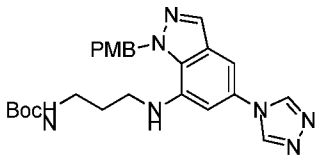
tert-butyl(3-((1-(4-methoxybenzyl)-5-(4H-1,2,4-triazol-4-yl)-1H-indazol-7-yl)amino)-3-oxopropyl)carbamate 2.078



To a mixture of **compound 2.077** (350 mg, 1.09 mmol) and 3-((tert-butoxycarbonyl)amino)propanoic acid (1.03 g, 5.46 mmol) in pyridine (10 mL) was added EDCI (2.09 g, 10.93 mmol). The mixture was stirred at 110 °C for 16 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM153) to afford **compound 2.078** (260 mg, 528.95 μmol, 48.41% yield) as a yellow solid.

LCMS (AM3): rt = 0.866 min, (492.2 $[M+H]^+$), 96.8% purity.

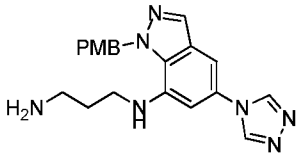
tert-butyl(3-((1-(4-methoxybenzyl)-5-(4H-1,2,4-triazol-4-yl)-1H-indazol-7-yl)amino)propyl)carbamate 2.079



To a mixture of **compound 2.078** (200 mg, 406.88 μmol) in THF (5 mL) was added BH_3-Me_2S (10 M, 0.45 mL) at 0 °C. The mixture was stirred at 30 °C for 16 h. The mixture was quenched with MeOH (10 mL) and stirred at 65 °C for 16 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM155) to afford **compound 2.079** (20 mg, 41.88 μmol, 10.29% yield) as a brown oil.

LCMS (AM3): rt = 0.929 min, (478.2 $[M+H]^+$), 98.7% purity.

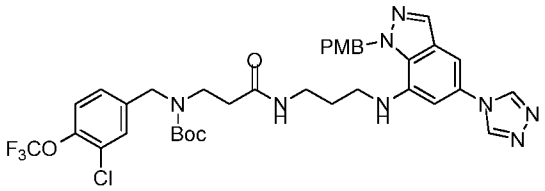
N1-(1-(4-methoxybenzyl)-5-(4H-1,2,4-triazol-4-yl)-1H-indazol-7-yl)propane-1,3-diamine 2.080



A mixture of **compound 2.079** (20 mg, 41.88 μmol) in HCl/MeOH (4 M, 2 mL) was stirred at 30 °C for 1 h. The mixture was concentrated in *vacuo* to afford **compound 2.080** (17 mg, crude, HCl salt) as a brown solid, which was used directly for the next step.

LCMS (AM3): rt = 0.735 min, (378.2 $[M+H]^+$), 97.8% purity.

tert-butyl3-chloro-4-(trifluoromethoxy)benzyl(3-((3-((1-(4-methoxybenzyl)-5-(4H-1,2,4-triazol-4-yl)-1H-indazol-7-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.081

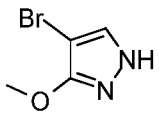


To a mixture of **compound 2.080** (17 mg, 41.07 μmol, HCl salt) and **compound 1.243** (17.92 mg, 45.04 μmol) in DMF (1 mL) were added HATU (20.55 mg, 54.05 μmol) and DIPEA (17.46 mg, 135.12 μmol). The mixture was stirred at 30 °C for 2 h. The mixture was diluted with water (20 mL) and extracted with EA (10 mL × 3). The combined organic phase was washed (brine, 20 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM121) to afford **compound 2.081** (40 mg, crude) as a yellow oil.

LCMS (AM3): rt = 1.027 min, (757.3 $[M+H]^+$), 92.56% purity.

Synthesis of Intermediate 2.086

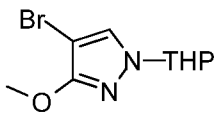
4-bromo-3-methoxy-1H-pyrazole 2.083



To a mixture of 5-Methoxy-1H-pyrazole (CAS 215610-30-3, 900 mg, 9.17 mmol) in ACN (10 mL) was added NBS (1.96 g, 11.01 mmol). The mixture was stirred at RT for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM87) to afford **compound 2.083** (1.2 g, 6.78 mmol, 73.90% yield) as a white solid.

LCMS (AM3): rt = 0.502min, (177.0 $[M+H]^+$), 99% purity.

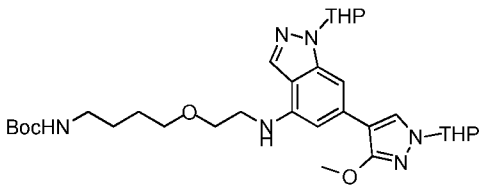
4-bromo-3-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole 2.084



To a mixture of **compound 2.083** (1.2 g, 6.78 mmol) and DHP (920.00 mg, 10.94 mmol) in THF (10 mL) was added $TsOH.H_2O$ (644.81 mg, 3.39 mmol). The mixture was stirred at 60 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM88) to afford **compound 2.084** (1.3 g, 4.98 mmol, 73.43% yield) as a yellow oil.

^{1}H NMR (400MHz, MeOH-d_4) δ 7.70 (s, 1H), 5.19 (dd, J =10.0, 2.4Hz, 1H), 4.07 - 3.97 (m, 1H), 3.92 (s, 3H), 3.76 - 3.63 (m, 1H), 2.20 - 1.89 (m, 3H), 1.80 - 1.58 (m, 3H) ppm.

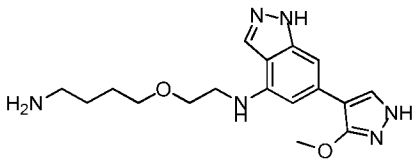
tert-butyl(4-(2-((6-(3-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 2.085



To a mixture of **compound 2.084** (280.51 mg, 1.07 mmol) and **compound 1.919** (300 mg, 537.14 μmol) in dioxane (10 mL) and H_2O (1 mL) were added BrettPhos Pd G3 (48.69 mg, 53.71 μmol) and K_2CO_3 (148.47 mg, 1.07 mmol). The mixture was stirred at 80 °C for 12 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM35) to afford **compound 2.085** (270 mg, crude) as a yellow oil.

LCMS (AM3): rt = 1.009min, (613.4 $[M+H]^+$), 64% purity.

N-(2-(4-aminobutoxy)ethyl)-6-(3-methoxy-1H-pyrazol-4-yl)-1H-indazol-4-amine 2.086

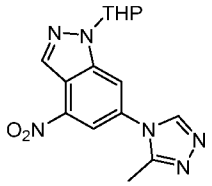


A mixture of **compound 2.085** (260 mg, 424.31 μmol) in HCl/dioxane (4 M, 5 mL) was stirred at 20 °C for 0.5 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM89) to afford **compound 2.086** (160 mg, 420.09 μmol, 99.01% yield, HCl salt) as a brown solid.

LCMS (AM5): rt = 0.789min, (345.4 $[M+H]^+$), 82% purity.

Synthesis of Intermediate 2.093

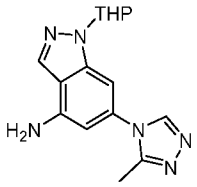
6-(3-methyl-4H-1,2,4-triazol-4-yl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.089



To a mixture of acetohydrazide (406.76 mg, 5.49 mmol) in ACN (5 mL) was added DMF-DMA (654.28 mg, 5.49 mmol). The mixture was stirred at 50 °C for 0.5 h, then **compound 1.271** (1.2 g, 4.58 mmol) and AcOH (10.50 g, 174.85 mmol) was added. The mixture was stirred at 120 °C for 12 h. The mixture was adjusted to pH=8 by saturated Na_2CO_3 solution and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM22) to afford **compound 2.089** (360 mg, 1.10 mmol, 23.96% yield) as a brown oil.

LCMS (AM3): rt = 0.789 min, (329.1 $[M+H]^+$), 47.4% purity.

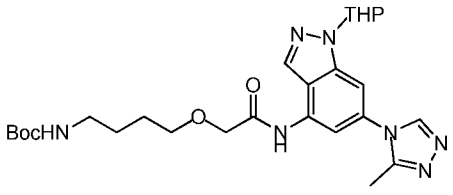
6-(3-methyl-4H-1,2,4-triazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.090



To a solution of **compound 2.089** (360 mg, 1.10 mmol) in MeOH (10 mL) was added Pd/C (80 mg, 10% purity) under N_2. The suspension was degassed and purged with H_2 (x3). The mixture was stirred at 30°C for 12 h under H_2 (15psi). The catalyst was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.090** (320 mg, crude) as a yellow oil, which was used directly for the next step.

LCMS (AM5): rt = 0.842min, (299.6 $[M+H]^+$), 45.3% purity.

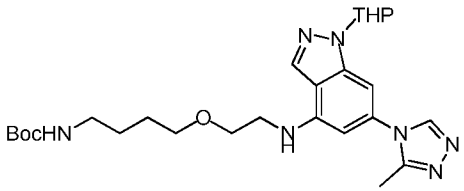
tert-butyl(4-(2-((6-(3-methyl-4H-1,2,4-triazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)-2-oxoethoxy)butyl)carbamate 2.091



To a mixture of **compound 2.090** (270 mg, 905.00 μmol) and **compound 1.891** (447.59 mg, 1.81 mmol) in pyridine (5 mL) was added EDCI (693.96 mg, 3.62 mmol). The mixture was stirred at 80 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM88) to afford **compound 2.091** (250 mg, crude) as a pink solid.

LCMS (AM3): rt = 0.893min, (528.3 $[M+H]^+$), 49% purity.

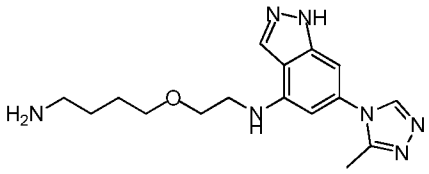
tert-butyl(4-(2-((6-(3-methyl-4H-1,2,4-triazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 2.092



To a mixture of **compound 2.091** (150 mg, 284.30 μmol) in THF (3 mL) was added BH_3-Me_2S (10 M, 284.30 μL) at 0 °C. The mixture was stirred at 30 °C for 3 h. The mixture was quenched with MeOH (5 mL) and followed by NaOH (1N, 3 mL). The mixture was stirred at 60 °C for 3 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM122) to afford **compound 2.092** (85 mg, crude) as a yellow oil.

LCMS (AM3): rt = 0.907min, (514.3 $[M+H]^+$), 96% purity.

N-(2-(4-aminobutoxy)ethyl)-6-(3-methyl-4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine 2.093

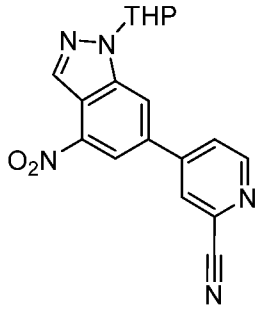


A mixture of **compound 2.092** (85 mg, 165.49 μmol) in HCl/dioxane (4 M, 3 mL) was stirred at 25 °C for 1 h. The mixture was concentrated in *vacuo* to afford **compound 2.093** (60 mg, crude, HCl salt) as a yellow oil, which was used directly for the next step.

LCMS (AM5): rt = 0.683min, (330.3 $[M+H]^+$), 70% purity.

Synthesis of Intermediate 2.095

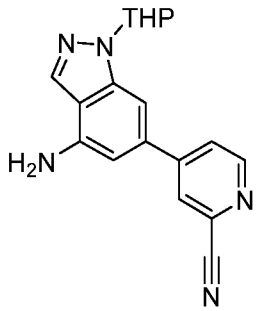
4-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)picolinonitrile 2.094



To a mixture of **compound 1.943** (400 mg, 989.46 μmol) and 4-bromopicolinonitrile (217.29 mg, 1.19 mmol) in dioxane (2 mL) and H_2O (0.2 mL) was added K_2CO_3 (273.51 mg, 1.98 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (80.80 mg, 98.95 μmol) under N_2. The mixture was stirred at 90°C for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM50) to afford **compound 2.094** (350 mg, 811.52 μmol, 82.02% yield) as a yellow solid.

LCMS (AM3): rt = 0.965 min, (350.5 $[M+H]^+$), 81.7% purity

4-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)picolinonitrile 2.095

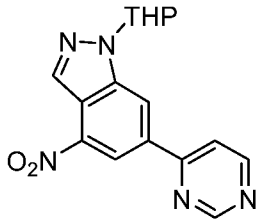


To a mixture of **compound 2.094** (200 mg, 463.73 μmol) and NH_4Cl (248.05 mg, 4.64 mmol) in EtOH (5 mL) and H_2O (1 mL) was added Fe (51.79 mg, 927.46 μmol) under N_2. The mixture was stirred at 65°C for 1 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.095** (150 mg, crude) as a yellow solid, which was used without further purification.

LCMS (AM3): rt = 0.871 min, (320.2 $[M+H]^+$), 79.7% purity

Synthesis of Intermediate 2.098

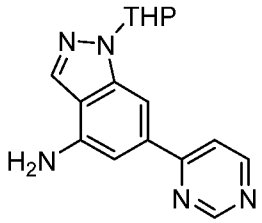
4-nitro-6-(pyrimidin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.097



To a mixture of **compound 1.943** (900 mg, 1.45 mmol) and 4-chloropyrimidine (263.32 mg, 1.74 mmol) in dioxane (2 mL) and H_2O (0.2 mL) was added K_2CO_3 (401.71 mg, 2.91 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (118.68 mg, 145.33 μmol) under N_2. The mixture was stirred at 90°C for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM50) to afford **compound 2.097** (240 mg, 442.64 μmol, 30.46% yield) as a brown solid.

LCMS (AM3): rt = 0.738 min, (325.9 $[M+H]^+$), 60.0% purity

6-(pyrimidin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.098

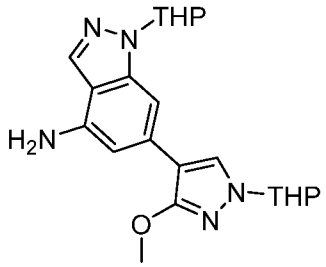


To a mixture of **compound 2.097** (230 mg, 424.20 μmol) and NH_4Cl (226.90 mg, 4.24 mmol) in EtOH (5 mL) and H_2O (1 mL) was added Fe (47.38 mg, 848.39μmol) under N_2. The mixture was stirred at 65°C for 1 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.098** (150 mg, crude) as a yellow oil, which was used without further purification.

LCMS (AM3): rt = 0.678 min, (296.1 $[M+H]^+$), 75.2% purity

Synthesis of Intermediate 2.100

6-(3-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.100

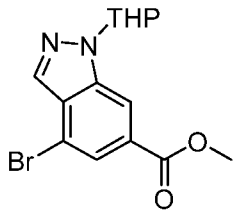


To a mixture of **compound 2.084** (200 mg, 766.04 μmol) and **compound 1.952** (240.03 mg, 919.24 μmol) in dioxane (2 mL) and H_2O (0.2 mL) was added K_2CO_3 (211.75 mg, 1.53 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (62.56 mg, 76.60 μmol) under N_2. The mixture was stirred at 90°C for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM50) to afford **compound 2.100** (170 mg, 402.04 μmol, 52.48% yield) as a yellow oil.

LCMS (AM3): rt = 0.767 min, (398.1 $[M+H]^+$), 74.9% purity

Synthesis of Intermediate 2.103

methyl 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 2.103

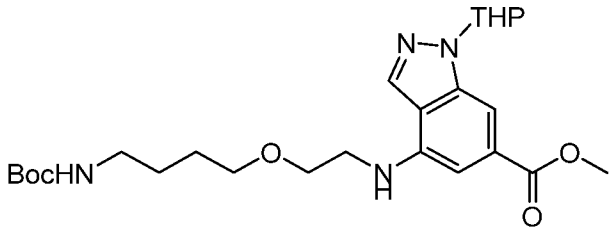


To a mixture of DHP (2.47 g, 29.40 mmol) and Methyl 4-bromo-1H-indazole-6-carboxylate (CAS 885518-47-8, 5 g, 19.60 mmol) in THF (10 mL) was added $TsOH.H_2O$ (1.86 g, 9.80 mmol) under N_2. The mixture was stirred at 60 °C for 12 h. The mixture was filtered and concentrated in *vacuo* to give a residue, which was purified (PM60) to afford **compound 2.103** (5 g, 14.30 mmol, 72.94% yield) as a light-yellow solid.

LCMS (AM3): rt = 0.963 min, (257.1 $[M-THP+H]^+$), 97.6% purity

Synthesis of Intermediate 2.105

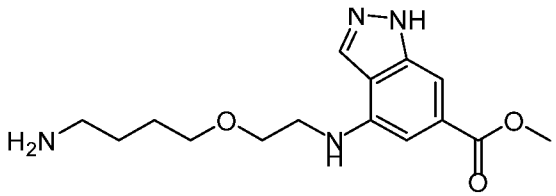
methyl4-((2-(4-((tert-butoxycarbonyl)amino)butoxy)ethyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 2.104



To a mixture of **compound 2.103** (2 g, 5.90 mmol) and tert-Butyl (4-(2-aminoethoxy)butyl)carbamate (CAS 2830620-37-4, 1.64 g, 7.08 mmol) in DMF (3mL) was added K_2CO_3 (1.63 g, 11.79 mmol), (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid (309.28 mg, 2.36 mmol) and CuI (224.60 mg, 1.18 mmol) under N_2. The mixture was stirred at 110 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM125) to afford **compound 2.104** (0.2 g, 395.44 μmol, 6.71% yield) as a brown oil.

LCMS (AM3): rt = 0.986 min, (491.3 $[M+H]^+$), 97.4% purity

methyl 4-((2-(4-aminobutoxy)ethyl)amino)-1H-indazole-6-carboxylate 2.105

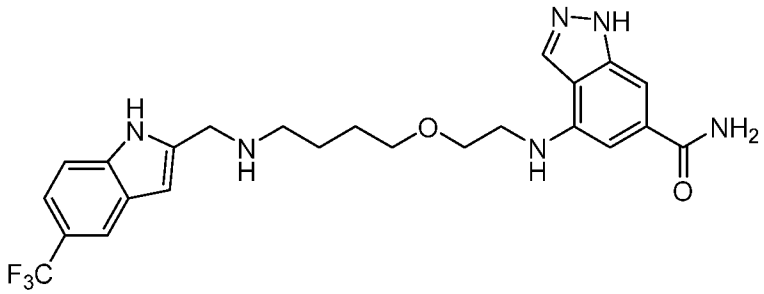


To a mixture of **compound 2.104** (390 mg, 794.96 μmol) in DCM (10 mL) was added TFA (3.08 g, 27.01 mmol) in one portion. The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated in *vacuo* to afford **compound 2.105** (300 mg, crude, TFA salt) as a brown oil, which was used for the next step without further purification.

LCMS (AM3): rt = 0.679 min, (307.1 $[M+H]^+$), 86.6% purity

Synthesis of Intermediate 2.108

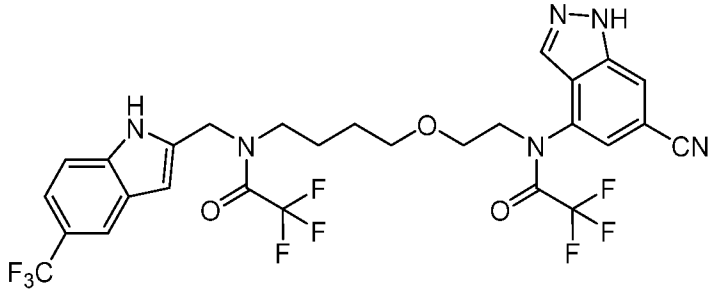
4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxamide 2.107



To a mixture of **EXAMPLE 84** (60 mg, 119.16 μmol) in MeOH (10 mL) was added NH_3 (81.17 mg, 4.77 mmol) at -60°C. The mixture was stirred at 85 °C for 12 h in a sealed tube. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM92) to afford **compound 2.107** (40 mg, 70.42 μmol, 59.10% yield) as a brown solid.

LCMS (AM3): rt = 0.806 min, (489.2 $[M+H]^+$), 86.4% purity

N-(6-cyano-1H-indazol-4-yl)-2,2,2-trifluoro-N-(2-(4-(2,2,2-trifluoro-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)acetamido)butoxy)ethyl)acetamide 2.108

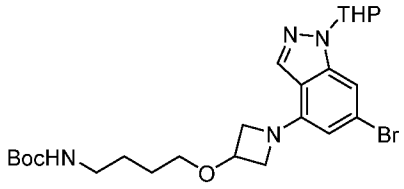


To a mixture of **compound 2.107** (30 mg, 52.81 μmol) in DCM (4 mL) was added TEA (16.03 mg, 158.44 μmol) and TFAA (22.19 mg, 105.63 μmol) at 0°C under N_2. The mixture was stirred at 25 °C for 1 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.108** (30 mg, crude) as a yellow oil, which was used for the next step without further purification.

LCMS (AM3): rt = 1.085 min, (663.2 $[M+H]^+$), 79.0% purity

Synthesis of Intermediate 2.113

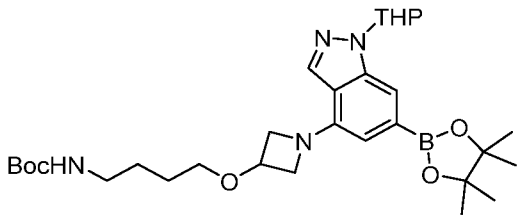
tert-butyl (4-((1-(6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.110



A mixture of tert-butyl (4-(azetidin-3-yloxy)butyl)carbamate (CAS 2830620-55-6, 16.34 g, 66.86 mmol), 6-bromo-4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (10 g, 33.43 mmol, Organic Letters, 2020, vol. 22, # 22, p. 9047 - 9052) and DIPEA (8.64 g, 66.86 mmol, 11.65 mL) in NMP (250 mL) was stirred at 140°C for 15 h under N_2. The mixture was cooled to RT, poured into water (500 mL) and extracted with EA (200 mL × 2). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM42) to afford **compound 2.110** (8.5 g, 16.24 mmol, 48.57% yield) as a yellow oil.

LCMS (AM3): rt = 1.073 min, (525.4 $[M+H]^+$), 42.37% purity

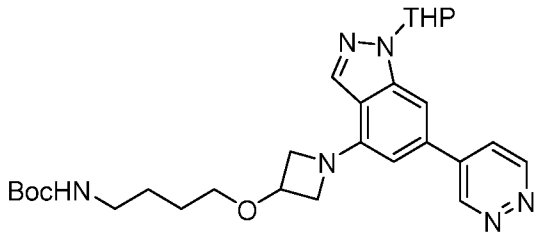
tert-butyl(4-((1-(1-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.111



To a mixture of B_2Pin_2 (2.91 g, 11.46 mmol) and **compound 2.110** (4 g, 7.64 mmol) in dioxane (50 mL) was added Pd(dppf)Cl_2 (559.13 mg, 764.14 μmol) and KOAc (1.50 g, 15.28 mmol) in one portion under N_2. The mixture was stirred at 85°C for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM50) to afford **compound 2.111** (3.1 g, 4.46 mmol, 58.31% yield) as a yellow oil.

LCMS (AM3): rt = 0.913 min, (571.3 $[M+H]^+$), 82.0% purity

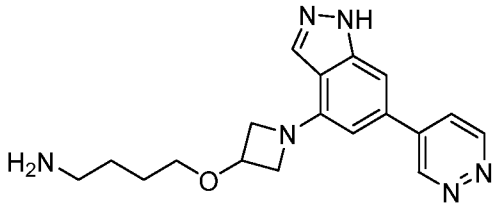
tert-butyl (4-((1-(6-(pyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.112



To a mixture of 4-bromopyridazine (1.39 g, 5.79 mmol) and **compound 2.111** (3.1 g, 4.46 mmol) in dioxane (30 mL) and H_2O (3 mL) was added K_2CO_3 (1.23 g, 8.91 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (363.86 mg, 445.55 μmol) in one portion under N_2. The mixture was stirred at 90 °C for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM125) to afford **compound 2.112** (1.8 g, 2.62 mmol, 58.75% yield) as a brown solid.

LCMS (AM3): rt = 0.968 min, (523.5 $[M+H]^+$), 76.8% purity

4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl) azetidin-3-yl) oxy) butan-1-amine 2.113

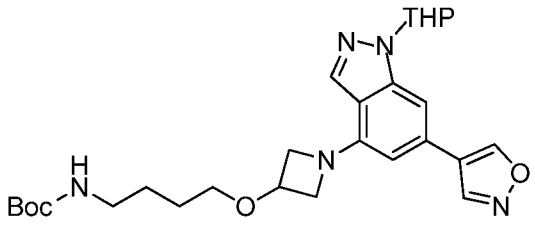


To a mixture of **compound 2.112** (1.8 g, 2.62 mmol) in DCM (40 mL) was added TFA (25.82 g, 226.42 mmol) at 0 °C. The mixture was stirred at 25 °C for 2 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM126) to afford **compound 2.113** (1.2 g, crude) as a brown gum, which was used without further purification.

LCMS (AM3): rt = 0.485 min, (423.1 $[M+H]^+$), 62.0% purity

Synthesis of Intermediate 2.115

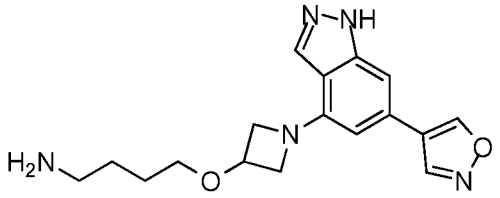
tert-butyl (4-((1-(6-(isoxazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.114



A mixture of **compound 2.110** (5 g, 9.55mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (2.24 g, 11.46 mmol), $Pd(dppf)Cl_2$ (698.91 mg, 955.18 μmol) and KF (1.66 g, 28.66 mmol) in DMF (95 mL) and H_2O (28 mL) was stirred at 60 °C for 2.5 h under N_2. The mixture was poured into water (100 mL) and extracted with EA (80 mL × 3). The combined organic phase was washed (brine, 200 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM3) to afford **compound 2.114** (2.8 g, 4.98 mmol, 52.14% yield) as a yellow oil.

LCMS (AM3): rt = 0.987 min, (512.5 $[M+H]^+$), 91% purity.

4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine 2.115

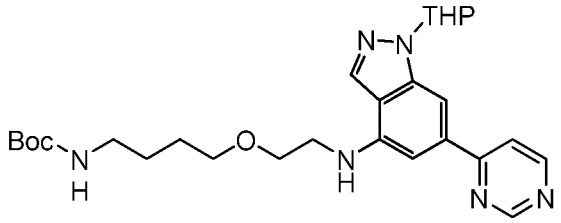


A solution of **compound 2.114** (2.8g, 5.47 mmol) in TFA (35.93 g, 315.15 mmol) was stirred at 20 °C for 0.5 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM88) to afford **compound 2.115** (800 mg, 2.10 mmol, 38.36% yield, FA salt) as a green solid.

LCMS (AM3): rt = 0.717 min, (328.4 $[M+H]^+$), 98.4% purity.

Synthesis of Intermediate 2.117

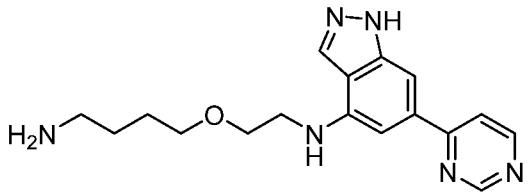
tert-butyl (4-(2-((6-(pyrimidin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 2.116



To a mixture of **compound 1.919** (300 mg, 537.14 μmol) and 4-chloropyrimidine (CAS 17180-93-7, 89.21 mg, 590.85 μmol, HCl salt) in dioxane (10 mL) and H_2O (1 mL) was added K_2CO_3 (222.71 mg, 1.61 mmol) and $Pd(dppf)Cl_2$ (39.30 mg, 53.71 μmol). The mixture was stirred at 80 °C for 12 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM32) to afford **compound 2.116** (100 mg, 195.84 μmol, 36.46% yield) as a yellow oil.

LCMS (AM3): rt = 0.947 min, (511.5 $[M+H]^+$), 74.6% purity

N-(2-(4-aminobutoxy)ethyl)-6-(pyrimidin-4-yl)-1H-indazol-4-amine 2.117

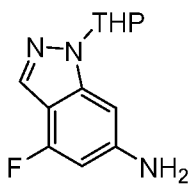


A mixture of **compound 2.116** (400 mg, 783.35 μmol) in HCl/MeOH (4 M, 5 mL) was stirred at 20 °C for 1 h. The mixture was concentrated in *vacuo* to afford **compound 2.117** (340 mg, crude, HCl salt) as a red oil, which was used without further purification.

LCMS (AM5): rt = 0.797 min, (327.3 $[M+H]^+$), 96.79% purity

Synthesis of Intermediate 2.221

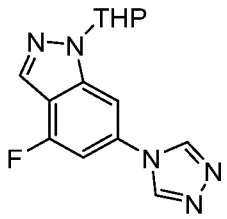
4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-amine 2.118



A mixture of 6-bromo-4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (20 g, 66.86 mmol), CuI (2.55 g, 13.38 mmol), K_2CO_3 (28 g, 202.59 mmol), $NH_3.H_2O$ (324.54 mmol, 50 mL, 25% purity) and (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid (3.51 g, 26.74 mmol) in DMSO (200 mL) was stirred at 90 °C for 18 h under N_2. Water (600 mL) was added and the mixture was extracted with EA (100 mL × 4). The combined organic phases were washed (brine, 200 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.118** (13.7 g, 55.90 mmol, 83.62% yield) as a brown solid, which was used without further purification.

LCMS (AM3): rt = 0.769 min, (236.2 $[M+H]^+$), 96.2% purity.

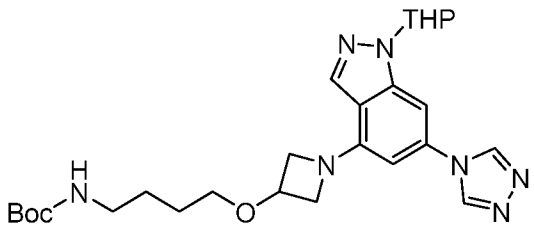
4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazole 2.119



To a mixture of **compound 2.118** (13.7 g, 58.23 mmol), N-formamidoformamide (25.65 g, 291.22 mmol) and TEA (409.52 mmol, 57 mL) in pyridine (200 mL) was added TMSCl (866.72 mmol, 110 mL) under N_2. The reaction mixture was stirred at 120 °C for 14 h under N_2. The reaction mixture was concentrated in *vacuo* to give a residue. Water (200 mL) and EA (200 mL) were added and a solid precipitated. The solid was filtered and the filter cake was dried under vacuum to afford **compound 2.119** (10 g, 34.81 mmol, 59.77% yield) as a white solid.

LCMS (AM3): rt = 0.818 min, (288.1 $[M+H]^+$), 92.3% purity.

tert-butyl (4-((1-(1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.220

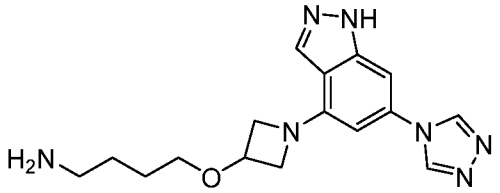


A mixture of tert-butyl (4-(azetidin-3-yloxy)butyl)carbamate (Ref: WO2022185041, 5.10 g, 20.88 mmol), **compound 2.119** (3 g, 10.44 mmol) and DIPEA (2.70 g, 20.88 mmol) in NMP (30 mL) was stirred at 140 °C for 15 h under N_2. The reaction mixture was diluted with H_2O (60 mL) and extracted with EA (80 mL × 2). The organic layers were washed (brine, 100 mL),

dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM127) to afford **compound 2.220** (4 g, 7.82 mmol, 74.87% yield) as a yellow oil.

LCMS (AM3): rt = 0.812 min, (512.2 $[M+H]^+$), 100% purity.

4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine 2.221

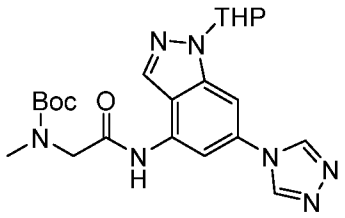


To a solution of **compound 2.220** (4 g, 7.82 mmol) in DCM (1 mL) was added TFA (30.80 g, 270.12 mmol). The resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM63) to afford **compound 2.221** (2.8 g, 7.50 mmol, 95.91% yield, FA salt) as a yellow solid.

LCMS (AM5): rt = 0.741 min, (328.1 $[M+H]^+$), 81.2% purity.

Synthesis of Intermediate 2.225

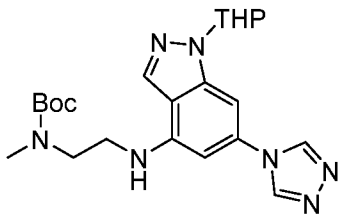
tert-butyl methyl(2-oxo-2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)carbamate 2.222



To a solution of N-(tert-butoxycarbonyl)-N-methylglycine (732.04 mg, 3.87 mmol) in pyridine (4 mL) was added EDCI (2.02 g, 10.55 mmol) and **compound 1.273** (1 g, 3.52 mmol). The mixture was stirred at 80 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM128) and lyophilized to afford **compound 2.222** (459 mg, 1.01 mmol, 28.65% yield) as a light-yellow solid.

LCMS (AM3): rt = 0.849 min, (456.2 $[M+H]^+$), 19.5% purity

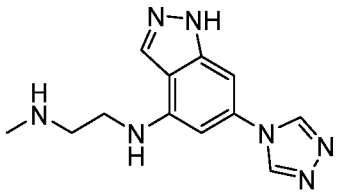
tert-butyl methyl(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)carbamate 2.223



A solution of **compound 2.222** (459 mg, 1.01 mmol) in THF (10 mL) was added BH_3.THF (1 M, 10.08 mL) at 0 °C, then the mixture was stirred at 20 °C for 3 h. The mixture was quenched with methanol (5 mL) and concentrated in *vacuo* to give the residue, which was purified (PM129) to afford **compound 2.223** (210 mg, 475.62 μmol, 47.20% yield) as a red solid.

LCMS (AM3): rt = 0.835 min, (442.2 $[M+H]^+$), 66.4% purity

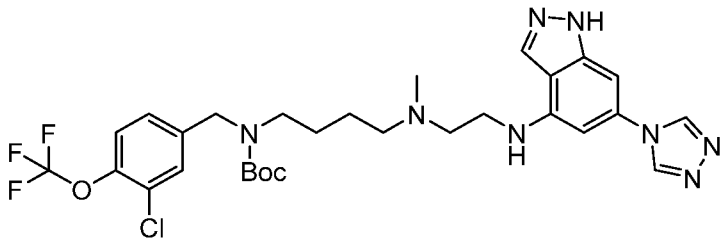
N1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-N2-methylethane-1,2-diamine 2.224



A mixture of **compound 2.223** (210 mg, 475.62 μmol) in HCl/MeOH (4 M, 4 mL) was stirred at 25 °C for 0.5 h. The mixture was concentrated in *vacuo* to afford **compound 2.224** (190 mg, crude, HCl salt) as a red solid, which was used directly for the next step.

LCMS (AM3): rt = 0.120 min, (258.6 $[M+H]^+$), 68.6% purity

tert-butyl (4-((2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)(methyl)amino)butyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate 2.225

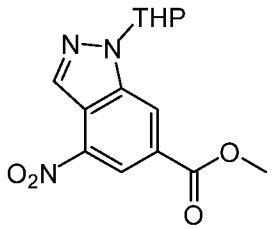


A solution of **compound 2.224** (100 mg, 340.42 μmol, HCl salt) and **Intermediate I** (134.74 mg, 340.42 μmol) in MeOH (3 mL) was added $NaBH_3CN$ (64.18 mg, 1.02 mmol) and DIPEA (87.99 mg, 680.84 μmol). The mixture was stirred at 25 °C for 2 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM156) to afford **compound 2.225** (90 mg, 141.27 μmol, 41.50% yield) as a red solid.

LCMS (AM3): rt = 0.864 min, (637.2 $[M+H]^+$), 71% purity

Synthesis of Intermediate 2.231

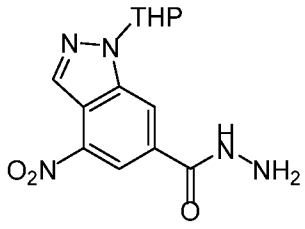
methyl 4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 2.228



To a solution of methyl 4-nitro-1H-indazole-6-carboxylate (CAS 72922-61-3,1.8 g, 8.41 mmol) in THF (8 mL) was added 3,4-dihydro-2H-pyran (2.74 g, 32.55 mmol) followed by TsOH (280.30 mg, 1.63 mmol). The mixture was heated to 70 °C and stirred for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM42) to afford **compound 2.228** (1.7 g, 5.57 mmol, 68.42% yield) as a yellow oil.

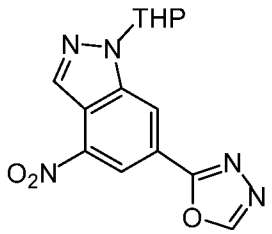
^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.77-8.78 (m, 1H), 8.69 (d, *J* = 6.0 Hz, 2H), 5.88 (dd, *J* = 9.2 Hz, 2.8 Hz, 1H), 4.04 (s, 3H), 3.89 - 3.73 (m, 2H), 2.62 - 2.45 (m, 2H), 1.82-1.72 (m, 4H) ppm.

4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carbohydrazide 2.229



To a solution of methyl **compound 2.228** (1.7 g, 5.57 mmol) in EtOH (25 mL) was added N_2H_4•H_2O (1.14 g, 22.27 mmol, 98% purity) at 20 °C. The mixture was heated to 70 °C and stirred for 2 h. The mixture was cooled to 20 °C and filtered. The filter cake was washed with EtOH (10 mL × 3), filtered and dried under vacuum to afford **compound 2.229** (1.1 g, 3.60 mmol, 64.71% yield) as a yellow solid.

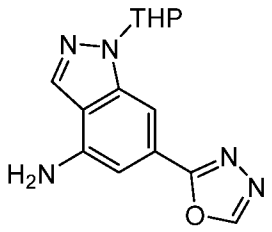
2-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-1,3,4-oxadiazole 2.230



To a solution of **compound 2.229** (1.1 g, 3.60 mmol) in dioxane (30 mL) was added trimethoxymethane (3.87 g, 36.49 mmol) and TsOH (62.05 mg, 360.31 µmol). The mixture was heated to 90 °C and stirred for 4 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM38) to afford **compound 2.230** (940 mg, 2.94 mmol, 81.50% yield) as a white solid.

LCMS (AM12): rt = 0.530 min, (316.1 $[M+H]^+$), 98.51% purity.

6-(1,3,4-oxadiazol-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.231

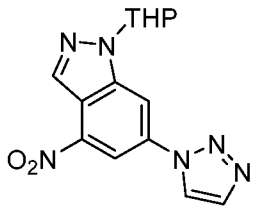


To a mixture of **compound 2.230** (940 mg, 2.98 mmol) in MeOH (15 mL) and H_2O (5 mL) was added NH_4Cl (1.28 g, 23.85 mmol) and Fe (998.99 mg, 17.89 mmol) at 20 °C. The mixture was heated to 50 °C and stirred for 2 h. The mixture was poured onto sat. $NaHCO_3$ (aq.) (50 mL) and extracted with EA (60 mL × 2). The combined organic phase was washed (brine, 40 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.231** (800 mg, 2.75 mmol, 92.17% yield) as a yellow solid.

LCMS (AM12): rt = 0.388 min, (286.0 $[M+H]^+$),98.01% purity.

Synthesis of Intermediate 2.235

4-nitro-1-(tetrahydro-2H-pyran-2-yl)-6-(1H-1,2,3-triazol-1-yl)-1H-indazole 2.234

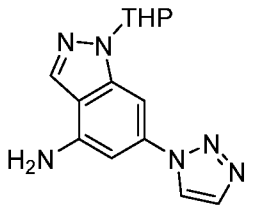


To a mixture of **compound 1.271** (3 g, 11.44 mmol) in ACN (30 mL) was added isopentyl nitrite (13.40 g, 114.39 mmol) followed by $TMSN_3$ (13.18 g, 114.39 mmol) in portions at 0°C. The mixture was stirred at 25°C for 16 h. To the above mixture was added vinyl acetate (4.93 g, 57.24 mmol). The mixture was heated to 80 °C and stirred for 48 h. The mixture was poured into water (150 mL) and extracted with EA (150 mL × 3). The combined organic phase was washed (brine, 150 mL), dried with anhydrous sodium sulfate, filtered and concentrated in *vacuo* to give a residue, which was purified (PM27) to afford **compound 2.234** (1.9 g, 6.05 mmol, 52.81% yield) as a brown solid.

LCMS (AM12): rt = 0.666 min, (315.2 $[M+H]^+$), 59.9% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.72 (s, 1H), 8.55 (s, 1H), 8.49 (d, J = 1.6 Hz, 1H), 8.20 (d, J = 1.2 Hz, 1H), 7.96 (d, J = 1.2 Hz, 1H), 5.90 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 4.03 - 3.97 (m, 1H), 3.84 - 3.78 (m, 1H), 2.61 - 2.54 (m, 1H), 2.26 - 2.17 (m, 2H), 1.84 - 1.74 (m, 3H) ppm.

1-(tetrahydro-2H-pyran-2-yl)-6-(1H-1,2,3-triazol-1-yl)-1H-indazol-4-amine 2.235

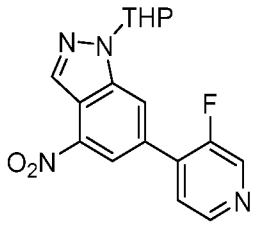


To a mixture of **compound 2.234** (1.57 g, 5.00 mmol) in MeOH (20 mL) and H_2O (4 mL) was added Fe (1.39 g, 24.98 mmol) and NH_4Cl (1.87 g, 34.97 mmol). The mixture was heated to 50 °C and stirred for 6 h. The mixture was filtered and the filter cake was washed with MeOH (20 mL). The filtrate was concentrated in *vacuo* to afford **compound 2.235** (920 mg, 3.24 mmol, 64.78% yield) as a brown solid.

LCMS (AM12): rt = 0.408 min, (285.1 $[M+H]^+$), 99.5% purity.

Synthesis of Intermediate 2.238

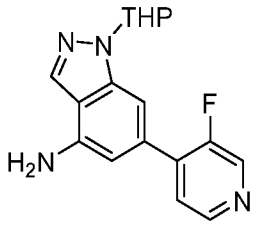
6-(3-fluoropyridin-4-yl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.237



To a solution of **compound 1.943** (1 g, 2.68 mmol) in dioxane (10 mL) and H_2O (1 mL) was added 4-bromo-3-fluoro-pyridine (565.86 mg, 3.22 mmol) followed by addition of $Pd(dppf)Cl_2$ (196.06 mg, 267.95 μmol) and Cs_2CO_3 (1.75 g, 5.36 mmol). The reaction mixture was stirred at 100 °C for 16 h. The residue was diluted with water (50 mL) and extracted with EA (40 mL × 4). The combined organic layers were washed with saturated brine (50 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM27) to afford **compound 2.237** (937 mg, 2.68 mmol, 95.25% yield) as a grey solid.

LCMS (AM7): rt = 0.931 min, (343.0 $[M+H]^+$), 97.93% purity.

6-(3-fluoropyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.238

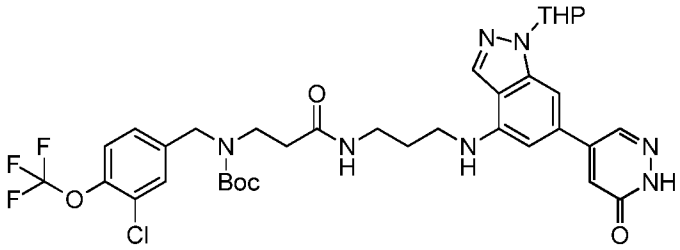


To a solution of **compound 2.237** (750 mg, 2.19 mmol) in a mixture solvent of EtOH (7.5 mL) and H_2O (1.5 mL) was added NH_4Cl (585.96 mg, 10.95 mmol) and Fe (611.76 mg, 10.95 mmol). The reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was filtered. The filtrate was concentrated in *vacuo* to remove the organic solvent. The residue was diluted with water (35 mL) and extracted with EA (30 mL × 4). The combined organic layers were washed (brine, 30 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM38) to afford **compound 2.238** (657 mg, 2.04 mmol, 87.13% yield) as a red oil.

LCMS (AM7): rt = 0.743 min, (313.1 $[M+H]^+$), 97.11% purity.

Synthesis of Intermediate 2.241

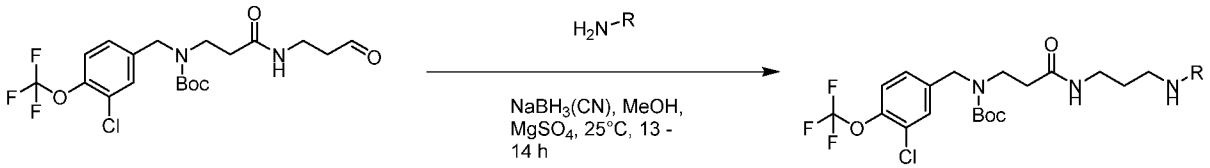
tert-butyl 3-chloro-4-(trifluoromethoxy)benzyl(3-oxo-3-((3-((6-(6-oxo-1,6-dihydropyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 2.241



To a solution of **compound 1.950** (152.73 mg, 337.25 μmol) and **compound 1.953 (**70 mg, 224.84 μmol) in MeOH (1 mL) was added $MgSO_4$ (135.32 mg, 1.12 mmol). The mixture was stirred for 12 h, then $NaBH_3CN$ (49.45 mg, 786.93 μmol) was added and the mixture was stirred at 20 °C for 2 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM135) to afford **compound 2.241** (55 mg, 57.57 μmol, 25.60% yield) as a white solid.

LCMS (AM16): rt = 0.756 min, (748.4 $[M+H]^+$), 78.31% purity.

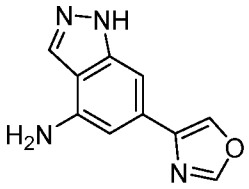
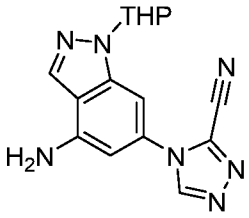
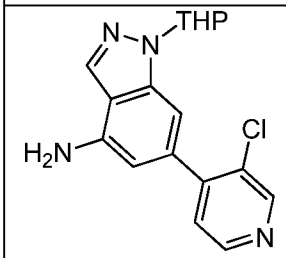
[00664] The following Intermediates in Table 4 were made with non-critical changes or substitutions to the exemplified procedure for Intermediate 1.950 that would be understood by one skilled in the art, wherein R may or may not contain a THP protecting group.

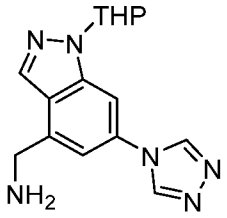


intermediate 1.950

Table 4

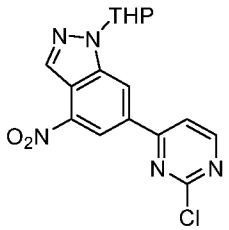
H_2N-R Reactant IUPAC name (Intermediate No.)	Product IUPAC name (Intermediate No.)	Analytical

 6-(oxazol-4-yl)-1H-indazol-4-amine **2.340**	tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((6-(oxazol-4-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.341**	**LCMS** (AM14): rt = 0.651 min, (637.3 $[M+H]^+$), 99.20% purity. **Purification Method** PM178
 4-(4-amino-1-(tetrahydro-2 pyran-2-yl)-1H-indazol-6-y 4H-1,2,4-triazole-3-carbonitrile **2.457**	tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((6-(3-cyano-4H-1,2,4-triazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.459**	**LCMS** (AM11): rt = 0.564 min, (746.2, $[M+H]^+$), 95.36% purity. **Purification Method** PM198
 6-(3-chloropyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.479**	tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((6-(3-chloropyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate **2.481**	**LCMS** (AM12): rt = 0.688 min, (765.6, $[M+H]^+$), 89.15% purity. **Purification Method** PM202

 (1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)methanamine **2.488**	tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-oxo-3-((3-(((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)methyl)amino)propyl)amino)propyl)carbamate **2.489**	**LCMS** (AM14): rt = 0.903 min, (735.4, $[M+H]^+$), 99.46% purity **Purification Method** PM203

Synthesis of Intermediate 2.243

6-(2-chloropyrimidin-4-yl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.242

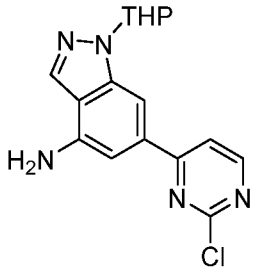


To a solution of **compound 1.943** (2 g, 5.36 mmol) in dioxane (10 mL) and H_2O (1 mL) was added 2,4-dichloropyrimidine (725.78 mg, 4.87 mmol), K_2CO_3 (2.02 g, 14.62 mmol) and $Pd(dppf)Cl_2$ (356.47 mg, 487.17 μmol). The mixture was stirred at 80 °C for 16 h under N_2. The mixture was filtered and the filter cake was washed with EA (10 mL). The filtrate was concentrated in *vacuo* to give a residue, which was purified (PM35) to afford **compound 2.242** (1.59 g, 4.25 mmol, 87.20% yield) as a white solid.

LCMS (AM11): rt = 0.464 min, (360.1 $[M+H]^+$), 96.77% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.83 (s, 1H), 8.81 - 8.74 (m, 2H), 8.71 (s, 1H), 7.84 (d, *J* = 5.2 Hz, 1H), 5.98 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 4.04 - 3.94 (m, 1H), 3.91 - 3.77 (m, 1H), 2.67 - 2.53 (m, 1H), 2.26 - 2.15 (m, 2H), 1.89 - 1.73 (m, 3H) ppm.

6-(2-chloropyrimidin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.243

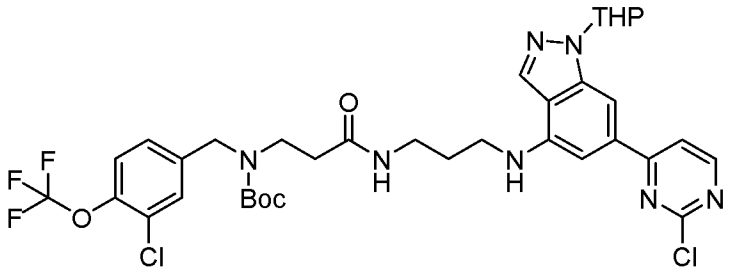


To a solution of **compound 2.242** (500 mg, 1.39 mmol) in MeOH (10 mL) and H_2O (2 mL) was added Fe (232.84 mg, 4.17 mmol) and NH_4Cl (371.71 mg, 6.95 mmol). The mixture was stirred at 50 °C for 5 h. The mixture was filtered and washed with MeOH (10 mL). The filtrate was concentrated in *vacuo* to afford **compound 2.243** (371 mg, 933.73 μmol, 67.19% yield) as a yellow solid.

LCMS (AM16): rt = 0.608 min, (330.1 $[M+H]^+$), 83.56% purity.

Synthesis of Intermediate 2.247

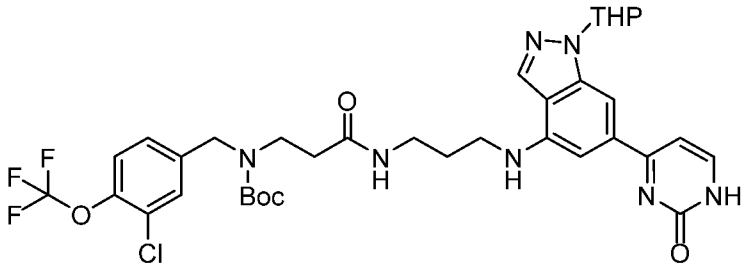
tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((6-(2-chloropyrimidin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.246



To a solution of **compound 2.243** (100 mg, 303.23 μmol) in MeOH (2 mL) was added **compound 1.950** (137.32 mg, 303.23 μmol) and $MgSO_4$ (182.50 mg, 1.52 mmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (66.69 mg, 1.06 mmol) was added. The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was poured into water (10 mL) and extracted with EA (10 mL × 3). The combined organic phase was washed (brine, 10 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM23) to afford **compound 2.246** (62 mg, 77.94 μmol, 25.70% yield) as a yellow oil.

LCMS (AM16): rt = 0.867 min, (766.4 $[M+H]^+$), 96.37% purity.

tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-oxo-3-((3-((6-(2-oxo-1,2-dihydropyrimidin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 2.247

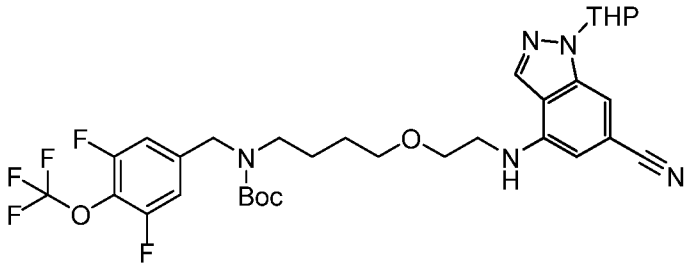


To a solution of **compound 2.246** (62 mg, 80.87 μmol) in dioxane (1 mL) and H_2O (1 mL) was added DABCO (9.07 mg, 80.87 μmol) and K_2CO_3 (22.35 mg, 161.75 μmol). The mixture was stirred at 70 °C for 12 h. The reaction mixture was poured into water (10 mL) and extracted with EA (10 mL × 3). The combined organic phase was washed (brine, 10 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.247** (50.15 mg, 54.11 μmol, 66.91% yield) as a yellow solid.

LCMS (AM16): rt = 0.654 min, (748.4 $[M+H]^+$), 80.73% purity.

<u>Synthesis of Intermediate 2.248</u>

tert-butyl(4-(2-((6-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)(3,5-difluoro-4-(trifluoromethoxy)benzyl)carbamate 2.248

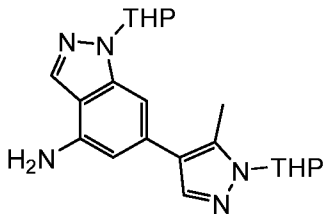


To a mixture of **compound 1.941** (100 mg, 226.56 μmol) and **compound 1.87** (54.89 mg, 226.56 μmol) in MeOH (2 mL) was added $MgSO_4$ (136.35 mg, 1.13 mmol) and AcOH (13.60 mg, 226.56 μmol). The mixture was stirred at 20 °C for 12 h, then to the mixture was added $NaBH_3CN$ (49.83 mg, 792.95 μmol). The resulting mixture was stirred at 20 °C for 1 h. The mixture was poured into water (20 mL) and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 20 mL), dried with anhydrous sodium sulfate, filtered and concentrated in *vacuo* to give a residue, which was purified (PM157) to afford **compound 2.248** (71 mg, 105.49 μmol, 46.56% yield) as a yellow oil.

LCMS (AM12): rt = 0.735 min, (668.5 $[M+H]^+$), 99.20% purity.

Synthesis of Intermediate 2.251

6-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.251

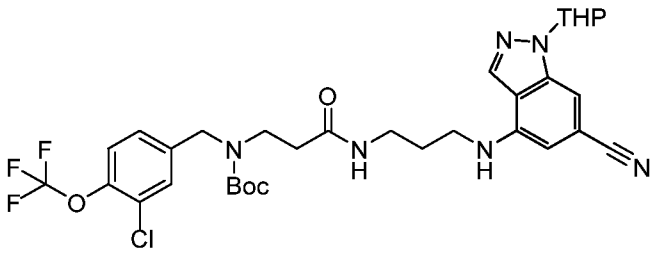


To a solution of **compound 1.952** (2 g, 5.83 mmol) in H_2O (2 mL) and dioxane (20 mL) was added 4-Bromo-5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole (Ref: WO2021127166, 1.71 g, 6.99 mmol) followed by $Pd(dppf)Cl_2$ (426.37 mg, 582.70 μmol) and Cs_2CO_3 (3.80 g, 11.65 mmol). The reaction mixture was stirred at 100°C for 16 h. The residue was diluted with water (60 mL) and extracted with EA (40 mL × 3). The combined organic layers were washed (brine, 60 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM34) to afford **compound 2.251** (1 g, 2.54 mmol, 43.64% yield) as a brown solid.

LCMS (AM7): rt = 0.787 min, (382.2 $[M+H]^+$), 97.0% purity.

Synthesis of Intermediate 2.253

tert-butyl(3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((6-cyano-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.253



To a mixture of **compound 1.950** (120 mg, 264.99 μmol) in MeOH (2 mL) was added **compound 1.87** (64.20 mg, 264.99 μmol). The mixture was stirred at 25 °C for 16 h, then to the mixture was added $NaBH_3CN$ (49.96 mg, 794.96 μmol) in one portion, the mixture was stirred at 25 °C for 1 h. The mixture was poured into water (10 mL) and extracted with EA (10 mL × 3). The combined organic phase was washed (brine, 10 mL × 3), dried (Na_2SO_4), filtered

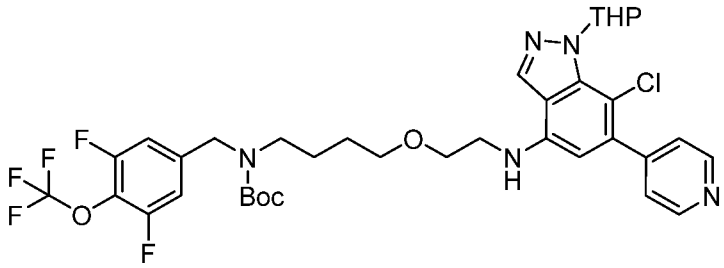
and concentrated in *vacuo* to give a residue, which was purified (PM24) to afford **compound 2.253** (63 mg, 92.77 μmol, 35.01% yield) as a yellow oil.

LCMS (AM11): rt = 0.545 min, (679.2 $[M+H]^+$), 37.2% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.15 (s, 1H), 7.35 - 7.32 (m, 1H), 7.30 - 7.28 (m, 1H), 7.26 (s, 1H), 7.17 - 7.08 (m, 1H), 6.34 (s, 1H), 5.65 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 5.60 - 5.47 (m, 1H), 4.41 - 4.35 (m, 2H), 4.06 - 4.00 (m, 1H), 3.78 - 3.72 (m, 1H), 3.52 - 3.56 (m, 2H), 3.42 - 3.30 (m, 4H), 2.53 - 2.47 (m, 2H), 2.20 - 2.05 (m, 2H), 2.02 - 1.97 (m, 1H), 1.87 - 1.82 (m, 2H), 1.80 - 1.66 (m, 2H), 1.48 - 1.45 (m, 9H) ppm.

Synthesis of Intermediate 2.255

tert-butyl(4-(2-((7-chloro-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)(3,5-difluoro-4-(trifluoromethoxy)benzyl)carbamate 2.255

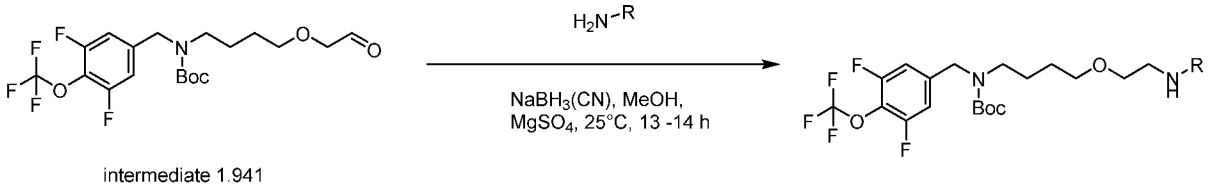


To a solution of **compound 2.024** (55 mg, 167.28 μmol) in MeOH (1.5 mL) was added **compound 1.941** (73.83 mg, 167.28 μmol), AcOH (12.05 mg, 200.73 μmol) and $MgSO_4$ (100.67 mg, 836.39 μmol). The mixture was stirred at 20°C for 12 h, then $NaBH_3CN$ (36.79 mg, 585.47 μmol) was added in portions at 20°C. The resulting mixture was stirred at 20°C for 1 h. The reaction mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM160) to afford **compound 2.255** (48 mg, 62.80 μmol, 37.55% yield) as a light-yellow oil.

LCMS (AM16): rt = 0.987 min, (754.4 $[M+H]^+$),98.68% purity.

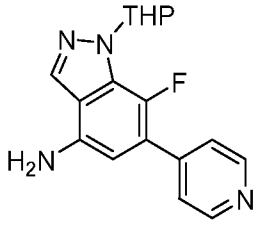
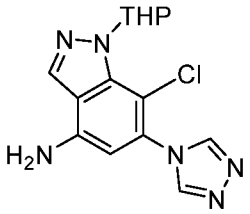
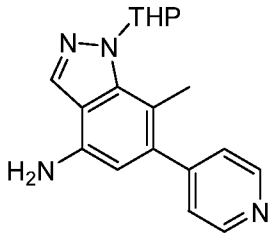
The following Intermediates in Table 5 were made with non-critical changes or substitutions to the exemplified procedure for Intermediate 2.255 that would be understood by one skilled

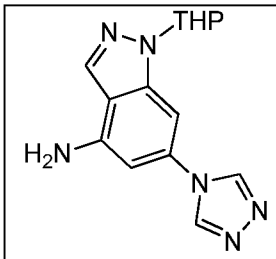
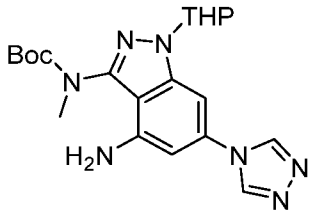
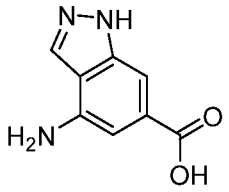
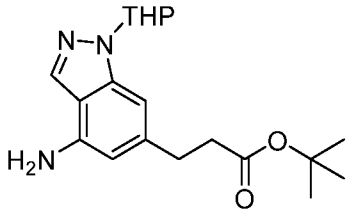
in the art, wherein R may or may not contain a THP protecting group.



intermediate 1.941

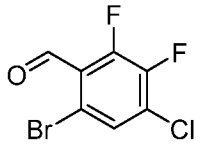
Table 5

NH_2-R Reactant IUPAC name (Intermediate No.)	Product IUPAC name (Intermediate No.)	Analytical
 7-fluoro-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.263**	tert-butyl(3,5-difluoro-4-(trifluoromethoxy)benzyl)(4-(2-((7-fluoro-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate **2.264**	**LCMS** (AM1): rt = 0.514 min, (738.2 $[M+H]^+$), 96.3% purity. **Purification Method** PM70
 7-chloro-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine **2.321**	tert-butyl (4-(2-((7-chloro-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)(3,5-difluoro-4-(trifluoromethoxy)benzyl)carbamate **2.376**	**LCMS** (AM14): rt = 0.765 min, (744.3 $[M+H]^+$), 99.25% purity. **Purification Method** PM195
 7-methyl-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine **2.025**	tert-butyl (3,5-difluoro-4-(trifluoromethoxy)benzyl)(4-(2-((7-methyl-6-(pyridin-4-yl)-1- (tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate **2.382**	**LCMS** (AM7): rt = 1.238 min, (734.3$[M+H]^+$), 96.68% purity. **Purification Method** PM190

 1-(Tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine **1.273**	tert-butyl 3,5-difluoro-4-(trifluoromethoxy)benzyl(4-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate **2.395**	**LCMS** (AM14): rt = 0.729 min, (710.4, $[M+H]^+$), 99.1% purity. **Purification Method** PM172
 tert-butyl (4-amino-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-3-yl)(methyl)carbamate **2.498**	tert-butyl (4-((2-(4-((tert-butoxycarbonyl)(3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-3-yl)(methyl)carbamate **2.499**	**LCMS** (AM11): rt = 0.633 min, (839.5, $[M+H]^+$), 84.45% purity. **Purification Method** PM178
 4-amino-1H-indazole-6-carboxylic acid **2.511**	4-((2-(4-((tert-butoxycarbonyl)(3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxylic acid **2.512**	**LCMS** (AM11): rt = 0.573 min, (603.3, $[M+H]^+$), 99.76% purity. **Purification Method** PM180
 tert-butyl 3-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)propanoate **2.514**	tert-butyl 3-(4-((2-(4-((tert-butoxycarbonyl)(3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)propanoate **2.515**	**LCMS** (AM11): rt = 0.674 min, (771.8, $[M+H]^+$), 91.89% purity. **Purification Method** PM181

Synthesis of Intermediate 2.263

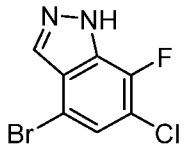
6-bromo-4-chloro-2,3-difluorobenzaldehyde 2.259



To a solution of LDA (2 M, 5.28 mL) in THF (30 mL) was added a solution of 5-Bromo-1-chloro-2,3-difluorobenzene (CAS 1060813-07-1, 2 g, 8.79 mmol) in THF (10 mL) dropwise at -70 °C under N_2. The mixture was stirred at -70 °C for 15 min, then a solution of DMF (1.29 g, 17.59 mmol) was added at -70°C. The resulting mixture was stirred at -70°C for 15 min. The reaction mixture was added into iced water (50 mL) and acidified to pH = 4 by 1 M HCl aqueous solution, then the mixture was extracted with EA (50 mL × 2). The combined organic phase was washed by brine (50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM31) to afford **compound 2.259** (1.24 g, 4.85 mmol, 55.20% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 10.26 (s, 1H), 7.58 (dd, *J* = 5.6 Hz, 2.0 Hz, 1H).

4-bromo-6-chloro-7-fluoro-1H-indazole 2.260

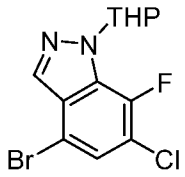


To a solution of **compound 2.259** (1.24 g, 4.85 mmol) in dioxane (25 mL) was added $N_2H_4.H_2O$ (770 mg, 15.07 mmol, 98% purity). The mixture was heated to 80 °C and stirred for 12 h. The reaction mixture was poured into water (60 mL) and extracted with EA (50 mL × 3). The combined organic phase was washed by brine (50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.260** (1.2 g, 4.76 mmol, 98.10% yield) as a yellow solid.

LCMS (AM1): rt = 0.461 min, (250.9 $[M+2+H]^+$), 99.0% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 10.80 (br s, 1H), 8.11 (d, *J* = 3.2 Hz, 1H), 7.34 (d, *J* = 5.6 Hz, 1H) ppm.

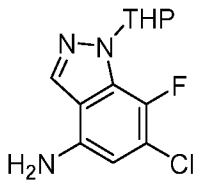
4-bromo-6-chloro-7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.261



To a solution of **compound 2.260** (1.23 g, 4.93 mmol) in THF (25 mL) was added DHP (1.24 g, 14.79 mmol) and TsOH (84.90 mg, 493.05 μmol) at 20 °C. The mixture was stirred at 60°C for 2 h. The reaction mixture was diluted with EA (50 mL), washed with sat. $NaHCO_3$ (aq.) (30 mL × 2) and brine (30 mL × 2). The organic phase was concentrated in *vacuo* to give a residue, which was purified (PM29) to afford **compound 2.261** (1.2 g, 3.54 mmol, 71.87% yield) as a yellow solid.

LCMS (AM1): rt = 0.673 min, (250.9 $[M\text{-}THP+2+H]^+$), 98.5% purity.

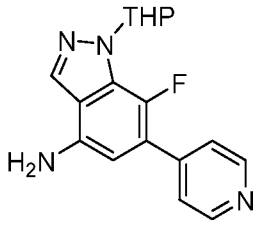
6-chloro-7-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.262



To a solution of **compound 2.261** (850 mg, 2.55 mmol) and $NH_3.H_2O$ (1.28 g, 10.19 mmol, 28% purity) in DMSO (15 mL) was added K_2CO_3 (704.32 mg, 5.10 mmol) and L-proline (117.34 mg, 1.02 mmol) followed by CuI (97.06 mg, 509.62 μmol). The mixture was degassed and purged with N_2 (x3), then the mixture was stirred at 100 °C for 12 h. The reaction mixture was poured onto water (100 mL) and extracted with EA (50 mL × 3). The combined organic phase was washed by brine (40 mL × 4), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.262** (650 mg, crude) as a brown solid

LCMS (AM1): rt = 0.503 min, (270.1 $[M+H]^+$), 77.5% purity.

7-fluoro-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.263

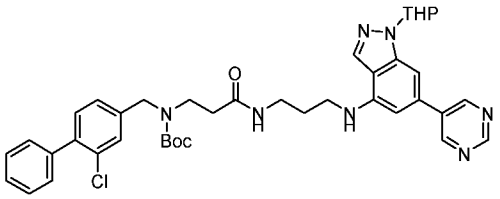


To a solution of **compound 2.262** (650 mg, 2.41 mmol) and 4-pyridylboronic acid (355.49 mg, 2.89 mmol) in dioxane (15 mL) and H_2O (1.5 mL) was added Xphos Pd G4 (207.38 mg, 241.01 μmol) followed by K_2CO_3 (666.17 mg, 4.82 mmol). The mixture was degassed and purged with N_2 (x3). The mixture was stirred at 100 °C for 3 h. The reaction mixture was cooled to 20 °C, diluted with EA (60 mL) and filtered. The filtrate was concentrated in *vacuo* to give a residue, which was purified (PM53) to afford **compound 2.263** (580 mg, 1.84 mmol, 76.51% yield) as a brown solid.

LCMS (AM1): rt = 0.350 min, (313.0 $[M+H]^+$), 99.3% purity.

Synthesis of Intermediate 2.265

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((6-(pyrimidin-5-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 2.265

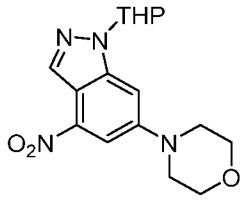


To a solution of **compound 1.382** (140 mg, 193.07 μmol) in H_2O (0.2 mL) and dioxane (2 mL) was added K_2CO_3 (53.37 mg, 386.15 μmol), pyrimidin-5-yl boronic acid (28.71 mg, 231.69 μmol) and $Pd(dppf)Cl_2$ (14.13 mg, 19.31 μmol). The mixture was stirred at 90 °C for 0.5 h under microwave irradiation. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM100) to afford **compound 2.265** (90 mg, 116.18 μmol, 60.18% yield) as a yellow solid.

LCMS (AM3): rt = 1.068 min, (724.2 $[M+H]^+$), 93.50% purity.

Synthesis of Intermediate 2.267

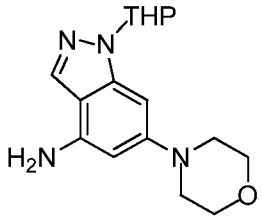
4-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)morpholine 2.266



To a solution of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Ref: WO2019027960, 0.5 g, 1.53 mmol) in DMSO (5 mL) was added CuI (29.20 mg, 0.15 mmol), morpholine (160.27 mg, 1.84 mmol), 2-(2, 6-dimethylanilino)-2-oxo-acetic acid (59.24 mg, 0.31 mmol) and K_3PO_4 (650.84 mg, 3.07 mmol). The mixture was stirred at 110 °C for 12 h under N_2. H_2O (50 mL) was added and extracted by EA (30 mL × 2). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM45) to afford **compound 2.266** (200 mg, 39.2% yield) as a red oil.

LCMS (AM3): rt =0.959 min, (333.6 $[M+H]^+$), 100% purity.

6-morpholino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.267

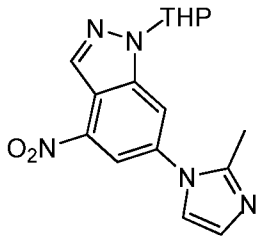


To a solution of **compound 2.266** (190 mg, 0.57 mmol) in MeOH (10 mL) was added Pd/C (200 mg, 0.057 mmol, 10% purity) under N_2 atmosphere. The suspension was degassed and purged with H_2 (x3). The mixture was stirred at 25 °C for 1 h under H_2 (15 Psi). The catalyst was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM161) to afford **compound 2.267** (180 mg, 91.9% yield) as a light-yellow oil.

LCMS (AM3): rt = 0.662 min, (303.6 $[M+H]^+$), 88.3% purity.

Synthesis of Intermediate 2.270

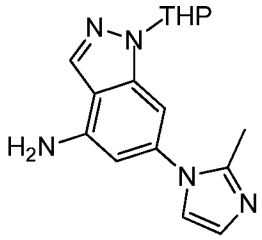
6-(2-methyl-1H-imidazol-1-yl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.269



To a solution of **compound 1.943** (565 mg, 1.94 mmol) in DMF (1 mL) was added $Cu(OAc)_2$ (423.09 mg, 2.33 mmol), 2-methyl-1H-imidazole (239.06 mg, 2.91 mmol), 4Å molecular sieve (1 g, 1.94 mmol) and TEA (785.69 mg, 7.76 mmol). The mixture was stirred at 65 °C for 12 h under oxygen. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM44) to afford **compound 2.269** (200 mg, 28.7% yield) as a yellow solid.

LCMS (AM3): rt = 0.223 min, (327.9 $[M+H]^+$), 91.4% purity.

6-(2-methyl-1H-imidazol-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.270

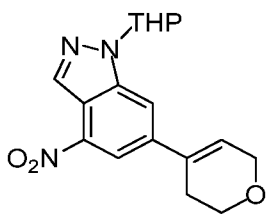


To a solution of $NiCl_2.6H_2O$ (72.61 mg, 0.30 mmol) in MeOH (5 mL) was added $NaBH_4$ (11.56 mg, 0.31 mmol) at 0 °C. After 5 min, **compound 2.269** (200 mg, 0.61 mmol) and $NaBH_4$ (69.35 mg, 1.83 mmol) was added. The mixture was stirred at 0 °C for 25 min. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM163) to afford **compound 2.270** (180 mg, 88.1% yield) as a yellow oil.

LCMS (AM3): rt =0.489 min, (297.9 $[M+H]^+$), 74.3% purity.

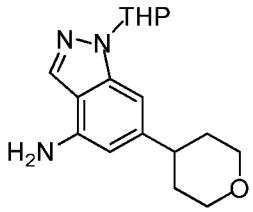
<u>Synthesis of Intermediate 2.277</u>

6-(3,6-dihydro-2H-pyran-4-yl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.272



To a solution of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (WO2019027960, 1 g, 3.07 mmol) in dioxane (10 mL) and H_2O (1 mL) was added K_3PO_4 (1.30 g, 6.13 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (772.94 mg, 3.68 mmol) and $Pd(dppf)Cl_2$ (224.35 mg, 0.31 mmol). The mixture was stirred at 80 °C for 12 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM45) to afford **compound 2.272** (2.8 g, 92.4% yield) as a yellow solid.

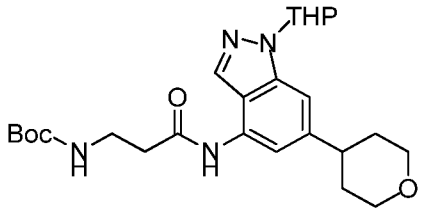
1-(tetrahydro-2H-pyran-2-yl)-6-(tetrahydro-2H-pyran-4-yl)-1H-indazol-4-amine 2.273



To a solution of **compound 2.272** (2.8 g, 8.50 mmol) in MeOH (50 mL) was added Pd/C (2 g, 0.85 mmol, 10% purity) under N_2 atmosphere. The mixture was degassed and purged with H_2 (x3). The mixture was stirred at 25 °C for 12 h under H_2 (15 Psi). The catalyst was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.273** (2.4 g, 90.4% yield) as a black-brown solid.

LCMS (AM3): rt = 0.800 min, (302.2 $[M+H]^+$), 96.5% purity.

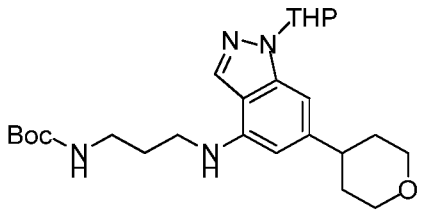
tert-butyl (3-oxo-3-((1-(tetrahydro-2H-pyran-2-yl)-6-(tetrahydro-2H-pyran-4-yl)-1H-indazol-4-yl)amino)propyl)carbamate 2.274



To a solution of **compound 2.273** (2 g, 6.64 mmol) in pyridine (50 mL) was added EDCI (12.72 g, 66.36 mmol) and 3-((tert-butoxycarbonyl)amino)propanoic acid (1.51 g, 7.96 mmol).The mixture was stirred at 100 °C for 12 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM89) to afford **compound 2.274** (2 g, 63.3% yield) as a yellow solid.

LCMS (AM3): rt = 0.935 min, (473.2 $[M+H]^+$), 99.3% purity.

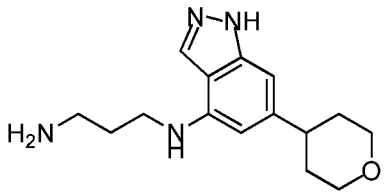
tert-butyl (3-((1-(tetrahydro-2H-pyran-2-yl)-6-(tetrahydro-2H-pyran-4-yl)-1H-indazol-4-yl)amino)propyl)carbamate 2.275



To a solution of **compound 2.274** (2 g, 4.23 mmol, 1 eq) in THF (30 mL) was added BH_3-Me_2S (10 M, 4.23 mL) at 0 °C. The mixture was stirred at 25°C for 2 h. MeOH (30 mL) was slowly dropped into the mixture until no gas was evolved, then the mixture was concentrated in *vacuo* to give a residue, which was purified (PM165) to afford **compound 2.275** (1.3 g, 42.0% yield) as a light-red solid.

LCMS (AM3): rt = 0.876 min, (459.3 $[M+H]^+$), 61.8% purity.

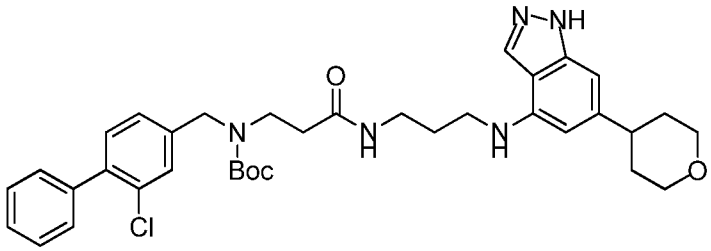
N1-(6-(tetrahydro-2H-pyran-4-yl)-1H-indazol-4-yl)propane-1,3-diamine 2.276



A solution of **compound 2.275** (900 mg, 1.23 mmol) in HCl/dioxane (4 M, 22.50 mL) was stirred at 25 °C for 2 h. The mixture was concentrated in *vacuo* to give a residue, which was triturated with EA (30 mL) at 25 ˚C for 30 min. The mixture was filtered to give **compound 2.276** (500 mg, crude, HCl salt) as a light-yellow solid.

LCMS (AM8): rt = 1.510 min, (275.1 $[M+H]^+$), 98.5% purity.

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-oxo-3-((3-((6-(tetrahydro-2H-pyran-4-yl)-1H-indazol-4-yl)amino)propyl)amino)propyl)carbamate 2.277



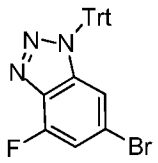
To a solution of **intermediate D** (487.67 mg, 1.25 mmol) in pyridine (10 mL) was added EDCI (999.12 mg, 5.21 mmol) and **compound 2.276** (0.4 g, 1.04 mmol, HCl salt). The mixture was stirred at 100 °C for 12 h. The reaction mixture was concentrated in *vacuo* to give a residue,

which was purified (PM166) to afford **compound 2.277** (130 mg, 18.1% yield) as a yellow solid.

LCMS (AM3): rt = 0.919 min, (646.1 $[M+H]^+$), 93.8% purity.

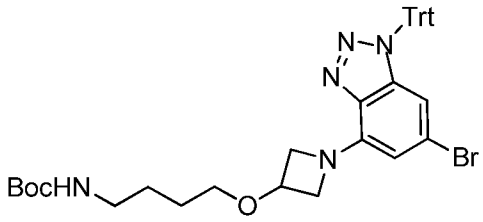
Synthesis of Intermediate 2.285

6-bromo-4-fluoro-1-trityl-1H-benzo[d][1,2,3]triazole 2.280



To a solution of **compound 2.040** (5 g, 23.15 mmol) in THF (75 mL) was added NaH (1.02 g, 25.46mmol, 60% purity) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, then TrtCl (6.78 g, 24.30 mmol) was added and the mixture was stirred at 25°C for 3 h. The reaction mixture was quenched with water (50 mL) and extracted with EA (100 mL × 2). The combined organic layers were washed (brine, 100 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.280** (10.5 g, 22.91 mmol, 98.97% yield) as an off-white solid, which was used for the next step without further purification.

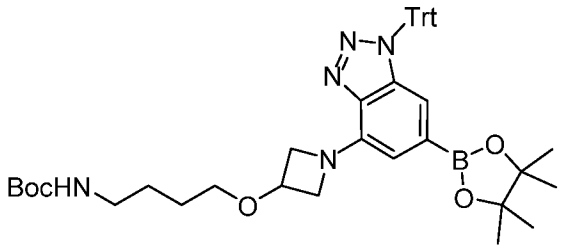
tert-butyl(4-((1-(6-bromo-1-trityl-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.281



To a solution of tert-butyl (4-(azetidin-3-yloxy)butyl)carbamate (Ref: WO2022185041, 3.84 g, 15.71 mmol) and **compound 2.280** (6 g, 13.09 mmol) in DMF (40 mL) was added K_2CO_3 (3.62 g, 26.18 mmol). The mixture was stirred at 75 °C for 7 h. The reaction mixture was quenched with water (60 mL) and extracted with EA (100 mL × 2). The combined organic layers were washed (brine, 50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM55) to afford **compound 2.281** (6.46 g, 9.46 mmol, 72.29%yield) as a yellow oil.

LCMS (AM3): rt = 1.172 min, (706.0 $[M+H]^+$), 79.3% purity

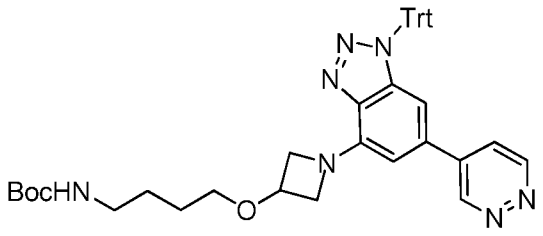
tert-butyl(4-((1-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-trityl-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.282



To a mixture of **compound 2.281** (1.35 g, 1.98 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (602.62 mg, 2.37 mmol) in 1,4-dioxane (10 mL) was added KOAc (388.16 mg, 3.96 mmol) and $Pd(dppf)Cl_2$ (144.70 mg, 197.76 μmol). The mixture was stirred at 85 °C for 16 h under N_2. Water (50 mL) was added and extracted with EA (50 mL × 2). The combined organic layers were washed (brine, 30 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM36) to afford **compound 2.282** (1.35 g, 1.85 mmol, 93.55% yield) as a light-yellow oil.

LCMS (AM3): rt = 1.282 min, (752.7 $[M+Na]^+$), 81.68% purity

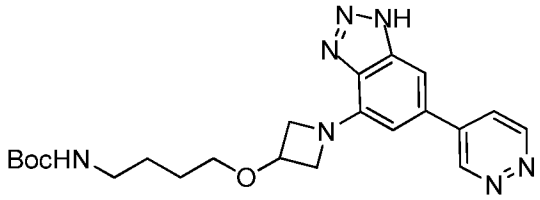
tert-butyl(4-((1-(6-(pyridazin-4-yl)-1-trityl-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.283



To a mixture of 4-bromopyridazine (421.63 mg, 1.76 mmol, HBr salt) and **compound 2.282** (1.35 g, 1.85 mmol) in 1,4-dioxane (13.5mL) and H_2O (1.5 mL) was added K_2CO_3 (767.08 mg, 5.55 mmol) and $Pd(dppf)Cl_2$ (135.37 mg, 185.00 μmol) at 25 °C. The mixture was stirred at 85 °C for 16 h under N_2. Water (50 mL) was added and extracted with EA (50 mL × 2). The combined organic layers were washed (brine, 50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM30) to afford **compound 2.283** (800 mg, 1.17 mmol, 63.42% yield) as a yellow solid

LCMS (AM3): rt = 1.082 min, (682.3 $[M+H]^+$), 75.23% purity

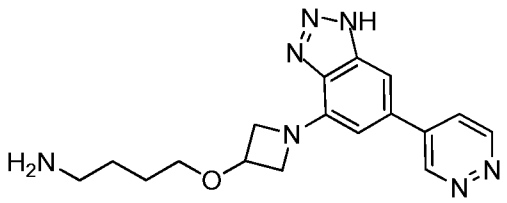
tert-butyl(4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.284



To a solution of **compound 2.283** (570 mg,835.99 μmol) in DCM (60 mL) was added Et_3SiH (194.41 mg, 1.67 mmol, 267.05 μL) followed by TFA (1.91 g,16.72 mmol, 1.24 mL) at 0 °C under N_2. The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated in *vacuo* to afford **compound 2.284** (460 mg, 831.03 μmol, 99.41% yield, TFA salt) as a brown oil, which was used for the next step directly.

LCMS (AM3): rt = 0.863 min, (440.3 $[M+H]^+$), 48% purity

4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butan-1-amine 2.285

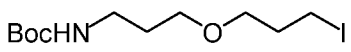


To a solution of **compound 2.284** (460 mg, 831.03 μmol, TFA salt) in DCM (20 mL) was added TFA (3.08 g, 27.01 mmol, 2 mL) and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM88) to afford **compound 2.285** (400 mg, 830.27 μmol) as a brown oil

LCMS (AM3): rt = 0.641 min, (340.4 $[M+H]^+$), 96.69% purity

Synthesis of Intermediate 2.289

tert-butyl (3-(3-iodopropoxy)propyl)carbamate 2.287

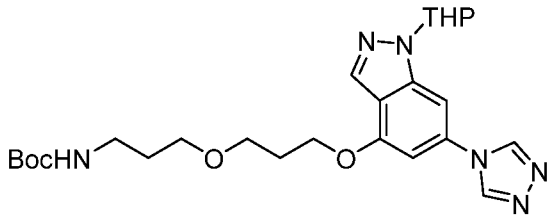


To a mixture of tert-butyl N-[3-(3-hydroxypropoxy)propyl]carbamate (CAS 1312905-31-9, 500 mg, 2.14 mmol) in DCM (10 mL) was added imidazole (291.81 mg, 4.29 mmol) and PPh_3

(1.12 g, 4.29 mmol) in one portion at 0 °C under N_2, then I_2 (1.09 g, 4.29 mmol) was added at 0°C and the mixture was stirred at 25 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue and saturated Na_2SO_3 (30 mL) solution was added. The aqueous phase was extracted with EA (50 mL × 3). The combined organic phase was washed (brine, 50 mL × 1), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM46) to afford **compound 2.287** (560 mg, 1.63 mmol, 76.14% yield) as a yellow oil.

^{1}H NMR (400MHz, MeOH-d_4) δ 3.50 (t, *J* = 4.4 Hz, 4H), 3.33 (t, *J* = 6.8 Hz, 2H), 3.14 (t, *J* = 6.8 Hz, 2H), 2.07 - 2.01 (m, 2H), 1.75 - 1.72 (m, 2H), 1.45 (s, 9H) ppm

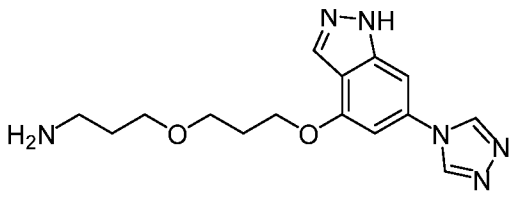
tert-butyl(3-(3-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propoxy)propyl)carbamate 2.288



To a mixture of **compound 1.360** (200 mg, 701.01 μmol) in DMF (2 mL) was added K_2CO_3 (193.77 mg, 1.40 mmol) and c**ompound 2.287** (360.88 mg, 1.05 mmol). The mixture was stirred at 80°C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM167) to afford **compound 2.288** (200 mg, 331.61 μmol, 47.30% yield) as a brown gum.

LCMS (AM3): rt = 0.918 min, (501.2 $[M+H]^+$), 83.28% purity.

3-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propoxy)propan-1-amine 2.289

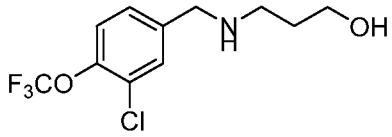


A mixture of **compound 2.288** (200 mg, 331.61 μmol) in HCl/dioxane (4 M, 5.53 mL) was stirred at 20°C for 2 h. The mixture was concentrated in *vacuo* to afford **compound 2.289** (200 mg, crude, HCl salt) as a brown solid, which was used without further purification.

LCMS (AM3): rt = 0.549 min, (317.4 $[M+H]^+$), 98.32% purity.

Synthesis of Intermediate 2.294

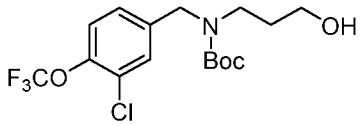
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propan-1-ol 2.291



To a solution of 3-aminopropan-1-ol (668.48 mg, 8.90 mmol) in MeOH (10 mL) was added 3-chloro-4-(trifluoromethoxy)benzaldehyde (CAS 83279-39-4, 1 g, 4.45 mmol). The resulting mixture was stirred at 20°C for 13 h, then $NaBH(OAc)_3$ (943.79 mg, 4.45 mmol) was added. The mixture was stirred for 2 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM90) to afford **compound 2.291** (230 mg, 578.33 μmol, 13.00% yield, TFA salt) as a yellow oil.

LCMS (AM3): rt = 0.840 min, (284.0 $[M+H]^+$), 86.50% purity.

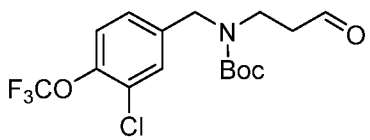
Tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-hydroxypropyl)carbamate 2.292



To a solution of **compound 2.291** (230 mg, 578.33 μmol, TFA salt) in THF (10 mL) was added $NaHCO_3$ (72.88 mg, 867.49 μmol), Boc_2O (151.46 mg, 694.00 μmol). The reaction mixture was stirred at 20°C for 12 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with EA (20 mL × 3). The organic layer was washed (brine, 30 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.292** (615 mg, crude) as a yellow oil.

LCMS (AM3): rt = 1.000 min, (284.5 $[M-100+H]^+$), 94.46% purity.

Tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-oxopropyl)carbamate 2.293

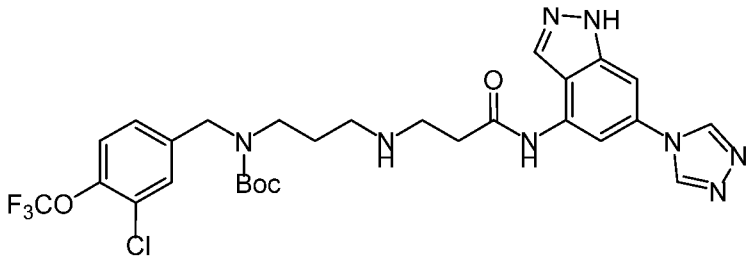


A mixture of **compound 2.292** (590 mg, 1.54 mmol) and DMP (800 mg, 1.89 mmol) in DCM (15 mL) was stirred at 16 °C for 15 h. The reaction mixture was filtered and the filtrate was

concentrated in *vacuo* to give a residue, which was purified (PM11) to afford **compound 2.293** (370 mg, 59.26% yield) as a colourless oil.

LCMS (AM3): rt = 1.038min, (326.2 $[M-C_4H_8+H]^+$), 94.47% purity.

Tert-butyl (3-((3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)-3-oxopropyl)amino)propyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate 2.294

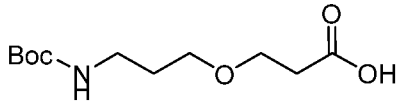


A mixture of **compound 2.293** (40 mg, 104.77 μmol), **compound 1.285** (40 mg, 129.98 μmol, HCl salt) and DIPEA (459.30 μmol) in MeOH (4 mL) was stirred at 25 °C for 16 h, then $NaBH_3CN$ (40 mg, 636.54 μmol) was added and the reaction was stirred for 1 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM168) to afford **compound 2.294** (30 mg, 38.12% yield) as a white solid.

LCMS (AM3): rt = 0.872 min, (637.2 $[M+H]^+$), 100% purity.

Synthesis of Intermediate 2.298

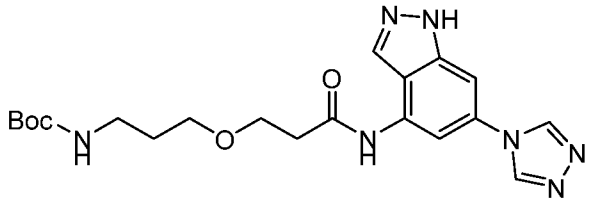
3-(3-((tert-butoxycarbonyl)amino)propoxy)propanoic acid 2.296



To a mixture of tert-butyl N-[3-(3-hydroxypropoxy)propyl]carbamate (CAS 1312905-31-9, 1.1 g, 4.71 mmol) in DCM (10 mL) and H_2O (10 mL) was added TEMPO (220 mg, 1.40 mmol) followed by [acetoxy(phenyl)-iodanyl] acetate (3.04 g, 9.43 mmol). The reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was poured to NaOH solution (1 N, 80 mL). The resultant mixture was extracted with EA (30 mL × 3). The pH of the aqueous phase was adjusted to ~3 with conc. HCl, then the mixture was extracted with EA (30 mL × 3). The combined organic phase was washed (brine, 50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.296** (850 mg, 3.44 mmol, 72.90% yield) as a brown oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (t, *J* = 5.6 Hz, 1H), 3.57 (t, *J* = 4.4 Hz, 2H), 3.47 (t, *J* = 7.6 Hz, 2H), 2.99 - 2.87 (m, 2H), 2.42 (t, *J* = 6.0 Hz, 2H), 1.63 - 1.48 (m, 2H), 1.37 (s, 9H) ppm

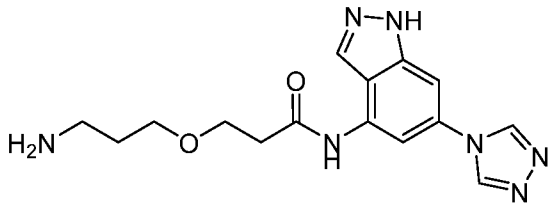
tert-butyl (3-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)-3-oxopropoxy)propyl)carbamate 2.297



A mixture of **compound 2.296** (400 mg, 1.62 mmol), **compound 1.273** (400 mg, 1.41 mmol) and EDCI (808 mg, 4.21 mmol) in pyridine (10 mL) was stirred at 80 °C for 16 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM169) to afford **compound 2.297** (250 mg, 34.60% yield) as a brown solid.

LCMS (AM3): rt = 0.861min, (514.4 $[M+H]^+$), 100% purity.

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-(3-aminopropoxy)propanamide 2.298

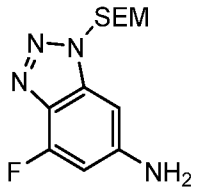


A mixture of **compound 2.297** (250 mg, 486.77 μmol) in HCl/dioxane (4 M, 10 mL) was stirred at 25 °C for 1 h. The reaction mixture was concentrated in *vacuo* to afford **compound 2.298** (180 mg, crude, HCl salt) as a brown solid, which was used for the next step directly without further purification.

LCMS (AM3): rt = 0.229 min, (330.1 $[M+H]^+$), ~70% purity.

Synthesis of Intermediate 2.304

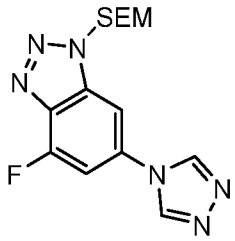
4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-6-amine 2.300



To a solution of 6-bromo-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazole (9 g, 25.99 mmol, Ref: WO202256449) in DMSO (120 mL) was added $NH_3.H_2O$ (10.93 g, 77.97 mmol, 12.01 mL, 25% purity), K_2CO_3 (10.78 g, 77.97 mmol), CuI (990.01 mg, 5.20 mmol) and (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid (1.36 g, 10.40 mmol). The reaction mixture was stirred at 80°C for 12 h. The reaction mixture was diluted with H_2O (150 mL) and extracted with EA (200 mL × 2). The organic layer was washed (brine, 200 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM25) to afford **compound 2.300** (3.32 g, 11.76 mmol, 45.23% yield) as a red oil.

LCMS (AM3): rt = 0.914min, (283.1 $[M+H]^+$), 99.20% purity.

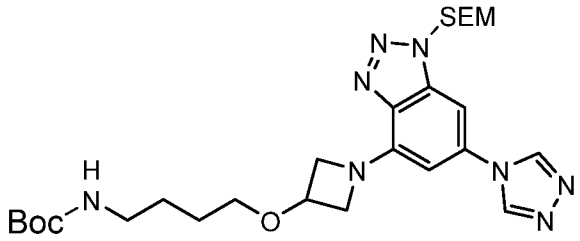
4-fluoro-6-(4H-1,2,4-triazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazole 2.301



To a solution of N-formamidoformamide (5.15 g, 58.43 mmol) and **compound 2.300** (3.3 g, 11.69 mmol) in pyridine (75 mL) was added TEA (8.28 g, 81.80 mmol, 11.39 mL) and TMSCl (19.04 g, 175.29 mmol). The mixture was stirred at 120 °C for 16 h. The reaction mixture was diluted with water (50 mL) and extracted with EA (100 mL × 2). The combined organic layers were washed (brine, 50 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM23) to afford **compound 2.301** (2.2 g, 6.58 mmol, 56.29% yield) as a grey solid

LCMS (AM3): rt = 0.809 min, (335.1 $[M+H]^+$), 99.53% purity.

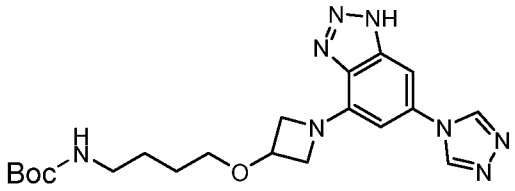
tert-butyl (4-((1-(6-(4H-1,2,4-triazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.302



To a solution of tert-butyl (4-(azetidin-3-yloxy)butyl)carbamate (WO2022185041, 109.59 mg, 448.53 μmol) and **compound 2.301** (100 mg, 299.02 μmol) in DMF (2 mL) was added K_2CO_3 (82.66 mg, 598.04 μmol). The mixture was stirred at 80 °C for 3 h. The reaction mixture was diluted with water (20 mL) and extracted with EA (30 mL × 2). The combined organic layers were washed (brine, 30 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM90) to afford **compound 2.302** (95 mg, 170.02 μmol, 56.86% yield) as a brown solid

LCMS (AM3): rt = 0.975 min, (559.2 $[M+H]^+$), 66.88% purity.

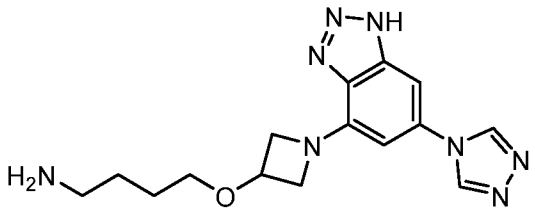
tert-butyl (4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)carbamate 2.303



A mixture of **compound 2.032** (2.16 g, 3.87 mmol) and TBAF in THF (1 M, 25 mL) was stirred at 65 °C for 80 min. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM23) then further purified (PM170) to afford **compound 2.303** (1.29 g, 3.01 mmol, 77.88% yield) as a yellow solid.

LCMS (AM3): rt = 0.805 min, (429.2 $[M+H]^+$), 96.84% purity.

4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butan-1-amine 2.304

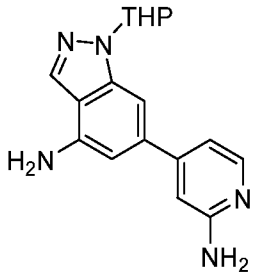


To a solution of **compound 2.303** (0.1 g, 233.38 μmol) in DCM (3 mL) was added TFA (4.05 mmol, 0.3 mL). The reaction mixture was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM170) to afford **compound 2.304** (80 mg, 197.87 μmol, 84.78% yield, FA salt) as a yellow solid.

LCMS (AM3): rt = 0.294min, (329.2 $[M+H]^+$), 92.60% purity.

<u>Synthesis of Intermediate 2.306</u>

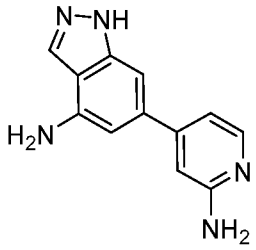
6-(2-aminopyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.305



To a mixture of **compound 1.952** (630 mg, 1.84 mmol) and 4-chloropyridin-2-amine (CAS 19798-80-2, 247.77 mg, 1.93 mmol) in dioxane (10 mL) and H_2O (0.1 mL) was added Cs_2CO_3 (897.07 mg, 2.75 mmol) followed by $Pd(dppf)Cl_2$ (134.31 mg, 183.55 μmol). The mixture was heated to 100°C and stirred for 12 h. The reaction mixture was diluted with DCM (30mL) and filtered. The filtrate was concentrated in *vacuo* to give a residue, which was purified (PM22) to afford **compound 2.305** (250 mg, 750.89 μmol, 40.91% yield) as a yellow solid.

LCMS (AM12): rt = 0.340 min, (310.1 $[M+H]^+$), 92.92% purity.

6-(2-aminopyridin-4-yl)-1H-indazol-4-amine 2.306

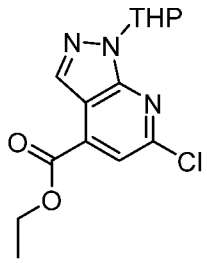


A mixture of **compound 2.305** (250 mg, 808.11 μmol) in HCl/dioxane (4 M, 3 mL) was stirred at 20°C for 1 h. The mixture was concentrated in *vacuo* to afford the **compound 2.306** (290 mg, crude, HCl salt) as a yellow solid.

LCMS (AM12): rt = 0.256 min, (226.1 $[M+H]^+$), 91.15% purity.

Synthesis of Intermediate 2.313

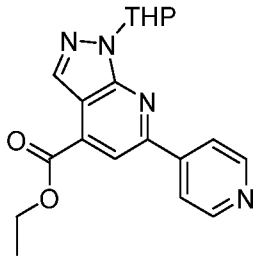
ethyl 6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-4-carboxylate 2.309



To a solution of ethyl 6-chloro-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (5.2 g, 23.05 mmol, US2013/150340) in THF (60 mL) was added DHP (5.82 g, 69.14 mmol) followed by TsOH (396.86 mg, 2.30 mmol). The mixture was heated to 50 °C and stirred for 2 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM48) to afford **compound 2.309** (7.2 g, 22.87 mmol, 99.25% yield) as a yellow solid.

LCMS (AM12): rt = 0.591 min, (332.0 $[M+Na]^+$), 98.47% purity.

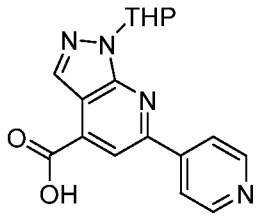
ethyl 6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-4-carboxylate 2.310



To a solution of **compound 2.309** (3 g, 9.69 mmol) in dioxane (50 mL) and H_2O (5 mL) was added pyridin-4-ylboronic acid (1.43 g, 11.62 mmol) and K_2CO_3 (2.01 g, 14.53 mmol) followed by $Pd(dppf)Cl_2$ (708.68 mg, 968.53 μmol) at 20°C. The mixture was degassed and purged with N_2 (x3), the mixture was heated to 80 °C and stirred for 3 h. The reaction mixture was cooled to 20°C, diluted with EA (50 mL) and filtered. The filtrate was concentrated in *vacuo* to give a residue, which was purified (PM33) to afford **compound 2.310** (2.23 g, 5.99 mmol, 61.88% yield) as a yellow solid.

LCMS (AM12): rt = 0.442 min, (353.1 $[M+H]^+$), 94.70% purity.

6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridine-4-carboxylic acid 2.311

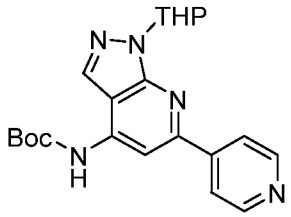


To a solution of **compound 2.310** (1 g, 2.84 mmol) in MeOH (15 mL) was added NaOH (113.50 mg, 2.84 mmol) and H_2O (5 mL). The mixture was stirred at 20°C for 2 h. The reaction mixture was concentrated in *vacuo*. The residue was dissolved in H_2O (40 mL) and acidified to pH = 6 (1 N HCl (aq.)). The mixture was filtered. The filter cake was dried under vacuum to afford **compound 2.311** (647 mg, 1.96 mmol, 69.11% yield) as an off-white solid.

LCMS (AM11): rt = 0.304 min, (325.1 $[M+H]^+$), 98.31% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.19 (br s, 1H), 8.78 (d, J = 5.6 Hz, 2H), 8.49 (s, 1H), 8.35 (s, 1H), 8.23 (d, J = 5.6 Hz, 2H), 6.23 (d, J = 8.8 Hz, 1H), 4.05 - 3.94 (m, 1H), 3.86 - 3.70 (m, 1H), 2.73 - 2.56 (m, 1H), 2.13 - 1.95 (m, 2H), 1.91 - 1.78 (m, 1H), 1.68 - 1.52 (m, 2H) ppm.

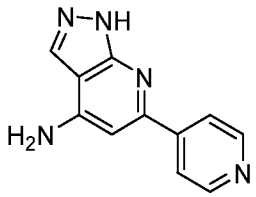
tert-butyl (6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)carbamate 2.312



To a solution of **compound 2.311** (547 mg, 1.69 mmol) in toluene (18 mL) was added DPPA (510.55 mg, 1.86 mmol) and TEA (426.65 mg, 4.22 mmol) followed by *t*-BuOH (2.29 g, 30.94 mmol). The mixture was heated to 105 °C and stirred for 12 h under N_2. The reaction mixture was cooled to 20 °C, poured onto H_2O (40 mL) and extracted with EA (60 mL × 3). The combined organic phases were washed (brine, 40 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM32) to afford **compound 2.312** (479 mg, 1.21 mmol, 71.55% yield) as a white solid.

LCMS (AM12): rt = 0.458 min, (396.1 $[M+H]^+$), 99.62% purity.

6-(pyridin-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine 2.313

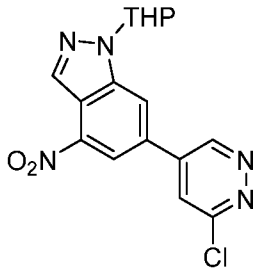


A solution of **compound 2.312** (660 mg, 1.67 mmol) in HCl/MeOH (4 M, 20 mL) was stirred at 20 °C for 15 h. The mixture was concentrated in *vacuo* to give a residue. The residue was dissolved in H_2O (20 mL) and basified to pH=9 (sat. $NaHCO_3$ (aq.)). The precipitated solid was filtered and washed with H_2O (2 mL × 2). The filter cake was collected and dried under vacuum to afford **compound 2.313** (240 mg, crude) as a grey solid.

LCMS (AM11**)**: rt = 0.318 min, (212.2 $[M+H]^+$), 92.08% purity.

Synthesis of Intermediate 2.317

6-(6-chloropyridazin-4-yl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.315

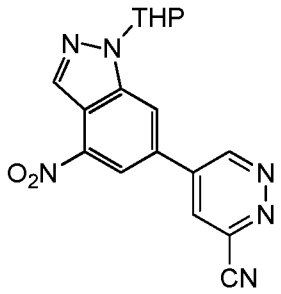


To a solution of **compound 1.943** (607 mg, 1.63 mmol) and 3,5-dichloropyridazine (290.76 mg, 1.95 mmol) in dioxane (12 mL) and H_2O (1.2 mL) was added K_3PO_4 (863.09 mg, 4.07 mmol) followed by $Pd(t\text{-}Bu_3P)_2$ (124.68 mg, 243.96 μmol). The mixture was degassed and purged with N_2 (x3), heated to 70°C and stirred for 2 h. The reaction mixture was cooled to 20°C, diluted with EA (40mL) and filtered. The filtrate was concentrated in *vacuo* to give a residue, which was triturated with MTBE (20 mL) at 20 °C and filtered. The filter cake was collected and dried under vacuum to afford **compound 2.315** (423 mg, 990.46 μmol, 60.90% yield) as a brown solid.

LCMS (AM11): rt = 0.478 min, (360.1 $[M+H]^+$), 84.24% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 9.51 (s, 1H), 8.72 (s, 1H), 8.42 (s, 1H), 8.30 (s, 1H), 7.84 (d, J = 2.0 Hz, 1H), 5.94 (dd, J = 8.0 Hz, 2.4 Hz, 1H), 4.03 - 3.96 (m, 1H), 3.86 - 3.78 (m, 1H), 2.61 - 2.51 (m, 1H), 2.26 - 2.19 (m, 2H), 1.87 - 1.76 (m, 3H) ppm.

5-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)pyridazine-3-carbonitrile 2.316

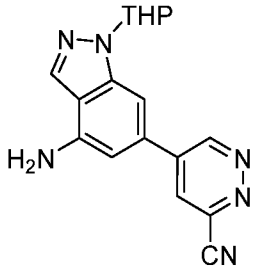


To a mixture of **compound 2.315** (313 mg, 870.01 μmol) in DMA (6 mL) was added DPPF (96.46 mg, 174.00 μmol), $Zn(CN)_2$ (153.25 mg, 1.31 mmol) and $Pd_2(dba)_3$ (79.67 mg, 87.00 μmol). The mixture was degassed and purged with N_2 (x3), the mixture was stirred at 120°C for 2 h. The reaction mixture was cooled to 20°C, diluted with DMF (6 mL) and filtered. The

filtrate was poured onto H_2O (50 mL) and filtered. The filter cake was dried under vacuum to afford **compound 2.316** (190 mg, 293.14 μmol, 33.69% yield) as a black-brown solid.

LCMS (AM12): rt = 0.522 min, (351.2 $[M+H]^+$), 54.05% purity.

5-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)pyridazine-3-carbonitrile 2.317

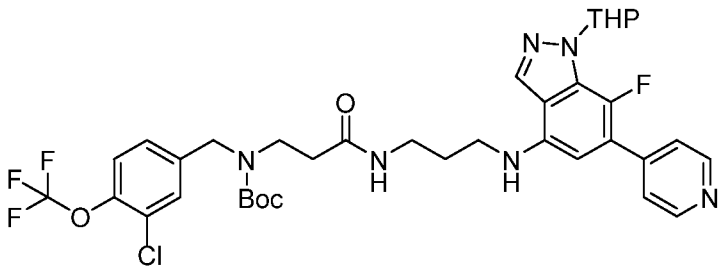


To a solution of **compound 2.316** (190 mg, 542.34 μmol) in MeOH (5 mL) and H_2O (2 mL) was added NH_4Cl (232.09 mg, 4.34 mmol) and Fe (181.72 mg, 3.25 mmol). The mixture was stirred at 60 °C for 1 h. The reaction mixture was diluted with MeOH (30 mL) and filtered. The filtrate was concentrated in *vacuo* to give a residue, which was purified (PM52) to afford **compound 2.317** (35 mg, 106.55 μmol, 19.65% yield) as a yellow solid.

LCMS (AM11): rt = 0.398 min, (320.9 $[M+H]^+$), 97.52% purity.

Synthesis of Intermediate 2.320

tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((7-fluoro-6-(pyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.320



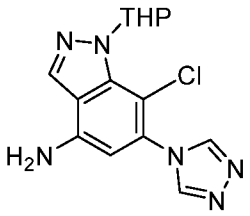
To a solution of **compound 2.263** (80 mg, 256.13 μmol) in MeOH (1 mL) was added **compound 1.950** (115.99 mg, 256.13 μmol) at 20 °C. The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (56.33 mg, 896.46 μmol) was added in portions at 0°C. The mixture was stirred at 20 °C for 1 h. The reaction mixture was purified (PM171) to give a solution, then the solution was basified to pH = 9 by saturated $NaHCO_3$ solution and extracted with EA (30 mL × 3). The combined organic phases were washed by brine (20 mL × 2), dried (Na_2SO_4), filtered

and concentrated in *vacuo* to afford **compound 2.320** (70 mg, 70.22 μmol, 27.41% yield) as a yellow solid.

LCMS (AM11): rt = 0.498 min, (749.30 $[M+H]^+$), 75.15% purity.

Synthesis of Intermediate 2.321

7-chloro-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine 2.321

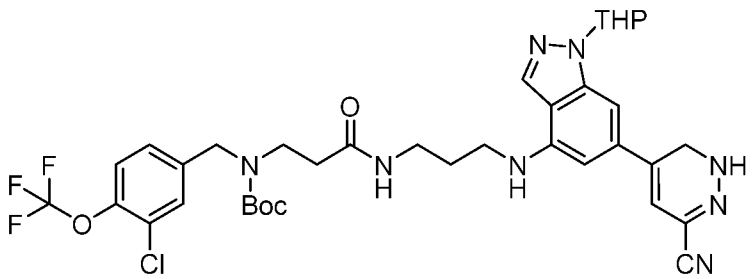


To a solution of **compound 1.302** (500 mg, 1.76 mmol) in DMF (5 mL) was added NCS (234.83 mg, 1.76 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. The reaction mixture was poured into water (30 mL) and extracted with EA (30 mL × 3). The combined organic phase was washed (brine, 30 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, then the residue was triturated with DMF (4 mL) and filtered. The filter cake was dried *in vacuo* to afford **compound 2.321** (183 mg, 505.78 μmol, 28.76% yield) as a yellow solid.

LCMS (AM14): rt = 0.430 min, (319.2 $[M+H]^+$), 88.1% purity.

Synthesis of Intermediate 2.326

tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((6-(6-cyano-2,3-dihydropyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.325

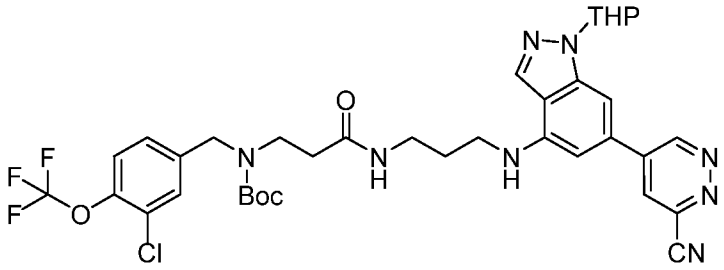


To a solution of **compound 2.317** (70 mg, 175.95 μmol, 80.52% purity) in MeOH (1 mL) was added **compound 1.950** (79.68 mg, 175.95 μmol) and AcOH (12.68 mg, 211.14 μmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (38.70 mg, 615.81 μmol) was added in

portions at 0 °C. The resulting mixture was stirred at 20 °C for 2 h. The mixture was filtered and the filtrate was purified (PM175) to afford **compound 2.325** (48 mg, 60.50 μmol, 34.38% yield) as a yellow solid.

LCMS (AM11): rt = 0.565 min, (781.3 $[M+Na]^+$), 95.69% purity.

tert-butyl (3-chloro-4-(trifluoromethoxy)benzyl)(3-((3-((6-(6-cyanopyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.326

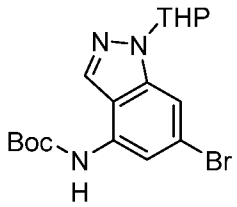


To a solution of **compound 2.325** (24 mg, 31.61 μmol) in DCM (2 mL) was added MnO_2 (21.99 mg, 252.89 μmol), then the mixture was stirred at 20 °C for 2 h. The reaction mixture was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.326** (36 mg, 43.80 μmol, 69.28% yield) as a yellow solid.

LCMS (AM11): rt = 0.570 min, (757.5 $[M+H]^+$), 92.13% purity.

Synthesis of Intermediate 2.335

tert-butyl (6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)carbamate 2.330

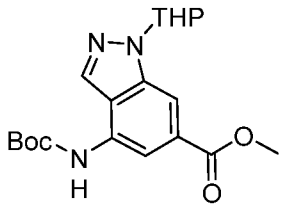


To a solution of **compound 1.381** (1.25 g, 4.22 mmol) in THF (100 mL) was added Boc_2O (2.76 g, 12.66 mmol) dropwise, then the mixture was heated to 70 °C and stirred for 12 h, then Boc_2O (3.96 g, 18.15 mmol) and TEA (896.88 mg, 8.86 mmol) were added to the mixture at 20 °C. The resulting mixture was stirred 70°C for 12 h. The reaction mixture was poured into water (100 mL) and extracted with EA (100 mL × 3). The combined organic phase was washed (brine, 100 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which

was purified (PM35) to afford **compound 2.330** (1.25 g, 3.09 mmol, 73.24% yield) as a brown oil.

LCMS (AM16): rt = 0.857 min, (398.1 $[M+2+H]^+$), 73.6% purity.

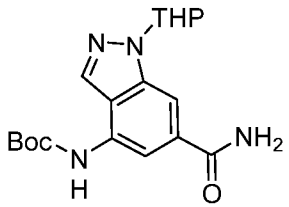
methyl 4-((tert-butoxycarbonyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 2.331



To a solution of **compound 2.330** (1.25 g, 3.15 mmol) in MeOH (20 mL) was added $Pd(dppf)Cl_2$ (230.81 mg, 315.44 µmol) and TEA (957.56 mg, 9.46 mmol) under N_2. The suspension was degassed and purged with CO (x3). The mixture was stirred at 70 °C for 16 h under CO (50 psi). The mixture was poured into water (50 mL) and extracted with EA (50 mL × 3). The combined organic phase was washed (brine, 50 mL), dried with anhydrous sodium sulfate, filtered and concentrated in *vacuo* to give a residue, which was purified (PM27) to afford **compound 2.331** (1.0 g, 2.66 mmol, 84.45% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.22 (s, 1H), 8.08 (s, 1H), 8.04 (s, 1H), 6.85 (s, 1H), 5.77 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 4.05 (d, *J* = 11.2 Hz, 1H), 3.96 (s, 3H), 3.82 - 3.76 (m, 1H), 2.61 - 2.53 (m, 1H), 2.24 - 2.08 (m, 2H), 1.85 - 1.72 (m, 3H), 1.58 (s, 9H) ppm.

tert-butyl (6-carbamoyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)carbamate 2.332

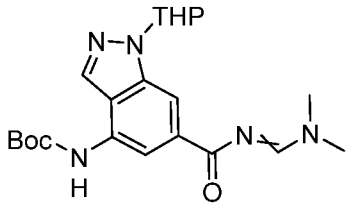


A solution of **compound 2.331** (1 g, 2.66 mmol) in NH_3/MeOH (7 M, 50 mL) was stirred at 80°C for 48 h in a 100 mL of sealed tube. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM24) to afford **compound 2.332** (892 mg, 2.43 mmol, 91.40% yield) as a yellow solid.

LCMS (AM12): rt = 0.464 min, (221.0 $[M-THP+2+H]^+$), 98.37% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.06 (s, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 6.91 (s, 1H), 5.76 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 4.06 (d, *J* = 10.2 Hz, 1H), 3.82 - 3.75 (m, 1H), 2.59 - 2.50 (m, 1H), 2.19 - 2.06 (m, 2H), 1.84 - 1.71 (m, 3H), 1.58 (s, 9H) ppm.

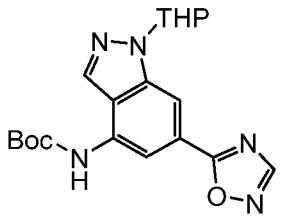
tert-butyl (6-(((dimethylamino)methylene)carbamoyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)carbamate 2.333



To a solution of **compound 2.332** (800 mg, 2.22 mmol) in toluene (10 mL) was added DMF-DMA (793.52 mg, 6.66 mmol). The mixture was heated to 100 °C and stirred for 2 h. The mixture was concentrated in *vacuo* to afford **compound 2.333** (1 g, crude) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.66 (s, 1H), 8.35 (s, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 6.76 (s, 1H), 5.80 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 4.06 (d, *J* = 10.8 Hz, 1H), 3.82 - 3.74 (m, 1H), 3.29 (s, 3H), 3.23 (s, 3H), 2.64 - 2.52 (m, 1H), 2.16 (s, 1H), 2.06 (d, *J* = 12.0 Hz, 1H), 1.83 - 1.67 (m, 3H), 1.57 (s, 9H) ppm.

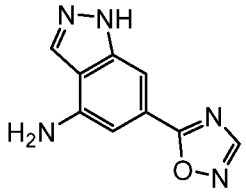
tert-butyl (6-(1,2,4-oxadiazol-5-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)carbamate 2.334



To a mixture of $NH_2OH.HCl$ (200.70 mg, 2.89 mmol) and NaOH (5 M, 0.577 mL) in AcOH (10 mL) and dioxane (10 mL) was added **compound 2.333** (1 g, 2.41 mmol) in one portion. The mixture was stirred at 25 °C for 30 min, then heated to 80 °C and stirred for 1 h. The mixture was poured into water (30 mL) and extracted with EA (30 mL × 3). The combined organic phase was washed (brine, 30 mL), dried with anhydrous sodium sulfate, filtered and concentrated in *vacuo* to give a residue, which was purified (PM24) to afford **compound 2.334** (489 mg, 1.27 mmol, 52.72% yield) as a yellow solid.

LCMS (AM12): rt = 0.591 min, (386.2 $[M+H]^+$), 74.7% purity.

6-(1,2,4-oxadiazol-5-yl)-1H-indazol-4-amine 2.335

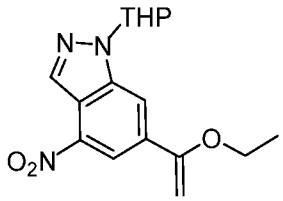


To a solution of **compound 2.334** (489 mg, 1.27 mmol) in DCM (5 mL) was added TFA (451.82 mg, 3.96 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was diluted with ACN (10 mL) and basified to pH = 8 by $NH_3 \cdot H_2O$. The mixture was filtered, the filter cake was dried *in vacuo* to afford **compound 2.335** (152 mg, 755.53 μmol, 59.55% yield) as a yellow solid.

LCMS (AM16): rt = 430 min, (202.2 $[M+H]^+$), 98.5% purity.

Synthesis of Intermediate 2.340

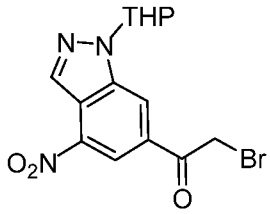
6-(1-ethoxyvinyl)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 2.337



The mixture of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Ref: WO2019027960, 5 g, 15.33 mmol) in DMF (50 mL) was added tributyl(1-ethoxyvinyl)stannane (5.81 g, 16.10 mmol) and $Pd(PPh_3)_4$ (1.77 g, 1.53 mmol). The mixture was heated to 100 °C and stirred for 2 h under N_2. The mixture was poured into saturated KF aqueous solution (100 mL) and stirred for 2 h. The mixture was filtered and the filtrate was extracted with EA (100 mL × 3). The combined organic phase was washed (brine, 100 mL × 3), dried with anhydrous sodium sulfate, filtered and concentrated in *vacuo* to give a residue, which was purified (PM27) to afford **compound 2.337** (3.6 g, 11.34 mmol, 74.00% yield) as a yellow solid.

LCMS (AM16): rt = 0.719 min, (318.2 $[M+H]^+$), 68.6% purity.

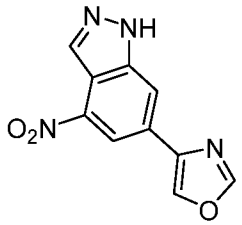
2-bromo-1-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)ethan-1-one 2.338



To a solution of **compound 2.337** (3 g, 9.45 mmol) in THF (30 mL) and H_2O (6 mL) was added NBS (1.68 g, 9.45 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was poured into water (50 mL) and extracted with EA (50 mL × 3). The combined organic phase was washed (brine, 50 mL), dried with anhydrous sodium sulfate, filtered and concentrated in *vacuo* to afford **compound 2.338** (3 g, crude) as a white solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.79 - 8.63 (m, 3H), 5.93 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 4.56 (s, 2H), 4.04 - 3.96 (m, 1H), 3.86 - 3.77 (m, 1H), 2.61 - 2.48 (m, 1H), 2.23 - 2.16 (m, 2H), 1.89 - 1.75 (m, 3H) ppm.

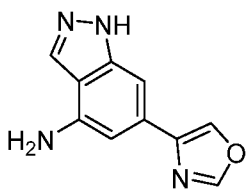
4-(4-nitro-1H-indazol-6-yl)oxazole 2.339



To a solution of **compound 2.338** (2.4 g, 6.52 mmol) in formamide (67.80 g, 1.51 mol) was added H_2SO_4 (4.48 g, 45.63 mmol) in one portion, then the mixture was heated to 100 °C and stirred for 1 h. The mixture was poured into water (240 mL) and filtered. The filter cake was washed with ACN (15 mL), filtered and dried under *vacuum* to afford **compound 2.339** (1.5 g, crude) as a brown solid.

LCMS (AM12): rt = 0.406 min, (231.2 $[M+H]^+$), 82.78% purity.

6-(oxazol-4-yl)-1H-indazol-4-amine 2.340

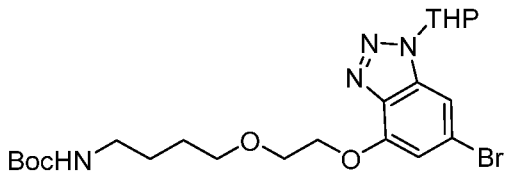


To a mixture of **compound 2.339** (500 mg, 1.78 mmol, 82% purity) in MeOH (15 mL) and H_2O (5 mL) was added Fe (497.36 mg, 8.91 mmol) and NH_4Cl (476.40 mg, 8.91 mmol). The mixture was stirred at 60 °C for 2 h. The mixture was filtered, the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM177) to afford **compound 2.340** (100 mg, 439.57 μmol, 24.68% yield) as a grey solid.

LCMS (AM14): rt = 0.325 min, (201.2 $[M+H]^+$), 88.74% purity.

Synthesis of Intermediate 2.347

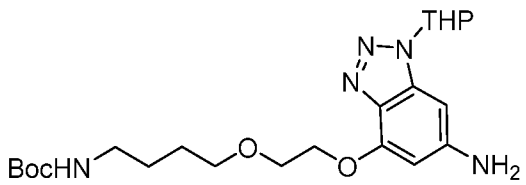
tert-butyl (4-(2-((6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butyl)carbamate 2.344



To a solution of tert-Butyl (4-(2-hydroxyethoxy)butyl)carbamate (CAS 2361304-25-6, 4.66 g, 19.99 mmol) in THF (200 mL) was added NaH (999.48 mg, 24.99 mmol, 60% purity). The reaction mixture was stirred at 0 °C for 1.5 h, then **compound 2.041** (5 g, 16.66 mmol) was added. The reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was diluted with H_2O (150 mL) and extracted with EA (100 mL × 2). The combined organic phases were washed (brine, 150 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM54) to afford **compound 2.344** (4.5 g, 8.76 mmol, 52.61% yield) as a yellow oil.

LCMS (AM3): rt = 1.016 min, (513.2 $[M+H^+]$), 79.57% purity

tert-butyl (4-(2-((6-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butyl)carbamate 2.345

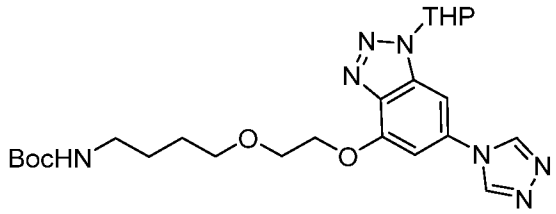


To a solution of **compound 2.344** (900 mg, 1.75 mmol) in DMSO (8 mL) was added $NH_3.H_2O$ (1.02 g, 7.30 mmol, 1.13 mL, 25% purity), K_2CO_3 (726.80 mg, 5.26 mmol), CuI (70.11 mg, 368.12 μmol) and (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid (94.24 mg, 718.70 μmol).

The reaction mixture was stirred at 90 °C for 12 h. The reaction mixture was diluted with H_2O (20 mL), then extracted with EA (15 mL × 2). The combined organic phases were washed (brine, 30 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.345** (800 mg, crude) as a yellow oil.

LCMS (AM3): rt = 0.857 min, (450.3 [M+H$^+$]), 95.77% purity.

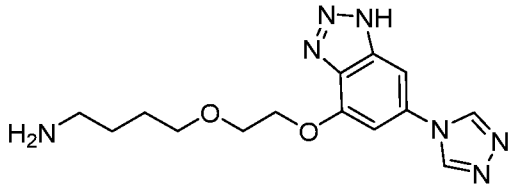
tert-butyl (4-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butyl)carbamate 2.346



To a solution of **compound 2.345** (700 mg, 1.56 mmol) in pyridine (20 mL) was added N-formamidoformamide (685.65 mg, 7.79 mmol), TMSCl (2.54 g, 23.36 mmol, 2.96 mL) and Et_3N (1.10 g, 10.90 mmol, 1.52 mL). The reaction mixture was stirred at 120 °C for 12 h. The reaction mixture was diluted with H_2O (150 mL) and extracted with EA (60 mL × 2). The organic layers were washed (brine, 40 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM23) to afford **compound 2.346** (300 mg, 523.35 μmol, 33.61% yield) as a yellow oil.

LCMS (AM3): rt = 0.899 min, (502.0 [M+H$^+$]), 89.27% purity.

4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butan-1-amine 2.347

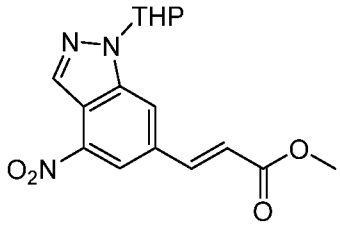


To a solution of **compound 2.346** (250 mg, 498.43 μmol) in dioxane (3 mL) was added HCl/ dioxane (4 M, 3 mL). The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated in *vacuo* to afford **compound 2.347** (200 mg, HCl salt, crude) as a yellow solid, which was used for the next step directly.

LCMS (AM3): rt = 0.707 min, (318.1 [M+H$^+$]), 98.32% purity

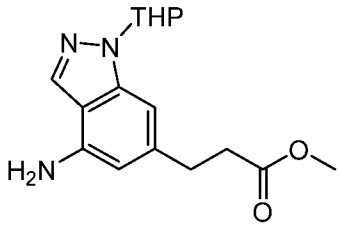
Synthesis of Intermediate 2.352

methyl (E)-3-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)acrylate 2.348



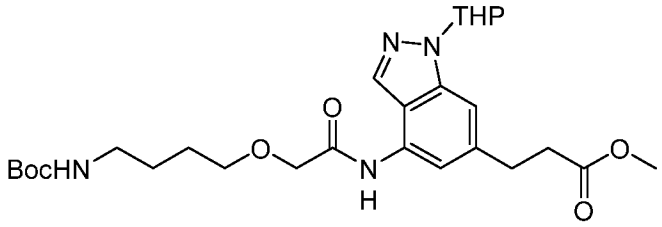
To a solution of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (WO2019027960, 1 g, 3.07 mmol), methyl prop-2-enoate (527.92 mg, 6.13 mmol) and PPh_3 (804.20 mg, 3.07 mmol) in DMF (1 mL) was added TEA (620.51 mg, 6.13 mmol) and $Pd(OAc)_2$ (13.77 mg, 61.32 μmol) at 110 °C. The mixture was stirred at 110 °C for 6 h. The reaction mixture was diluted with water 200 mL and extracted with EA (100 mL × 3). The combined organic layers were washed (brine, 100 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM27) to afford **compound 2.348** (500 mg, 1.51 mmol, 49.22% yield) as a yellow solid.

methyl 3-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)propanoate 2.349



To a solution of **compound 2.348** (500 mg, 1.51 mmol) in EA (5 mL) was added Pd/C (200 mg) at 20 °C. The mixture was stirred under a H_2 atmosphere at 20°C for 2 h. The catalyst was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.349** (450 mg, crude), which was used for the next step without further purification.

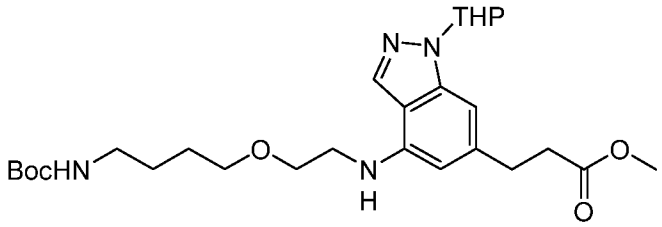
methyl 3-(4-(2-(4-((tert-butoxycarbonyl)amino)butoxy)acetamido)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)propanoate 2.350



To a solution of **compound 2.349** (450 mg, 1.48 mmol) and **compound 1.891** (366.83 mg, 1.48 mmol) in DMF (5 mL) was added HATU (846.05 mg, 2.23 mmol) and DIPEA (383.44 mg, 2.97 mmol) at 20 °C. The mixture was stirred at 20 °C for 10 min. The reaction mixture was diluted with water (200 mL) and extracted with EA (100 mL × 3). The combined organic layers were washed (brine, 100 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM88) to afford **compound 2.350** (300 mg, 535.08 μmol, 36.07% yield) as a yellow oil.

LCMS (AM3): rt = 0.940 min, (533.4 $[M+H]^+$), 94.00% purity.

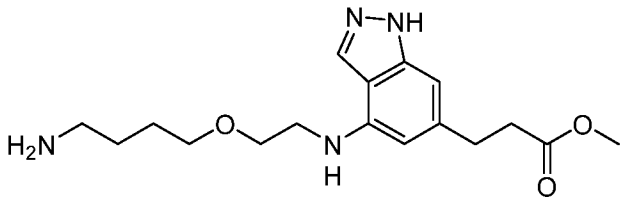
methyl 3-(4-((2-(4-((tert-butoxycarbonyl)amino)butoxy)ethyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)propanoate 2.351



To a solution of **compound 2.350** (300 mg, 563.25 μmol) in THF (2 mL) was added BH_3.THF (1 M, 1.13 mL) at 0 °C. The mixture was stirred at 20°C for 6 h. MeOH (20 mL) was added and the mixture was stirred at 20°C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM184) to afford **compound 2.351** (70 mg, 134.97 μmol, 23.96% yield) as a yellow oil.

LCMS (AM3): rt = 0.967 min, (519.3 $[M+H]^+$), 98.8% purity.

methyl 3-(4-((2-(4-aminobutoxy)ethyl)amino)-1H-indazol-6-yl)propanoate 2.352

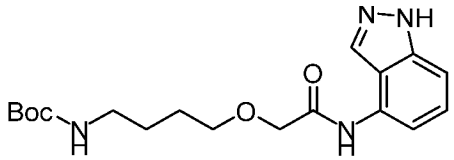


To a solution of **compound 2.351** (100 mg, 192.81 μmol) in MeOH (1 mL) was added HCl/MeOH (4 M, 513.48 μL) at 20°C. The mixture was stirred at 20°C for 30 min. The residue was concentrated to afford **compound 2.352** (60 mg, crude), which was used for the next step without further purification.

LCMS (AM3): rt = 0.670 min, (335.3 $[M+H]^+$), 73.83% purity.

<u>Synthesis of Intermediate 2.356</u>

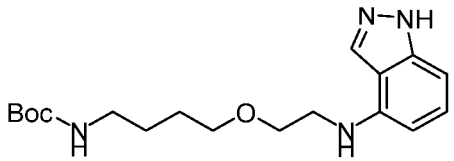
tert-butyl (4-(2-((1H-indazol-4-yl)amino)-2-oxoethoxy)butyl)carbamate 2.354



To a solution of 1H-indazol-4-amine (CAS 41748-71-4, 3 g, 22.53 mmol) and **compound 1.891** (6.13 g, 24.78 mmol) in DMF (22 mL) was added HATU (12.85 g, 33.80 mmol) and DIPEA (5.82 g, 45.06 mmol, 7.85 mL). The reaction was stirred at 20 °C for 1 h. The reaction mixture was diluted with water (50 mL) and then extracted with EA (100 mL × 3). The combined organic layers were washed (brine, 100 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM35) to afford **compound 2.354** (3 g, 8.28 mmol, 36.74% yield) as a yellow oil

LCMS (AM3): rt = 0.855 min, (363.2 $[M+H]^+$), 92.29% purity.

tert-butyl (4-(2-((1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 2.355

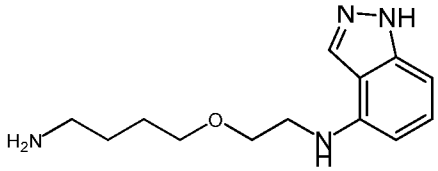


To a solution of **compound 2.354** (3 g, 8.28 mmol) in THF (30 mL) was added BH_3-DMS (628.84 mg, 8.28 mmol) at 0°C. The mixture was stirred at 20°C for 12 h. The reaction mixture

was diluted with water (100 mL) and extracted with EA (100 mL × 3). The combined organic layers were washed (brine, 100 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.355** (3 g, crude) as a yellow solid.

LCMS (AM3): rt = 0.743 min, (349.3 $[M+H]^+$), 94.07% purity.

N-(2-(4-aminobutoxy)ethyl)-1H-indazol-4-amine 2.356

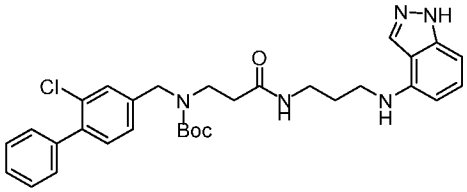


A mixture of **compound 2.355** (3 g, 8.61 mmol) in HCl/MeOH (4 M, 2.15 mL) was stirred at 20°C for 2 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM185) to afford **compound 2.356** (2 g, 7.02 mmol, 81.57% yield, HCl salt) as a yellow solid.

LCMS (AM3): rt = 0.224 min, (249.3 $[M+H]^+$), 80.87% purity.

Synthesis of Intermediate 2.357

tert-butyl (3-((3-((1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)carbamate 2.357

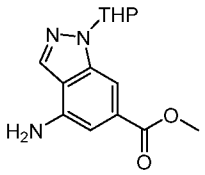


To a mixture of **intermediate H** (334.17 mg, 0.751 mmol) and 1H-indazol-4-amine (100 mg, 0.751 mmol) in DCE (10 mL) was added $NaBH(OAc)_3$ (318.35 mg, 1.50 mmol). The mixture was stirred at 25 °C for 12 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM186) to afford **compound 2.357** (100 mg, 0.178 mmol, 23.69% yield) as a white solid.

LCMS (AM3): rt = 0.941 min, (562.3 $[M+H^+]$), 99.53% purity.

Synthesis of Intermediate 2.360

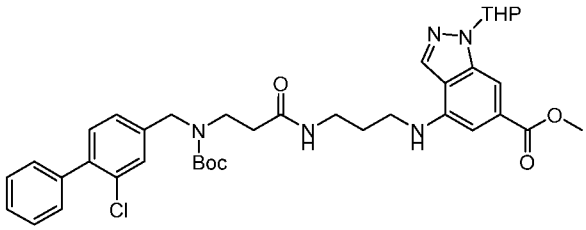
methyl 4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 2.358



A mixture of **compound 2.103** (0.5 g, 1.47 mmol), $NH_3.H_2O$ (546.00 mg, 3.89 mmol, 0.6 mL, 25% purity), CuI (58.96 mg, 309.57 μmol), (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid (79.25 mg, 604.39 μmol) and K_2CO_3 (629.54 mg, 4.56 mmol) in DMSO (10 mL) was stirred at 90 °C for 16 h under N_2. The mixture was diluted with water (20 mL) and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 40 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.358** (150 mg, 544.86 μmol, 36.96% yield) as a yellow oil, which was used directly for the next step.

LCMS (AM3): rt = 0.777 min, (276.1 [$M+H^+$]), 37.4% purity.

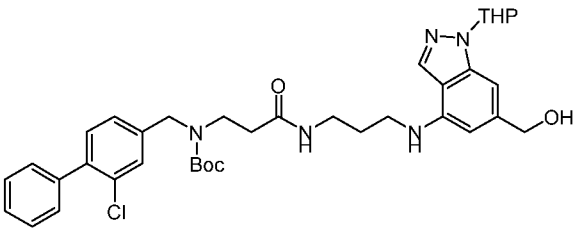
methyl 4-((3-(3-((tert-butoxycarbonyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 2.359



To a mixture of **Intermediate H** (242.43 mg, 544.86 μmol) and **compound 2.358** (150 mg, 544.86 μmol) in DCE (10 mL) was added $NaBH(OAc)_3$ (230.95 mg, 1.09 mmol). The mixture was stirred at 25 °C for 16 h. The mixture was concentrated in *vacuo* to afford a residue, which was purified (PM187) to afford **compound 2.359** (65 mg, 92.30 μmol, 16.94% yield) as a white solid.

LCMS (AM3): rt = 1.107 min, (704.4 [$M+H^+$]), 32.44% purity.

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(hydroxymethyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.360

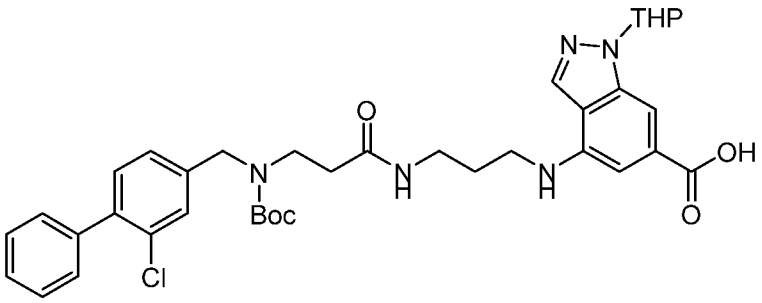


$LiAlH_4$ (5.39 mg, 141.99 μmol) was added to THF (10 mL) at 0 °C, then **compound 2.359** (50 mg, 71.00 μmol) in THF (2 mL) was added. The mixture was stirred at 25 °C for 16 h. The mixture was quenched with three drops of water and then Na_2SO_4 was added, then the mixture was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.360** (48 mg, crude) as a yellow oil which was used directly into the next step.

LCMS (AM3): rt = 0.966 min, (676.4 [$M+H^+$]), 75.17% purity.

Synthesis of Intermediate 2.362

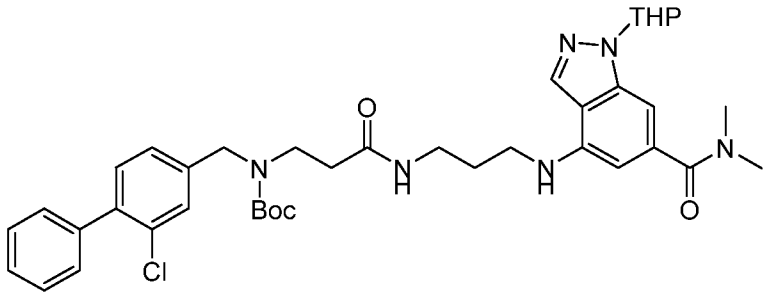
4-((3-(3-((tert-butoxycarbonyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylic acid 2.361



To a mixture of **compound 2.359** (360 mg, 511.18 μmol) in THF (18 mL), MeOH (0.2 mL) and H_2O (0.2 mL) was added $LiOH.H_2O$ (214.51 mg, 5.11 mmol). The mixture was stirred at 25 °C for 20 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM184) to afford **compound 2.361** (340 mg, 492.59 μmol, 96.36% yield) as a yellow solid.

LCMS (AM3): rt = 0987 min, (690.4 [$M+H^+$]), 86.73% purity.

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(3-((3-((6-(dimethylcarbamoyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)propyl)amino)-3-oxopropyl)carbamate 2.362

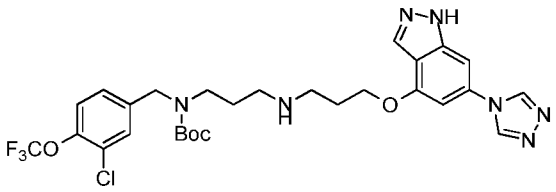


To a mixture of **compound 2.361** (50 mg, 72.44 μmol) and N-methylmethanamine;hydrochloride (11.81 mg, 144.88 μmol) in THF (2 mL) was added HATU (33.05 mg, 86.93 μmol) and DIPEA (28.09 mg, 217.32 μmol). The mixture was stirred at 25 °C for 12 h. The mixture was diluted with water (10 mL) and extracted with EA (15 mL × 2). The combined organic phase was washed (brine, 30 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.362** (52 mg, crude) as a yellow oil, which was used directly for the next step.

LCMS (AM3): rt = 0.991 min, (717.4 [M+H$^+$]), 84.8% purity.

<u>Synthesis of Intermediate 2.363</u>

tert-butyl(3-((3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propyl)amino)propyl)(3-chloro-4-(trifluoromethoxy)benzyl)carbamate 2.363

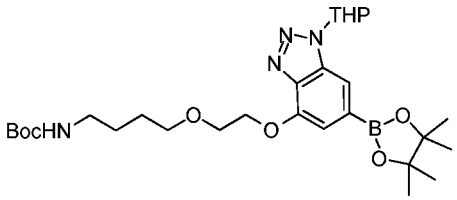


A mixture of **compound 2.293** (110 mg, 288.13 μmol), **compound 1.362** (100 mg, 339.28 μmol, HCl salt) and DIPEA (252.40 mg, 1.95 mmol) in MeOH (4 mL) was stirred at 20 °C for 12 h. $NaBH_3CN$ (181.06 mg, 2.88 mmol) was added and the mixture was stirred at 20 °C for 16 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM188) to afford **compound 2.363** (40 mg, 64.10 μmol, 22.25% yield) as a yellow solid.

LCMS (AM3): rt =0.887 min, (624.2 [M+H]$^+$), 100% purity.

Synthesis of Intermediate 2.367

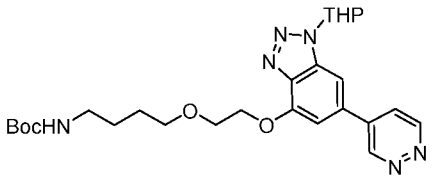
tert-butyl(4-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butyl)carbamate 2.365



To a mixture of **compound 2.344** (2 g, 3.90 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.05 g, 4.13 mmol) in dioxane (20 mL) were added KOAc (764.61 mg, 7.79 mmol) and $Pd(dppf)Cl_2$ (285.03 mg, 389.54 μmol). The mixture was stirred at 85 °C for 12 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM35) to afford **compound 2.365** (1.69 g, 3.02 mmol, 77.40% yield) as a brown oil.

LCMS (AM3): rt = 1.041 min, (561.8 $[M+H]^+$), 57.78% purity.

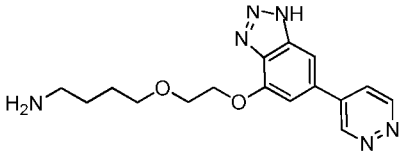
tert-butyl(4-(2-((6-(pyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butyl)carbamate 2.366



To a mixture of **compound 2.365** (1.49 g, 2.66 mmol) and 4-bromopyridazine (701.51 mg, 2.92 mmol, HBr) in dioxane (15 mL) and H_2O (1.5 mL) were added $Pd(dppf)Cl_2$ (194.52 mg, 265.84 μmol) and K_2CO_3 (1.10 g, 7.98 mmol). The mixture was stirred at 80 °C for 12 h under N_2. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM23) to afford **compound 2.366** (1.1 g, 2.15 mmol, 80.72% yield) as a yellow oil.

LCMS (AM3): rt = 0.878 min, (513.2 $[M+H]^+$), 60.88% purity.

4-(2-((6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butan-1-amine 2.367

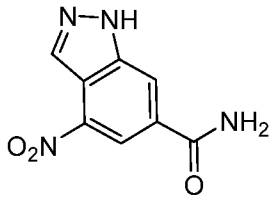


To a mixture of **compound 2.366** (1 g, 1.95 mmol) in MeOH (8 mL) was added HCl/dioxane (4 M). The mixture was stirred at 25 °C for 2 h. The mixture was concentrated in *vacuo* to afford **compound 2.367** (750 mg, crude, HCl salt) as a yellow solid, which was used directly for the next step.

LCMS (AM3): rt = 0.762 min, (329.1 $[M+H]^+$), 98% purity.

Synthesis of Intermediate 2.373

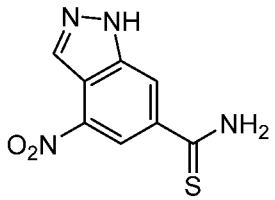
4-nitro-1H-indazole-6-carboxamide 2.369



To a 100 mL autoclave was placed a solution of methyl 4-nitro-1H-indazole-6-carboxylate (CAS 72922-61-3, 2 g, 9.04 mmol) in NH_3/MeOH (7 M, 50 mL). The mixture was stirred at 70 °C for 16 h. The reaction mixture was cooled to 20 °C and concentrated in *vacuo* to afford **compound 2.369** (1.6 g, 7.76 mmol, 85.83% yield) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.17 (br s, 1H), 8.85 - 8.52 (m, 3H), 8.47 (s, 1H), 7.76 (s, 1H) ppm.

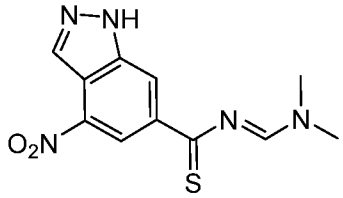
4-nitro-1H-indazole-6-carbothioamide 2.370



To a mixture of **compound 2.369** (1.5 g, 7.28 mmol) in THF (50 mL) was added Lawesson's reagent (2.35 g, 5.82 mmol). The mixture was heated to 60 °C and stirred for 2 h. The mixture was poured into water (150 mL). The suspension was filtered, the filter cake was collected and triturated with DCM (50 mL × 2) at 20 °C for 10 min. The mixture was filtered and the filter cake was washed with MeOH (5 mL) and dried *in vacuo* to afford **compound 2.370** (1 g, 4.31 mmol, 59.23% yield) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.22 (s, 1H), 10.25 (s, 1H), 9.96 (s, 1H), 8.74 (s, 1H), 8.58 (s, 1H), 8.54 (s, 1H) ppm.

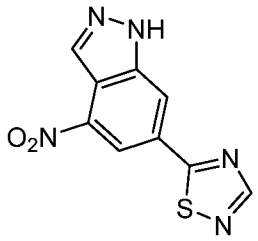
N-((dimethylamino)methylene)-4-nitro-1H-indazole-6-carbothioamide 2.371



To a solution of **compound 2.370** (1 g, 4.50 mmol) in dioxane (40 mL) was added DMF-DMA (1.61 g, 13.50 mmol). The mixture was heated to 80 °C and stirred for 2 h. The mixture was concentrated in *vacuo* to afford **compound 2.371** (1.2 g, crude) as a yellow oil.

LCMS (AM11): rt = 0.400 min, (277.9 $[M+H]^+$), 88.15% purity.

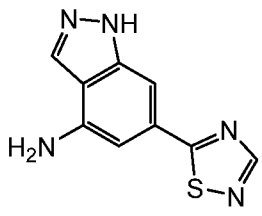
5-(4-nitro-1H-indazol-6-yl)-1,2,4-thiadiazole compound 2.372



To a solution of **compound 2.371** (1.2 g, 4.33 mmol) in EtOH (20 mL) was added O-(2,4-dinitrophenyl)hydroxylamine (861.68 mg, 4.33 mmol) and pyridine (342.30 mg, 4.33 mmol). The mixture was heated to 60 °C and stirred for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM189) to give a crude product thatwas triturated with ACN (2 mL) at 20 °C for 5 min and filtered. The filter cake was collected and dried *in vacuo* to afford **compound 2.372** (200 mg, 716.73 μmol, 16.56% yield) as a yellow solid.

LCMS (AM11): rt = 0.385 min, (248.0 $[M+H]^+$), 88.69% purity.

6-(1,2,4-thiadiazol-5-yl)-1H-indazol-4-amine compound 2.373

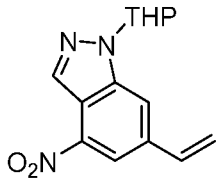


To a mixture of **compound 2.372** (200 mg, 808.95 μmol) in H_2O (5 mL) and EtOH (5 mL) was added Fe (316.23 mg, 5.66 mmol) and NH_4Cl (346.18 mg, 6.47 mmol). The mixture was stirred at 50 °C for 1 h. The mixture was diluted with MeOH (10 mL), filtered and washed with MeOH (2 mL × 2). The filtrate was concentrated in *vacuo* to afford **compound 2.373** (140 mg, 644.42 μmol, 79.66% yield) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 8.91 (s, 1H), 8.20 (s, 1H), 7.33 (s, 1H), 6.76 (s, 1H), 6.20 (s, 2H) ppm.

Synthesis of Intermediate 2.388

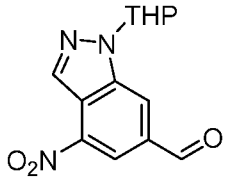
4-nitro-1-(tetrahydro-2H-pyran-2-yl)-6-vinyl-1H-indazole 2.384



To a solution of 6-bromo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (Ref: WO 2019027960, 1 g, 3.07 mmol) in dioxane (10 mL) and H_2O (1 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (519.45 mg, 3.37 mmol), K_2CO_3 (881.44 mg, 6.38 mmol) and $Pd(dppf)Cl_2$ (226.70 mg, 309.83 umol). The reaction mixture was degassed and purged with N_2 (x3) then stirred at 80 °C for 12 h. The reaction mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM7) to afford **compound 2.384** (700 mg, 2.56 mmol, 83.54% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.59 (s, 1H), 8.29 (s, 1H), 7.89 (s, 1H), 6.89 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.99 (d, *J* = 17.2 Hz, 1H), 5.84 - 5.80 (m, 1H), 5.51 (d, *J* = 10.8 Hz, 1H), 4.02 - 3.97 (m, 1H), 3.82 - 3.76 (m, 1H), 2.58 - 2.53 (m, 1H), 2.20 - 2.15 (m, 2H), 1.81 - 1.71 (m, 3H) ppm

4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carbaldehyde 2.385

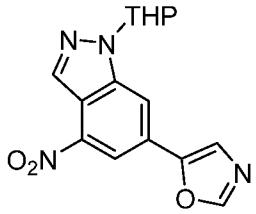


A solution of **compound 2.384** (3.15 g, 11.53 mmol) in DCM (50 mL) was purged with ozone at -70 °C for 0.2 h until the mixture turned blue. The mixture was then purged by N_2 at -70 °C for 0.1 h until the mixture turned clear. DMS (12.69 g, 204.25 mmol, 15 mL) was added at 0

°C and the mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM36) to afford **compound 2.385** (1.6 g, 5.81 mmol, 50.43% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 10.14 (s, 1H), 8.64 (s, 1H), 8.56 (s, 1H), 8.47 (s, 1H), 5.87 - 5.83 (m, 1H), 3.95 - 3.91 (m, 1H), 3.79 - 3.72 (m, 1H), 2.47 - 2.41 (m, 1H), 2.14 - 2.11 (m, 2H), 1.72 - 1.67 (m, 3H) ppm

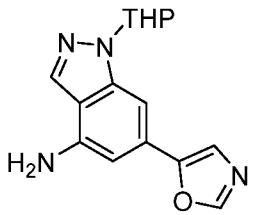
5-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)oxazole 2.386



To a solution of **compound 2.385** (1.48 g, 5.38 mmol) and 1-(isocyanomethylsulfonyl)-4-methyl-benzene (1 g, 5.12 mmol) in MeOH (20 mL) was added K_2CO_3 (1.06 g, 7.68 mmol). The mixture was stirred at 70°C for 2 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with EA (60 mL × 2). The organic layer was washed (brine, 100 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM36) to afford **compound 2.386** (1.5 g, 4.77 mmol, 93.18% yield) as a yellow solid.

LCMS (AM3): rt = 0.885 min, (315.0 $[M+H]^+$), 91.37% purity

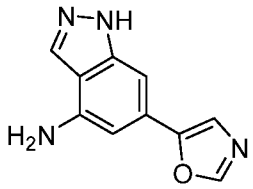
6-(oxazol-5-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.387



To a solution of **compound 2.386** (1.45 g, 4.61 mmol) in EtOH (40 mL) and H_2O (8 mL) was added Fe (1.29 g, 23.07 mmol) and NH_4Cl (1.23 g, 23.07 mmol). The reaction mixture was stirred at 80 °C for 0.5 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue. The residue was diluted with H_2O (100 mL) and extracted with EA (60 mL × 2). The organic layer was washed (brine, 100 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM25) to afford **compound 2.387** (1.2 g, 4.20 mmol, 91.03% yield, 99.5% purity) as a yellow solid.

LCMS (AM3): rt = 0.597 min, (284.9 $[M+H]^+$), 99.58% purity

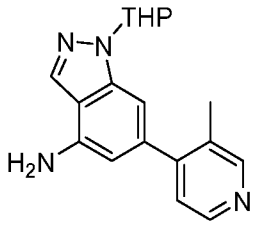
6-(oxazol-5-yl)-1H-indazol-4-amine 2.388



To a solution of **compound 2.387** (650 mg, 2.29 mmol) in DCM (5 mL) was added TFA (7.70 g, 67.53 mmol, 5 mL). The mixture was stirred at 25°C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM191) to afford **compound 2.388** (280 mg, 1.17 mmol, 51.33% yield) as a yellow solid.

Synthesis of Intermediate 2.392

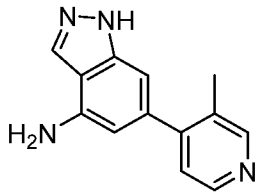
6-(3-methylpyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.391



A mixture of **compound 1.952** (1.5 g, 4.37 mmol), 4-chloro-3-methyl-pyridine (780.53 mg, 6.12 mmol), $Pd(dppf)Cl_2$ (319.78 mg, 437.03 μmol) and Cs_2CO_3 (4.27 g, 13.11 mmol) in dioxane (8 mL) and H_2O (1.6 mL) was degassed and purged with N_2 (x3), then the mixture was stirred at 100 °C for 12 h under N_2.The mixture was diluted with water (50 ml) and extracted with EA (60 mL × 3). The combined organic phase was washed (brine, 55 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM38) to afford **compound 2.391** (756 mg, 2.40 mmol, 54.97% yield) as a yellow solid.

LCMS (AM3): rt = 0.650 min, (309.0, $[M+H]^+$), 98.1% purity.

6-(3-methylpyridin-4-yl)-1H-indazol-4-amine 2.392

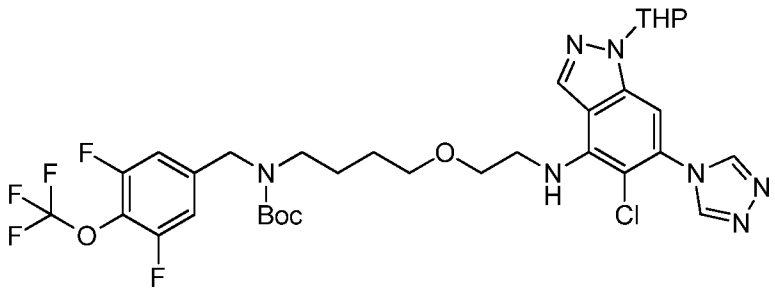


To a solution of **compound 2.391** (750 mg, 2.43 mmol) in MeOH (2 mL) was added HCl/dioxane (10 mL, 4 M). The mixture was stirred at 25 °C for 30 min. The reaction mixture was concentrated in *vacuo* to give a residue. The residue was dissolved in MeOH (10 mL), basified by $NH_3 \cdot H_2O$ to pH = 10 and filtered. The filtrate was purified (PM195) to afford **compound 2.392** (0.4 g, 1.76 mmol, 72.24% yield) as an off-white solid.

LCMS (AM7): rt = 0.721 min, (225.1, $[M+H]^+$), 98.5% purity.

Synthesis of Intermediate 2.396

tert-butyl (4-(2-((5-chloro-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)(3,5-difluoro-4-(trifluoromethoxy)benzyl)carbamate 2.396

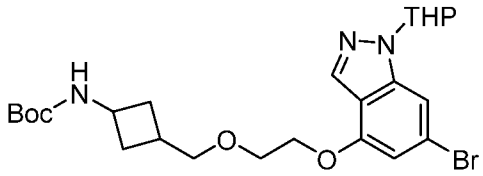


To a solution of **compound 2.395** (188 mg, 264.90 μmol) in DMF (2 mL) was added NCS (38.91 mg, 291.39 μmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. The reaction mixture was poured into saturated Na_2SO_3 aqueous solution (30 mL) and extracted with EA (30 mL × 3). The combined organic phase was washed (brine, 30 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give residue, which was purified by prep-TLC (EA) to afford **compound 2.396** (79 mg, 105.95 μmol, 40.00% yield) as a colourless gum.

LCMS (AM14): rt = 0.767 min, (744.3, $[M+H]^+$), 99.89% purity.

Synthesis of Intermediate 2.411

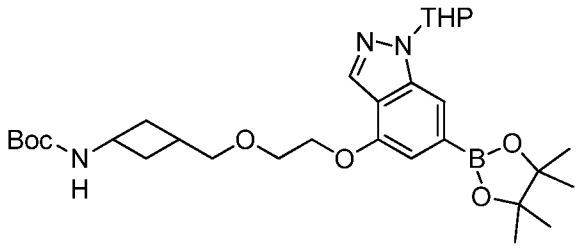
tert-butyl (3-((2-((6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)ethoxy)methyl)cyclobutyl)carbamate 2.408



To a solution of **compound 1.856** (1 g, 4.08 mmol) in DMF (10 mL) was added NaH (489.12 mg, 12.23 mmol, 60% purity). The mixture was stirred at 0 °C for 30 min, then a solution of 6-bromo-4-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (1.22 g, 4.08 mmol) in DMF (10 mL) was added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was dropwise added into saturated NH_4Cl aqueous solution (50 mL) at 0 °C and extracted with EA (40 mL × 3). The combined organic phase was washed by brine (50 mL × 4), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM24) to afford **compound 2.408** (1.12 g, 2.14 mmol, 52.39% yield) as a light-yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.04 (s, 1H), 7.37 (s, 1H), 6.67 - 6.62 (m, 1H), 5.61 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 4.72 (s, 1H), 4.27 (t, *J* = 4.4 Hz, 2H), 4.08 - 3.98 (m, 2H), 3.89 - 3.84 (m, 2H), 3.78 - 3.70 (m, 1H), 3.50 (d, *J* = 5.2 Hz, 2H), 2.55 - 2.40 (m, 3H), 2.27-2.16 (m, 2H), 2.16 - 2.10 (m, 1H), 1.80 - 1.72 (m, 2H), 1.69 - 1.62 (m, 3H), 1.45 - 1.40 (m, 9H) ppm.

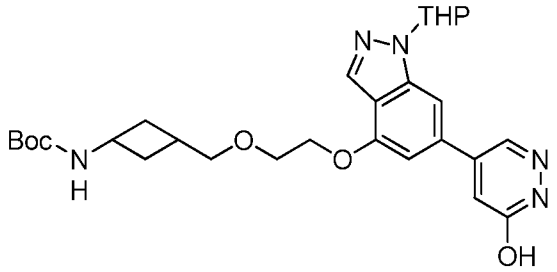
tert-butyl (3-((2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-4-yl)oxy)ethoxy)methyl)cyclobutyl)carbamate 2.409



To a solution of **compound 2.408** (1 g, 1.91 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (581.04 mg, 2.29 mmol) in dioxane (15 mL) was added KOAc (561.41 mg, 5.72 mmol) and $Pd(dppf)Cl_2$ (139.52 mg, 190.68 μmol). The mixture was degassed and purged with N_2 (x3), then heated to 80 °C and stirred for 3 h. The reaction mixture was diluted with EA (50 mL) and filtered, the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM28) to afford **compound 2.409** (1 g, 1.75 mmol, 91.76% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.12 (s, 1H), 7.63 (s, 1H), 6.91 - 6.88 (m, 1H), 5.78 - 5.72 (m, 1H), 4.71 (s, 1H), 4.34 (t, *J* = 4.4 Hz, 2H), 4.10 - 4.03 (m, 2H), 3.92 - 3.85 (m, 2H), 3.81 - 3.74 (m, 1H), 3.54 - 3.49 (m, 2H), 2.66 - 2.55 (m, 1H), 2.48 - 2.40 (m, 2H), 2.27 - 2.14 (m, 2H), 2.01 - 1.94 (m, 1H), 1.84 - 1.71 (m, 2H), 1.60 -1.57 (m, 3H), 1.44 - 1.40 (m, 9H), 1.38 (s, 12H) ppm.

tert-butyl (3-((2-((6-(6-hydroxypyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)oxy)ethoxy)methyl)cyclobutyl)carbamate 2.410

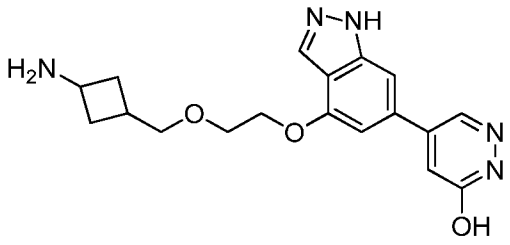


To a solution of **compound 2.409** (600 mg, 1.05 mmol) and 4-chloro-1H-pyridazin-6-one (150.76 mg, 1.16 mmol) in dioxane (6 mL) and H_2O (1 mL) was added K_2CO_3 (290.19 mg, 2.10 mmol) and $Pd(dppf)Cl_2$ (76.82 mg, 105.00 μmol). The mixture was degassed and purged with N_2, then heated to 100 °C and stirred for 12 h. The reaction mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM23) to afford **compound 2.410** (320 mg, 593.01 μmol, 56.48% yield) as a light-yellow solid.

LCMS (AM11): rt = 0.456 min, (540.4, $[M+H]^+$), 71.89% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 10.46 (s, 1H), 8.15 (s, 1H), 7.40 (s, 1H), 7.16 - 7.12 (m, 1H), 6.67 - 6.64 (m, 1H), 5.77 - 5.72 (m, 1H), 4.72 (s, 1H), 4.35 (t, *J* = 4.4 Hz, 2H), 4.08 - 4.01 (m, 1H), 3.95 - 3.89 (m, 2H), 3.81 - 3.74 (m, 1H), 3.53 (d, *J* = 5.6 Hz, 1H), 3.40 (t, *J* = 2.8 Hz, 1H), 2.86 (s, 1H), 2.63 - 2.51 (m, 1H), 2.49 - 2.40 (m, 2H), 2.27 - 2.13 (m, 2H), 2.04 - 1.97 (m, 1H), 1.82 - 1.70 (m, 3H), 1.70 - 1.62 (m, 2H), 1.45 - 1.40 (m, 9H) ppm.

5-(4-(2-((3-aminocyclobutyl)methoxy)ethoxy)-1H-indazol-6-yl)pyridazin-3-ol 2.411



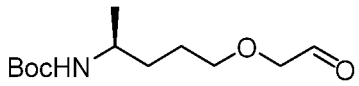
To a solution of **compound 2.410** (300 mg, 555.94 μmol) in MeOH (6 mL) was added HCl/dioxane (4 M, 3 mL). The mixture was stirred at 20 °C for 0.5 h. The mixture was concentrated in *vacuo* to give a residue, which was triturated with MTBE (5 mL) at 20 °C for

10 min and filtered. The filter cake was dried in *vacuum* to afford **compound 2.411** (227 mg, 529.99 μmol, 95.33% yield, HCl salt) as a yellow solid.

LCMS (AM11): rt = 0.247 min, (356.4, $[M+H]^+$), 89.41% purity.

Synthesis of Intermediate 2.432

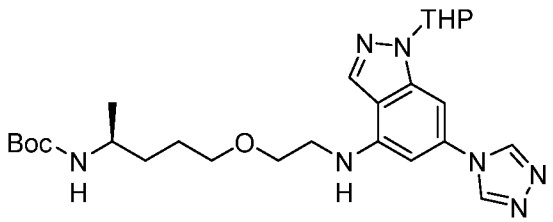
tert-butyl (S)-(5-(2-oxoethoxy)pentan-2-yl)carbamate 2.430



To a solution of oxalyl dichloride (615.84 mg, 4.85 mmol) in DCM (6 mL) was added a solution of DMSO (568.61 mg, 7.28 mmol) in DCM (3 mL) dropwise at -70 °C under N_2. The mixture was stirred at -70 °C for 0.5 h, then a solution of **compound 1.848** (600 mg, 2.43 mmol) in DCM (3 mL) was added dropwise at -70 °C and the resulting mixture was stirred at -70 °C for 0.5 h, then TEA (1.47 g, 14.56 mmol) was added dropwise at -70 °C and the mixture was stirred at -70 °C for 10 min. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM29) to afford **compound 2.430** (460 mg, 1.88 mmol, 77.30% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 9.74 (s, 1H), 4.45 - 4.28 (m, 1H), 4.07 (s, 2H), 3.73 - 3.61 (m, 1H), 3.56 (t, *J* = 6.4 Hz, 2H), 1.73 - 1.64 (m, 2H), 1.55 - 1.49 (m, 2H), 1.45 (s, 9H), 1.14 (d, *J* = 6.4 Hz, 3H) ppm.

tert-butyl ((2S)-5-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)carbamate 2.431

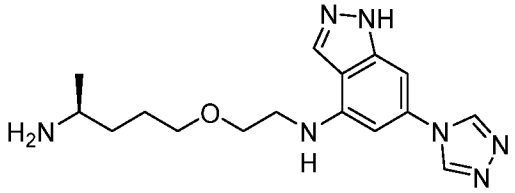


To a mixture of **compound 2.430** (446.51 mg, 1.82 mmol) and **compound 1.273** (450 mg, 1.58 mmol) in MeOH (6 mL) was added $MgSO_4$ (571.54 mg, 4.75 mmol) and HOAc (95.05 mg, 1.58 mmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (198.93 mg, 3.17 mmol) was added and the mixture was stirred at 20 °C for 1 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM194) to afford **compound 2.431** (420 mg, 783.36 μmol, 49.49% yield) as a yellow oil.

LCMS (AM11): rt = 0.446 min, (514.4, $[M+H]^+$), 95.80% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.53 (s, 2H), 8.10 (s, 1H), 6.87 (s, 1H), 6.13 (s, 1H), 5.65 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.37 - 4.48 (m, 1H), 4.04 (br d, *J* = 11.6 Hz, 1H), 3.80 - 3.68 (m, 4H), 3.55 - 3.45 (m, 4H), 2.59 - 2.47 (m, 1H), 2.21 - 2.07 (m, 2H), 1.72 - 1.63 (m, 5H), 1.50 (br s, 2H), 1.45 (s, 9H), 1.11 (d, *J* = 6.8 Hz, 3H) ppm

(S)-N-(2-((4-aminopentyl)oxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine 2.432

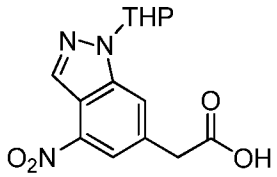


To a solution of **compound 2.431** (370 mg, 720.36 μmol) in MeOH (8 mL) was added HCl/dioxane (4 M, 8 mL). The mixture was stirred at 20 °C for 0.5 h. The mixture was concentrated in *vacuo* to afford **compound 2.432** (220 mg, crude, HCl salt) as a brown gum.

LCMS (AM11): rt = 0.247 min, (330.0, $[M+H]^+$), 93.47% purity.

Synthesis of Intermediate 2.454

2-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)acetic acid 2.449

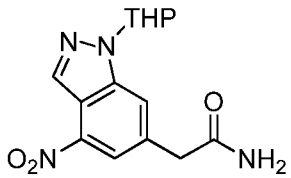


To a solution of **compound 1.991** (4 g, 13.92 mmol) in H_2O (40 mL), ACN (20 mL) and DCM (20 mL) was slowly added $RuCl_3.3H_2O$ (364.03 mg, 1.39 mmol) and $NaIO_4$ (11.91 g, 55.69 mmol,) at 0 °C, then the mixture was warmed to 20 °C and stirred for 2 h. The mixture was poured into water (100 mL) and extracted with EA (80 mL × 3). The aqueous phase was adjusted to pH = 6 by 1 M HCl and extracted with EA (80 mL × 3). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.449** (3.3 g, 10.81 mmol, 77.64% yield) as an off-white solid.

LCMS (AM11): rt = 0.369 min, (221.8 $[M-THP]^+$), 88.51% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H), 8.52 (s, 1H), 8.22 (s, 1H), 8.17 (s, 1H), 8.97 (dd, *J* = 10.0 Hz, 2.4 Hz, 1H), 3.94 (s, 2H), 3.92 - 3.87 (m, 1H), 3.81 - 3.73 (m, 1H), 2.45 - 2.36 (m, 1H), 2.10 - 2.00 (m, 2H), 1.82 - 1.69 (m, 1H), 1.64 - 1.56 (m, 2H) ppm.

2-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)acetamide 2.450

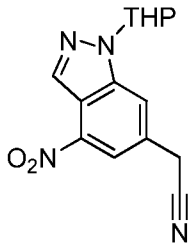


To a solution of **compound 2.449** (3.3 g, 10.81 mmol) in THF (40 mL) was added CDI (2.28 g, 14.05 mmol). The mixture was stirred at 20 °C for 1 h, then $NH_3.H_2O$ (5.41 g, 43.24 mmol, 28% purity) was added and the resulting mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into water (50 mL) and the mixture was filtered. The filter cake was dried in *vacuum* to afford **compound 2.450** (2.4 g, 7.89 mmol, 72.96% yield) as an off-white solid.

LCMS (AM11): rt = 0.336 min, (220.8 $[M\text{-}THP]^+$), 99.26% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.15 (s, 2H), 7.63 (s, 1H), 7.06 (s, 1H), 6.01 - 5.96 (m, 1H), 3.94 - 3.86 (m, 1H), 3.82 - 3.74 (m, 1H), 3.71 (s, 2H), 2.45 - 2.36 (m, 1H), 2.10 - 2.00 (m, 2H), 1.83 - 1.70 (m, 1H), 1.65 - 1.57 (m, 2H) ppm.

2-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)acetonitrile 2.451

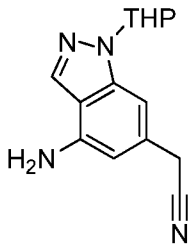


To a solution of **compound 2.450** (2.4 g, 7.89 mmol) in pyridine (40 mL) was added TFAA (6 mL, 43.14 mmol) at 0 °C, the mixture warmed to 20 °C and stirred for 0.5 h. The reaction was concentrated in *vacuo* to give a residue. The residue was resolved into water (80 mL), then extracted with EA (60 mL × 2). The combined organic phase was washed (brine, 80 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM27) to afford **compound 2.451** (1.9 g, 6.64 mmol, 84.15% yield) as a yellow solid.

LCMS (AM11): rt = 0.406 min, (202.8 $[M\text{-}THP]^+$), 99.21% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.63 (s, 1H), 8.09 (s, 1H), 8.04 (s, 1H), 5.84 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 4.02 (s, 1H), 4.01 - 3.96 (m, 1H), 3.84 - 3.76 (m, 1H), 2.60 - 2.48 (m, 1H), 2.24 - 2.12 (m, 2H), 1.88 - 1.79 (m, 1H), 1.79 - 1.68 (m, 2H) ppm.

2-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)acetonitrile 2.452

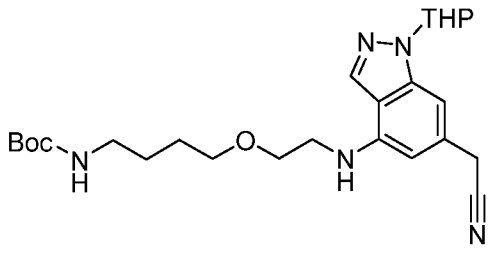


To a solution of **compound 2.451** (650 mg, 2.27 mmol) in MeOH (12 mL) and H_2O (6 mL) was added NH_4Cl (971.60 mg, 18.16 mmol) and Fe (760.76 mg, 13.62 mmol), then the mixture was heated to 60 °C and stirred for 1 h. The reaction mixture was poured into water (30 mL) and extracted with EA (30 mL × 3). The combined organic phase was washed (brine, 30 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.452** (583 mg, crude) as a yellow solid.

LCMS (AM11): rt = 0.329 min, (257.4 $[M+H]^+$), 99.36% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 6.71 (s, 1H), 6.16 (s, 1H), 6.00 (s, 2H), 5.63 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 3.96 (s, 2H), 3.91 - 3.83 (m, 1H), 3.73 - 3.64 (m, 1H), 2.42 - 2.31 (m, 1H), 2.06 - 1.99 (m, 1H), 1.96 - 1.86 (m, 1H), 1.80 - 1.66 (m, 1H), 1.60 - 1.51 (m, 2H) ppm.

tert-butyl (4-(2-((6-(cyanomethyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 2.453



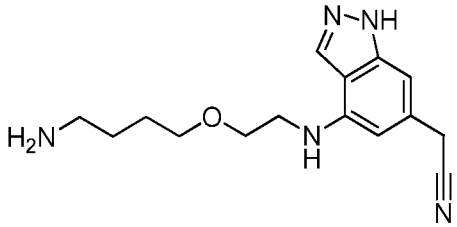
To a solution of **compound 2.452** (200 mg, 780.33 μmol) and tert-Butyl (4-(2-aminoethoxy)butyl)carbamate (CAS 2830620-37-4, .53 mg, 858.36 μmol) in MeOH (5 mL) was added $MgSO_4$ (281.78 mg, 2.34 mmol) and AcOH (46.86 mg, 780.33 μmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (98.07 mg, 1.56 mmol) was added and the mixture was stirred at 20 °C for 1 h. Additional tert-Butyl (4-(2-aminoethoxy)butyl)carbamate

(CAS 2830620-37-4, 30 mg, 129.78 μmol) was added, and the mixture was stirred at 20 °C for 12 h. The mixture was poured into water (20 mL) and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 20 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM196) to afford **compound 2.453** (155 mg, 328.67 μmol, 42.12% yield) as a brown oil.

LCMS (AM11): rt = 0.512 min, (472.2 $[M+H]^+$), 34.59% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 7.97 (s, 1H), 6.87 (s, 1H), 6.13 (s, 1H), 6.64 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 4.68 (s, 1H), 4.08 - 4.01 (s, 1H), 3.80 (s, 1H), 3.78 - 3.74 (m, 1H), 3.71 (t, *J* = 4.8 Hz, 2H), 3.54 - 3.44 (m, 4H), 3.19 - 3.10 (m, 2H), 2.60 - 2.49 (m, 1H), 2.19 - 2.11 (m, 1H), 2.04 - 2.00 (m, 1H), 1.81 - 1.73 (m, 3H), 1.60 - 1.52 (m, 4H), 1.44 (s, 9H) ppm.

2-(4-((2-(4-aminobutoxy)ethyl)amino)-1H-indazol-6-yl)acetonitrile 2.454

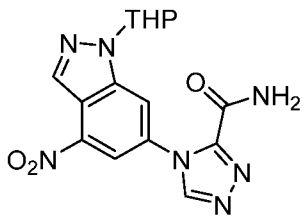


To a solution of **compound 2.453** (130 mg, 275.66 μmol) in DCM (10 mL) was added TFA (2 mL, 27.01 mmol), the mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated in *vacuo* to give residue, which was purified (PM197) to afford **compound 2.454** (110 mg, 213.42 μmol, 77.42% yield, 2TFA salt) as a brown oil.

LCMS (AM11): rt = 0.250 min, (288.0 $[M+H]^+$), 78.60% purity.

Synthesis of Intermediate 2.457

4-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-4H-1,2,4-triazole-3-carboxamide 2.455

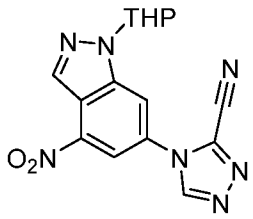


To a solution of **compound 1.272** (2 g, 6.36 mmol) in THF (40 mL) was added TEA (1.29 g, 12.73 mmol) followed by 2,2,2-trichloroacetyl chloride (1.16 g, 6.36 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, the mixture was warmed to 20 °C and NH_3/MeOH (7 M, 9.09 mL)

was added. The resulting mixture was stirred at 20 °C for 0.5 h. The mixture was concentrated in *vacuo* to give a residue. The residue was triturated with MeOH (10 mL × 2) at 20 °C and filtered. The filter cake was collected and dried under *vacuum* to afford **compound 2.455** (840 mg, 2.20 mmol, 34.54% yield) as a brown solid.

LCMS (AM14): rt = 0.456 min, (358.2, $[M+H]^+$), 93.59 % purity

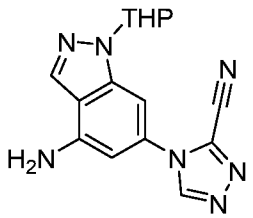
4-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-4H-1,2,4-triazole-3-carbonitrile 2.456



To a solution of **compound 2.455** (840 mg, 2.35 mmol) in DCM (20 mL) was added TEA (713.64 mg, 7.05 mmol) followed by TFAA (987.48 mg, 4.70 mmol) at 0 °C. The mixture was warmed to 20 °C and stirred for 1 h. The mixture was quenched by H_2O (10 mL) and concentrated in *vacuo* to give a residue, which was purified (PM108) to afford **compound 2.456** (640 mg, 1.88 mmol, 79.83% yield) as a yellow solid.

LCMS (AM14): rt = 0.559 min, (340.1, $[M+H]^+$), 99.54% purity

4-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-4H-1,2,4-triazole-3-carbonitrile 2.457

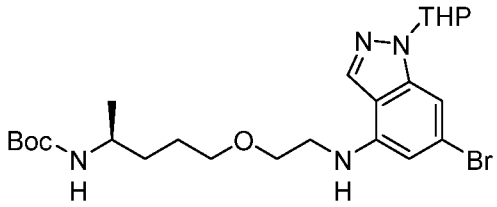


To a solution of **compound 2.456** (640 mg, 1.89 mmol) in H_2O (10 mL) and EtOH (10 mL) was added Fe (737.34 mg, 13.20 mmol) and NH_4Cl (807.16 mg, 15.09 mmol). The mixture was heated to 70 °C and stirred for 1 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM109) to afford **compound 2.457** (390 mg, 1.26 mmol, 66.84% yield) as a yellow gum,

LCMS (AM12): rt = 0.400 min, (310.0, $[M+H]^+$), 73.45% purity

Synthesis of Intermediate 2.463

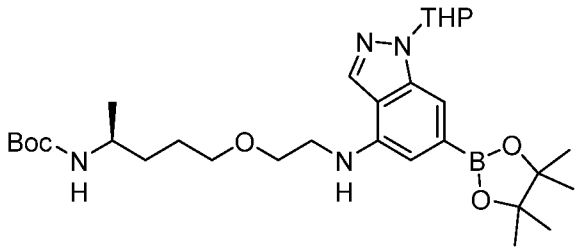
tert-butyl ((2S)-5-(2-((6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)carbamate 2.460



To a mixture of **compound 2.430** (2.39 g, 9.72 mmol) in MeOH (30 mL) was added **compound 1.381** (2.4 g, 8.10 mmol), $MgSO_4$ (2.93 g, 24.31 mmol) followed by HOAc (486.64 mg, 8.10 mmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (1.02 g, 16.21 mmol) was added. The mixture was stirred at 20 °C for 1 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM201) to afford **compound 2.460** (2.2 g, 3.93 mmol, 48.45% yield) as a yellow oil.

LCMS (AM11): rt = 0.540 min, (527.2, $[M+H]^+$), 93.10% purity.

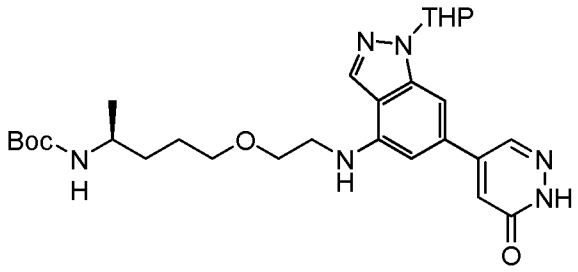
tert-butyl ((2S)-5-(2-((1-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)carbamate 2.461



To a solution of **compound 2.460** (1.7 g, 3.24 mmol) and B_2Pin_2 (985.83 mg, 3.88 mmol) in dioxane (15 mL) was added KOAc (635.01 mg, 6.47 mmol) followed by $Pd(dppf)Cl_2$ (236.72 mg, 323.52 μmol). The mixture was degassed and purged with N_2 (x3), then the mixture was heated to 90 °C and stirred for 2 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM27) to afford **compound 2.461** (1.8 g, 2.82 mmol, 87.17% yield) as a yellow gum.

LCMS (AM11): rt = 0.610 min, (573.3, $[M+H]^+$), 89.71% purity.

tert-butyl ((2S)-5-(2-((6-(6-oxo-1,6-dihydropyridazin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)carbamate 2.462

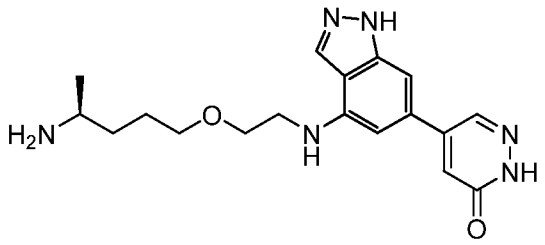


To a solution of **compound 2.461** (1.8 g, 3.14 mmol) and 5-chloropyridazin-3(2H)-one (492.45 mg, 3.77 mmol) in dioxane (20 mL) and H_2O (2 mL) was added K_2CO_3 (869.03 mg, 6.29 mmol) followed by Pd(dppf)Cl_2 (230.04 mg, 314.39 μmol). The mixture was degassed and purged with N_2 (x3), then the mixture was heated to 100 °C and stirred for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM38) to afford **compound 2.462** (1 g, 1.84 mmol, 58.60% yield) as a yellow solid.

LCMS (AM11): rt = 0.476 min, (541.4, $[M+H]^+$), 99.65% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.37 (d, *J* = 2.0 Hz, 1H), 8.20 (s, 1H), 7.22 (s, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 6.49 (s, 1H), 5.82 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.01 (d, *J* = 11.6 Hz, 1H), 3.84 (td, *J* = 11.2, 3.2 Hz, 1H), 3.75 - 3.70 (m, 2H), 3.57 - 3.49 (m, 5H), 2.56 - 2.43 (m, 1H), 2.17 - 2.09 (m, 1H), 2.01 - 1.97 (m, 1H), 1.90 - 1.78 (m, 1H), 1.77 - 1.65 (m, 2H), 1.63 - 1.56 (m, 2H), 1.52 - 1.42 (m, 2H), 1.41 (s, 9H), 1.03 (d, *J* = 6.4 Hz, 3H) ppm.

(S)-5-(4-((2-((4-aminopentyl)oxy)ethyl)amino)-1H-indazol-6-yl)pyridazin-3(2H)-one 2.463

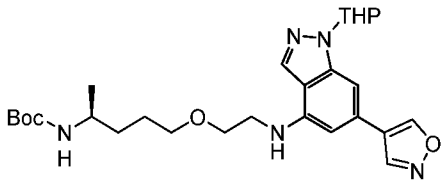


To a solution of **compound 2.462** (950 mg, 1.76 mmol) in MeOH (10 mL) was added HCl/dioxane (4 M, 15 mL). The mixture was stirred at 20 °C for 2 h. The mixture was concentrated in *vacuo* to afford **compound 2.463** (0.9 g, crude, HCl salt) as a red gum.

LCMS (AM11): rt = 0.251 min, (357.1 $[M+H]^+$), 93.9% purity.

Synthesis of Intermediate 2.468

tert-butyl ((2S)-5-(2-((6-(isoxazol-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)carbamate 2.467

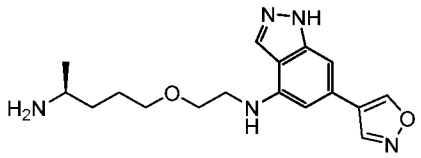


To a mixture of **compound 2.460** (390 mg, 742.18 μmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (173.69 mg, 890.62 μmol) in DMF (20 mL) and H_2O (2 mL) was added KF (86.24 mg, 1.48 mmol) followed by $Pd(dppf)Cl_2$ (54.31 mg, 74.22 μmol). The mixture was degassed and purged with N_2 (x3), then the mixture was heated to 70 °C and stirred for 10 min. The reaction mixture was poured into water (60 mL) and extracted with EA (40 mL × 3). The combined organic phase was washed (brine, 20 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM24) to afford **compound 2.467** (280 mg, 530.97 μmol, 71.54% yield) as a yellow gum.

LCMS (AM11): rt = 0.508 min, (514.4, $[M+H]^+$), 97.47% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 9.12 (s, 1H), 8.91 (s, 1H), 8.14 (s, 1H), 7.13 (s, 1H), 6.48 (s, 1H), 6.37 (d, *J* = 7.6 Hz, 1H), 5.76 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 3.84 (td, *J* = 11.2, 2.4 Hz, 1H), 3.75 - 3.70 (m, 2H), 3.54 - 3.50 (m, 4H), 2.56 - 2.4 (m, 1H), 2.18 - 2.09 (m, 1H), 2.01 -1.94 (m, 1H), 1.91 - 1.71 (m, 2H), 1.70 - 1.55 (m, 4H), 1.52 - 1.44 (m, 2H), 1.41 (s, 9H), 1.04 (d, *J* = 6.8 Hz, 3H) ppm.

(S)-N-(2-((4-aminopentyl)oxy)ethyl)-6-(isoxazol-4-yl)-1H-indazol-4-amine 2.468

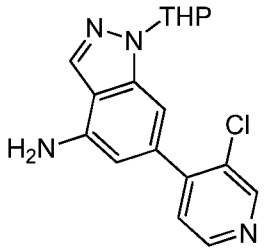


To a solution of **compound 2.467** (260 mg, 506.20 μmol) in DCM (20 mL) was added TFA (7.8 mL, 105.35 mmol) at 20 °C. The mixture was stirred at 20 °C for 10 min. The mixture was concentrated in *vacuo* to afford **compound 2.468** (400 mg, crude, TFA salt) as a yellow gum.

LCMS (AM11): rt = 0.262 min, (330.2, $[M+H]^+$), 74.40% purity.

Synthesis of Intermediate 2.479

6-(3-chloropyridin-4-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-amine 2.479

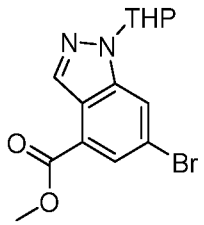


To a solution of **compound 1.952** (500 mg, 1.46 mmol) and 4-bromo-3-chloro-pyridine (CAS 73583-41-2, 308.37 mg, 1.60 mmol) in dioxane (8 mL) and H_2O (0.8 mL) was added K_2CO_3 (503.33 mg, 3.64 mmol) followed by $Pd(dppf)Cl_2$ (106.59 mg, 145.68 μmol). The mixture was degassed and purged with N_2 (x3), the mixture was heated to 100°C and stirred for 12 h. The reaction mixture was cooled to 20 °C, diluted with DCM (40 mL) and filtered. The filtrate was concentrated in *vacuo* to give a residue, which was purified (PM42) to afford **compound 2.479** (0.325 g, 868.75 μmol, 59.64% yield) as a brown oil.

LCMS (AM12): rt = 0.443 min, (329.2, $[M+H]^+$), 87.89% purity.

Synthesis of Intermediate 2.488

methyl 6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-4-carboxylate 2.483

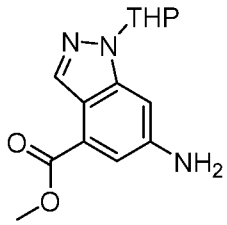


To a solution of methyl 6-bromo-1H-indazole-4-carboxylate (CAS 885518-49-0, 10 g, 39.21 mmol) and 3,4-dihydro-2H-pyran (9.89 g, 117.62 mmol) in THF (100 mL) was added TsOH (675.12 mg, 3.92 mmol). The mixture was heated to 50 °C and stirred for 12 h. The reaction mixture was concentrated in *vacuo* to give a residue. The residue was triturated with EA (30 mL × 2) at 20 °C and filtered. The filter cake was collected and dried under *vacuum* to afford **compound 2.483** (14.3 g, crude) as a white solid.

LCMS (AM12): rt = 0.608 min, (360.9, $[M+Na]^+$), 98.46% purity.

^{1}H NMR ($CHCl_3$-*d*, 400 MHz) δ 8.49 (s, 1H), 8.06 - 8.00 (m, 2H), 5.72 (dd, J = 9.2, 2.8 Hz, 1H), 4.04 - 3.99 (m, 4H), 3.82 - 3.73 (m, 1H), 2.58 - 2.48 (m, 1H), 2.23 - 20.5 (m, 2H), 1.83 - 1.68 (m, 3H) ppm.

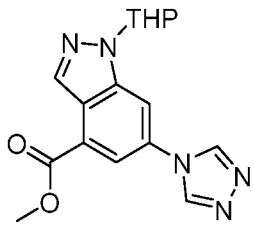
methyl 6-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-4-carboxylate 2.484



To a mixture of **compound 2.483** (14.3 g, 42.16 mmol) in DMSO (100 mL) was added K_2CO_3 (17.48 g, 126.48 mmol), $NH_3•H_2O$ (11.98 g, 126.48 mmol) and L-proline (2.91 g, 25.30 mmol) followed by CuI (2.41 g, 12.65 mmol). The mixture was degassed and purged with N_2 (x3), then heated to 75 °C and stirred for 12 h. The reaction mixture was poured into water (300 mL) and extracted with EA (200 mL × 3). The combined organic phase was washed (brine, 100 mL × 5), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.484** (6 g, 19.29 mmol, 45.75% yield) as a white solid.

LCMS (AM12): rt = 0.393 min, (276.2, $[M+H]^+$), 88.56% purity.

methyl 1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazole-4-carboxylate 2.485

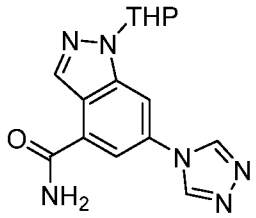


To a solution of **compound 2.484** (6 g, 21.79 mmol) and N'-formylformohydrazide (5.76 g, 65.38 mmol) in pyridine (100 mL) was added TEA (15.44 g, 152.56 mmol) followed by TMSCl (35.52 g, 326.91 mmol) dropwise at 20 °C. The mixture was heated to 100 °C and stirred for 12 h. The mixture was concentrated in *vacuo* to give a residue. The residue was triturated with MeOH (50 mL × 3) and filtered. The filter cake was collected and dried under *vacuum* to afford **compound 2.485** (6 g, 17.71 mmol, 81.24% yield) as an off-white solid.

LCMS (AM16): rt = 0.532 min, (314.2, $[M+H]^+$), 96.62% purity.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 8.67 - 8.53 (m, 3H), 7.94 (d, J = 1.6 Hz, 1H), 7.89 (s, 1H), 5.87 -5.77 (m, 1H), 4.07 (s, 3H), 4.04 - 3.95 (m, 1H), 3.84 - 3.74 (m, 1H), 2.59 - 2.46 (m, 1H), 2.23 - 2.12 (m, 2H), 1.89 - 1.70 (m, 3H) ppm.

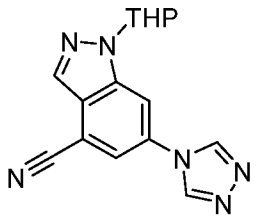
1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazole-4-carboxamide 2.486



A solution of **compound 2.485** (3 g, 9.16 mmol) in NH_3/MeOH (7 M, 20 mL) was heated to 80 °C and stirred for 48 h. The mixture was concentrated in *vacuo* to afford **compound 2.486** (2.5 g, 8.00 mmol, 81.62% yield) as a white solid.

LCMS (AM11): rt = 0.398 min, (313.2, $[M+H]^+$), 96.45% purity.

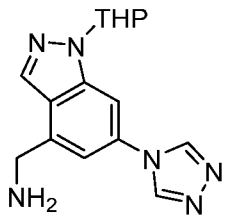
1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazole-4-carbonitrile 2.487



To a solution of **compound 2.486** (1.25 g, 4.00 mmol) in pyridine (30 mL) was added TFAA (2.52 g, 12.01 mmol). The mixture was stirred at 20 °C for 4 h. The mixture was quenched by water (10 mL) and concentrated in *vacuo* to give a residue, which was triturated with ACN (20 mL × 2) at 20 °C and filtered. The filter cake was collected and dried under *vacuum* to afford **compound 2.487** (950 mg, 3.19 mmol, 79.68% yield) as an off-white solid.

LCMS (AM16): rt = 0.518 min, (295.2, $[M+H]^+$), 98.85% purity.

(1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)methanamine 2.488



To a mixture of **compound 2.487** (1 g, 3.40 mmol) in MeOH (40 mL) was added $NH_3 \cdot H_2O$ (965.49 mg, 10.19 mmol) and Raney-Ni (300 mg, 3.50 mmol). The mixture was degassed and

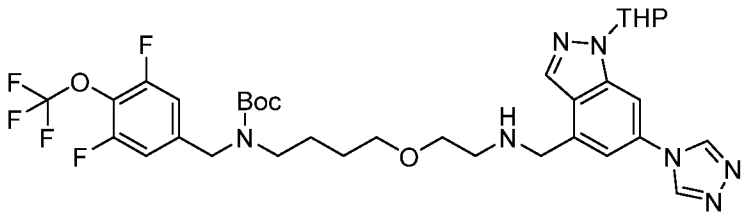
purged with H_2 (x3), then stirred at 20 °C for 1 h under H_2 (15 psi). The catalyst was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.488** (940 mg, 3.15 mmol, 92.73% yield) as a yellow solid.

LCMS (AM11): rt = 0.250 min, (298.9, $[M+H]^+$), 89.09% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 2H), 8.35 (s, 1H), 7.96 (s, 1H), 7.50 (d, J = 0.8 Hz, 1H), 5.86 (dd, J = 9.6, 2.0 Hz, 1H), 4.09 (s, 2H), 3.91 (br d, J = 11.6 Hz, 1H), 3.81 - 3.70 (m, 1H), 2.47 - 2.38 (m, 1H), 2.02 - 1.91 (m, 2H), 1.79 - 1.61 (m, 1H), 1.65 - 1.55 (m, 2H) ppm.

Synthesis of Intermediate 2.490

tert-butyl (3,5-difluoro-4-(trifluoromethoxy)benzyl)(4-(2-(((1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)methyl)amino)ethoxy)butyl)carbamate 2.490

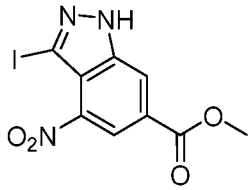


To a mixture of **compound 2.488** (100 mg, 335.19 μmol) in MeOH (1.5 mL) was added **compound 1.941** (147.95 mg, 335.19 μmol) and $MgSO_4$ (201.73 mg, 1.68 mmol). The mixture was stirred at 20 °C for 2 h, then $NaBH_3CN$ (57.45 mg, 914.14 μmol) was added and the mixture was stirred at 20 °C for 1 h. The reaction mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM199) to afford a solution. The solution was basified to pH=9 by saturated $NaHCO_3$ aqueous solution and extracted with EA (30 mL × 3). The combined organic phase was washed by brine (20 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.490** (90 mg, 118.22 μmol, 35.27% yield) as a yellow oil.

LCMS (AM14): rt = 0.576 min, (724.5, $[M+H]^+$), 95.07% purity.

Synthesis of Intermediate 2.498

methyl 3-iodo-4-nitro-1H-indazole-6-carboxylate 2.491

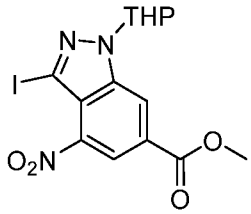


To a solution of methyl 4-nitro-1H-indazole-6-carboxylate (CAS 72922-61-3, 2 g, 9.04 mmol) in DMF (25 mL) was added NIS (2.24 g, 9.95 mmol) at 0 °C and stirred for 0.5 h, then the mixture was heated to 60 °C and stirred for 3 h. The mixture was poured into water (150 mL) and filtered. The filter cake was collected and dried under *vacuum* to afford **compound 2.491** (3 g, 8.48 mmol, 93.82% yield) as a yellow solid.

LCMS (AM11): rt = 0.405 min, (347.6, $[M+H]^+$), 98.15% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 14.65 (s, 1H), 8.49 (s, 1H), 8.24 (s, 1H), 3.95 (s, 3H) ppm.

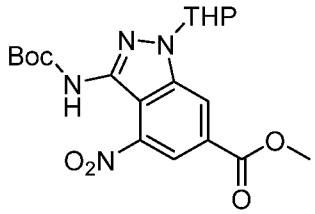
methyl 3-iodo-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 2.492



To a solution of **compound 2.491** (3 g, 8.64 mmol) in THF (35 mL) was added 3,4-dihydro-2H-pyran (2.18 g, 25.93 mmol) and TsOH (148.85 mg, 864.39 μmol). The mixture was heated to 60 °C and stirred for 3 h. The mixture was diluted with EA (50 ml) and washed with saturated $NaHCO_3$ aqueous solution (20 mL × 2) and brine (20 mL × 3), then the organic layers was dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was triturated with MTBE (5 mL) at 20 °C and filtered. The filter cake was collected and dried under *vacuum* to afford **compound 2.492** (2.9 g, 6.73 mmol, 77.81% yield) as a light-yellow solid.

^{1}H NMR(400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.30 (s, 1H), 6.23 (dd, J = 9.2 Hz, 2.0 Hz, 1H), 3.97 (s, 3H), 3.88 - 3.82 (m, 2H), 2.38 - 2.32 (m, 1H), 2.04 (d, J = 10.0 Hz, 2H), 1.83 -1.72 (m, 1H), 1.61 (d, J = 2.4 Hz, 2H) ppm.

methyl 3-((tert-butoxycarbonyl)amino)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 2.493



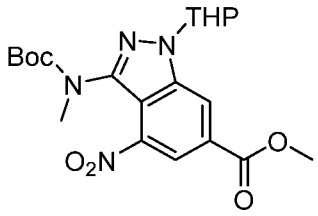
To a solution of **compound 2.492** (1.9 g, 4.41 mmol) in dioxane (20 mL) was added tert-butyl carbamate (1.14 g, 9.69 mmol), Xantphos (509.94 mg, 881.30 μmol), Cs_2CO_3 (2.87 g, 8.81 mmol) and $Pd_2(dba)_3$ (403.51 mg, 440.65 μmol). The mixture was degassed and purged with

N_2 (x3). The mixture was heated for 100 °C and stirred for 12 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM27) to afford **compound 2.493** (300 mg, 711.94 µmol, 16.16% yield) as a light-yellow solid.

LCMS (AM11): rt = 0.510 min, (443.0, $[M+Na]^+$), 99.77% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 8.73 (s, 1H), 8.25 (s, 1H), 6.16 (dd, *J* = 7.6 Hz, 2.0 Hz, 1H), 3.97 (s, 3H), 3.88 - 3.82 (m, 2H), 2.35 - 2.30 (m, 1H), 2.05 - 1.98 (m, 2H), 1.81 - 1.73 (m, 1H), 1.63 - 1.55 (m, 2H), 1.39 (s, 9H) ppm.

methyl 3-((tert-butoxycarbonyl)(methyl)amino)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 2.494

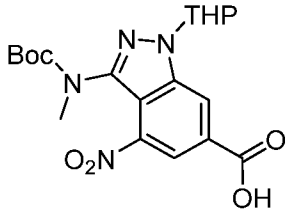


To a solution of **compound 2.493** (720 mg, 1.71 mmol) in DMF (10 mL) was added Cs_2CO_3 (1.39 g, 4.28 mmol) followed by a solution of CH_3I (364.62 mg, 2.57 mmol) in DMF (0.5 mL) at 0 °C. The mixture was stirred at 20 °C for 0.5 h. The mixture was poured into water (30 mL) and filtered. The filtrate was concentrated in *vacuo* to afford **compound 2.494** (720 mg, 1.66 mmol, 96.77% yield) as a yellow solid.

LCMS (AM11): rt = 0.541 min, (457.1, $[M+Na]^+$), 97.46% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (t, *J* = 8.0 Hz, 1H), 8.43 (s, 0.5H), 8.29 (s, 0.5H), 6.21 (d, *J* = 8.8 Hz, 1H), 3.98 (s, 3H), 3.90 - 3.81 (m, 2H), 3.40 - 3.32 (m, 3H), 2.37 - 2.31 (m, 1H), 2.08 - 2.00 (m, 2H), 1.83 - 1.73 (m, 1H), 1.64 - 1.57 (m, 2H), 1.44 (s, 4H), 1.15 (s, 5H) ppm.

3-((tert-butoxycarbonyl)(methyl)amino)-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylic acid 2.495

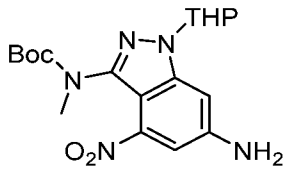


To a solution of **compound 2.494** (700 mg, 1.61 mmol) in MeOH (15 mL) and H_2O (4.5 mL) was added NaOH (257.78 mg, 6.45 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated in *vacuo*, acidified to pH = 6 by 1M HCl aqueous solution and

filtered. the filter cake was collected and dried under *vacuum* to afford **compound 2.495** (660 mg, 1.57 mmol, 97.43% yield) as a light-yellow solid.

LCMS (AM11): rt = 0.491 min, (443.1, $[M+Na]^+$), 93.89% purity.

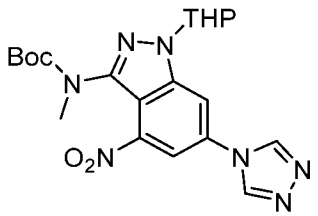
tert-butyl (6-amino-4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)(methyl)carbamate 2.496



To a solution of **compound 2.495** (650 mg, 1.55 mmol) in dioxane (15 mL) was added TEA (645.59 µL, 4.64 mmol) and DPPA (510.58 mg, 1.86 mmol). The mixture was stirred at 20 °C for 3 h, then H_2O (4.5 mL) was added. The mixture was heated to 100 °C and stirred for 3 h. The mixture was poured into water (30 mL) and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 20 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM24) to afford **compound 2.496** (430 mg, 1.06 mmol, 68.40% yield) as a yellow solid.

LCMS (AM11): rt = 0.473 min, (414.0, $[M+Na]^+$), 96.26% purity.

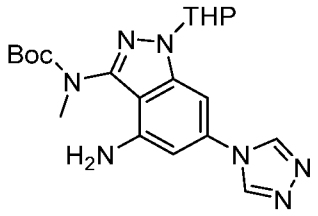
tert-butyl methyl(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-3-yl)carbamate 2.497



To a solution of **compound 2.496** (430 mg, 1.10 mmol) in pyridine (12 mL) was added N,N'-diformylhydrazine (484.71 mg, 5.50 mmol), TEA (778.14 mg, 7.69 mmol) and TMSCl (1.79 g, 16.48 mmol) dropwise at 0 °C. The mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was cooled to 20°C and quenched by water (2 mL) at 0 °C. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM204) to **compound 2.497** (370 mg, 834.36 µmol, 75.95% yield) as a yellow solid.

LCMS (AM11): rt = 0.436 min, (444.4, $[M+H]^+$), 100.00% purity.

tert-butyl (4-amino-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-3-yl)(methyl)carbamate 2.498



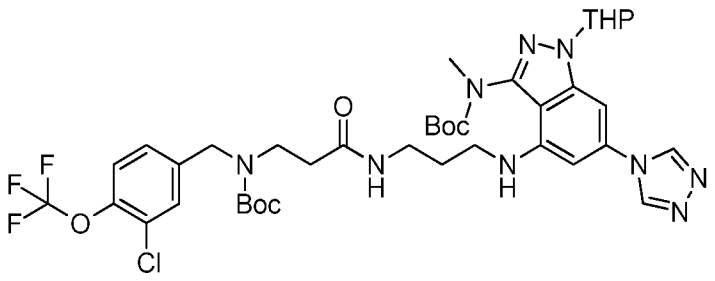
A solution of **compound 2.497** (370 mg, 834.36 μmol) in MeOH (5 mL) was degassed and purged with N_2 (x3), then Pd/C (80 mg, 10% purity) was added. The mixture was degassed and purged with H_2 (x3) and stirred at 20°C for 1 h under H_2 balloon (15 psi). The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM238) to afford **compound 2.498** (203 mg, 490.96 μmol, 58.84% yield) as a yellow solid.

LCMS (AM11): rt = 0.509 min, (414.2, $[M+H]^+$), 100.00% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 2H), 7.13 (s, 1H), 6.45 (s, 1H), 5.69 (d, *J* = 8.0 Hz, 1H), 5.61 (s, 2 H), 3.92 - 3.86 (m, 1H), 3.75 - 3.69 (m, 1H), 3.19 (s, 3H), 2.35 - 2.28 (m, 1H), 2.06 - 1.99 (m, 1H), 1.92 - 1.85 (m, 1H), 1.75 - 1.66 (m, 1H), 1.57 (s, 2H), 1.36 (s, 9H) ppm.

Synthesis of Intermediate 2.500

tert-butyl (4-((3-(3-((tert-butoxycarbonyl)(3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamido)propyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-3-yl)(methyl)carbamate 2.500

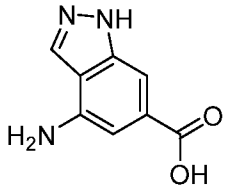


To a solution of **compound 2.498** (35 mg, 84.65 μmol) in MeOH (1 mL) was added **compound 1.950** (49.83 mg, 110.04 μmol) and AcOH (8.71 mg, 145.11 μmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (26.60 mg, 423.24 μmol) was added and the mixture was stirred at 20 °C for 2 h. The mixture was filtered and the filtrate was purified (PM179) to afford **compound 2.500** (40 mg, 47.04 μmol, 55.57% yield) as a white solid.

LCMS (AM11): rt = 0.554 min, (850.7[M+H]+), 100.00% purity.

Synthesis of Intermediate 2.511

4-amino-1H-indazole-6-carboxylic acid 2.511

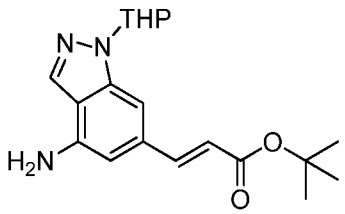


To a solution of methyl 4-amino-1H-indazole-6-carboxylate (CAS 885518-51-4, 400 mg, 2.09 mmol) in MeOH (10 mL) and H_2O (3 mL) was added NaOH (251.05 mg, 6.28 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was poured into water (40 mL) and extracted with EA (50 ml × 3). The combined organic phase was washed (brine, 20 ml), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.511** (70 mg, 297.25 μmol, 23.40% yield) as a brown oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 - 12.81 (m, 1H), 12.70 - 12.40 (m, 1H), 8.15 (s, 1H), 7.26 (s, 1H), 6.73 (s, 1H), 5.95 (s, 2H) ppm.

Synthesis of Intermediate 2.514

(E)-tert-butyl 3-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)acrylate 2.513



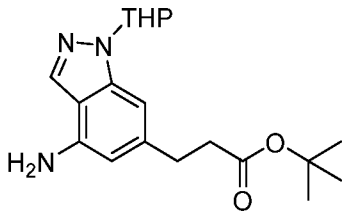
To a solution of **compound 1.381** (300 mg, 1.01 mmol) and tert-butyl acrylate (194.74 mg, 1.52 mmol) in ACN (6 mL) was added TEA (410.00 mg, 4.05 mmol), tris-o-tolylphosphine (61.66 mg, 202.59 μmol) followed by $Pd(OAc)_2$ (22.74 mg, 101.30 μmol). The mixture was degassed and purged with N_2 (x3), then the mixture was heated to 90°C and stirred for 6 h. The reaction mixture was poured into water (30 mL) and extracted with EA (20 mL × 3). The combined organic phase was washed by brine (30 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM27) to afford **compound 2.513** (340 mg, 917.28 μmol, 90.55% yield) as a yellow gum.

LCMS (AM11): rt = 0.487 min, (344.3, $[M+H]^+$), 92.65% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 7.51 (d, J = 15.6 Hz, 1H), 7.16 (s, 1H), 6.45 (s, 1H), 6.40 (d, J = 16.0 Hz, 1H), 5.93 (s, 2H), 5.74 (dd, J = 10.0, 2.4 Hz, 1H), 3.93 - 3.85 (m,

1H), 3.75 - 3.69 (m, 1H), 2.44 - 2.33 (m, 1H), 2.08 - 2.00 (m, 1H), 1.95 - 1.87 (m, 1H), 1.78 - 1.65 (m, 1H), 1.60 - 1.54 (m, 2H), 1.50 (s, 9H) ppm.

tert-butyl 3-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)propanoate 2.514

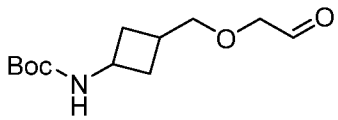


A solution of Pd/C (200 mg, 10% purity) in EA (20 mL) was degassed and purged with N_2 (x3), then **compound 2.513** (340 mg, 990.04 μmol) was added in one portion. The mixture was degassed and purged with H_2 (x3) and stirred at 20°C for 1 h under H_2 balloon (15 psi). The mixture was filtered and the filtrate was concentrated in *vacuo* to afford **compound 2.514** (310 mg, 858.74 μmol, 86.74% yield) as a brown gum.

LCMS (AM11): rt = 0.437 min, (346.4, $[M+H]^+$), 95.69% purity.

Synthesis of Intermediate 2.529

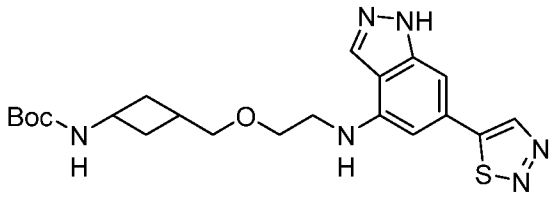
tert-butyl (3-((2-oxoethoxy)methyl)cyclobutyl)carbamate 2.527



To a solution of oxalyl dichloride (517.40 mg, 4.08 mmol) in DCM (2 mL) was added a solution of DMSO (477.75 mg, 6.11 mmol) in DCM (1 mL) dropwise at -70 °C under N_2. The mixture was stirred at -70 °C for 0.5 h, then a solution of **compound 1.856** (0.5 g, 2.04 mmol) in DCM (1 mL) was dropwise added at -70 °C and the resulting mixture was stirred at -70 °C for 0.5 h. Then TEA (1.24 g, 12.23 mmol) was added at -70 °C and the reaction was stirred at -70 °C for 10 min. The mixture was diluted with DCM (2 mL) and filtered. The filtrate was concentrated in *vacuo* to give a residue, which was purified (PM27) to afford **compound 2.527** (0.5 g, crude) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$-*d*) δ 9.74 - 9.70 (m, 1H), 4.09 - 4.03 (m, 2H), 3.50 - 3.40 (m, 2H), 3.15 - 3.06 (m, 1H), 2.50 - 2.39 (m, 3 H), 1.70 - 1.59 (m, 2 H), 1.43 (s, 9 H) ppm.

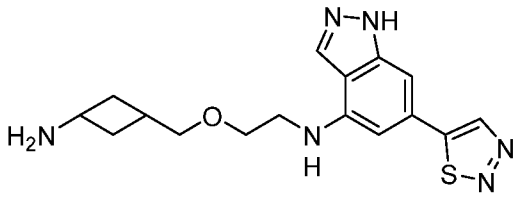
tert-butyl (3-((2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)methyl)cyclobutyl)carbamate 2.528



To a mixture of **compound 1.995** (200 mg, 920.60 μmol) and **compound 2.527** (447.96 mg, 1.84 mmol) in MeOH (5 mL) was added $MgSO_4$ (554.06 mg, 4.60 mmol) and HOAc (82.92 mg, 1.38 mmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (115.70 mg, 1.84 mmol) was added. The resulting mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water (40 mL) and extracted with EA (40 mL × 3). The combined organic phase was washed (brine, 20 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM24) to afford **compound 2.528** (150 mg, 283.43 μmol, 30.79% yield) as a yellow gum.

LCMS (AM11): rt = 0.459 min, (445.2, $[M+H]^+$), 84.22% purity.

N-(2-((3-aminocyclobutyl)methoxy)ethyl)-6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-amine 2.529

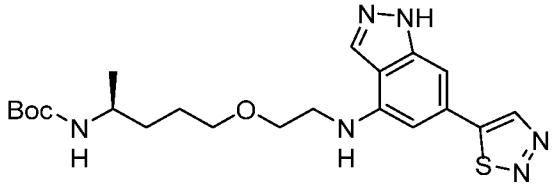


To a solution of **compound 2.528** (145 mg, 326.17 μmol) in DCM (20 mL) was added TFA (6.16 g, 54.02 mmol) at 20 °C. The mixture was stirred at 20 °C for 0.5 h. The mixture was concentrated in *vacuo* to afford **compound 2.529** (150 mg, crude, TFA salt) as a yellow gum.

LCMS (AM11): rt = 0.292 min, (334.9, $[M+H]^+$), 76.10% purity.

Synthesis of Intermediate 2.531

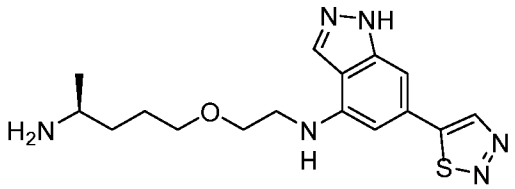
tert-butyl (S)-(5-(2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)carbamate 2.530



To a mixture of **compound 2.430** (293.59 mg, 1.20 mmol) and **compound 1.995** (200 mg, 920.60 μmol) in MeOH (20 mL) was added $MgSO_4$ (554.05 mg, 4.60 mmol) and HOAc (66.34 mg, 1.10 mmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (173.56 mg, 2.76) was added in portions at 0°C. The mixture was stirred at 20 °C for 1 h. The reaction mixture was diluted with water (40 mL) and extracted with EA (30 mL × 3). The combined organic phase was washed by brine (30 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM182) to afford **compound 2.530** (220 mg, 469.00 μmol, 50.95% yield) as a yellow gum.

LCMS (AM22): rt = 0.528 min, (447.3, $[M+H]^+$), 95.21% purity.

(S)-N-(2-((4-aminopentyl)oxy)ethyl)-6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-amine 2.531

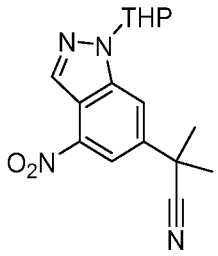


To a solution of **compound 2.530** (220 mg, 492.65 μmol) in MeOH (2 mL) was added HCl/dioxane (4 M, 3 mL). The mixture was stirred at 20 °C for 0.5 h. The mixture was concentrated in *vacuo* to afford **compound 2.531** (200 mg, 465.84 μmol, 94.56% yield, HCl salt) as a yellow solid.

LCMS (AM22): rt = 0.378 min, (347.2, $[M+H]^+$), 97.68% purity.

Synthesis of Intermediate 2.537

2-methyl-2-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)propanenitrile 2.534

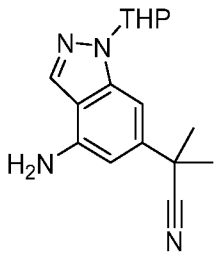


To a solution of **compound 2.451** (300 mg, 1.05 mmol) in DMF (4 mL) was added CH_3I (743.69 mg, 5.24 mmol), then Cs_2CO_3 (1.02 g, 3.14 mmol) was added in portions at 0°C. The mixture was stirred at 20°C for 2 h. The mixture was poured into saturated NH_4Cl aqueous solution (45 mL) and extracted with EA (30 mL × 3). The combined organic phase was washed by brine (60 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM26) to afford **compound 2.534** (290 mg, 922.57 μmol, 88.04% yield) as a yellow solid.

LCMS (AM11): rt = 0.492 min, (337.1, $[M+Na]^+$), 100% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.41 (s, 1H), 8.32 (s, 1H), 6.14 (d, J = 8.8 Hz, 1H), 3.93 - 3.86 (m, 1H), 3.78 - 3.85 (m, 1H), 2.46 - 2.37 (m, 1H), 2.13 - 2.06 (m, 1H), 2.02 - 1.97 (m, 1H), 1.85 (s, 6H), 1.80 - 1.70 (m, 1H), 1.65 - 1.54 (m, 2H) ppm.

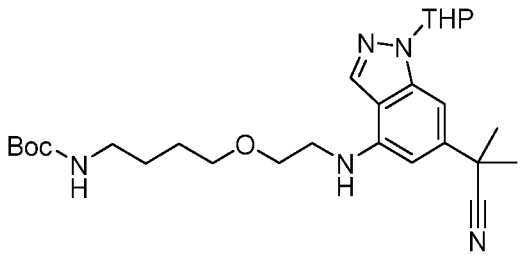
2-(4-amino-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-2-methylpropanenitrile 2.535



To a solution of **compound 2.534** (240 mg, 763.51 μmol) in MeOH (3 mL) and H_2O (1 mL) was added NH_4Cl (326.72 mg, 6.11 mmol) followed by Fe (255.83 mg, 4.58 mmol). The mixture was stirred at 50°C for 1.5 h. The reaction mixture was cooled to 20 °C, diluted with EA (30 mL), filtered and washed with EA (10 mL × 2). The filtrate was poured into water (40 mL) and extracted with EA (30 mL × 3). The combined organic phase was washed by brine (40 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.535** (245 mg, crude) as a brown gum.

LCMS (AM14): rt = 0.629 min, (285.2, $[M+H]^+$), 90.41% purity.

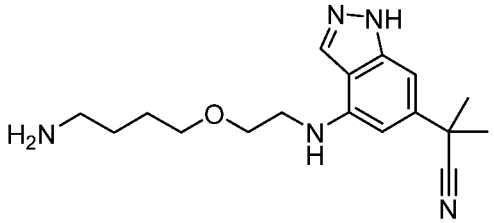
tert-butyl (4-(2-((6-(2-cyanopropan-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 2.536



To a solution of **compound 2.535** (240 mg, 844.01 μmol) in MeOH (5 mL) was added tert-Butyl (4-(2-aminoethoxy)butyl)carbamate (CAS 2830620-37-4, 234.25 mg, 1.01 mmol), $MgSO_4$ (304.78 mg, 2.53 mmol) and AcOH (101.37 mg, 1.69 mmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (106.08 mg, 1.69 mmol) was added. The resulting mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water (30 mL) and extracted with EA (30 mL × 3). The combined organic phase was washed (brine, 40 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM24) to afford **compound 2.536** (298 mg, 558.37 μmol, 66.16% yield) as a yellow gum.

LCMS (AM11): rt = 0.523 min, (500.4, $[M+H]^+$), 93.62% purity.

2-(4-((2-(4-aminobutoxy)ethyl)amino)-1H-indazol-6-yl)-2-methylpropanenitrile 2.537

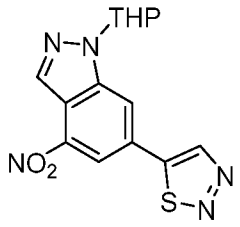


To a solution of **compound 2.536** (120 mg, 240.17 μmol) in DCM (6 mL) was added TFA (1.2 mL, 16.21 mmol). The mixture was stirred at 20 °C for 2 h. The mixture was concentrated in *vacuo* to afford **compound 2.537** (260 mg, crude) as a brown gum.

LCMS (AM22): rt = 0.289 min, (316.2, $[M+H]^+$), 77.55% purity.

Synthesis of Intermediate 2.548

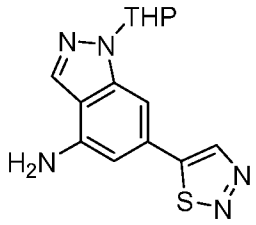
5-(4-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-1,2,3-thiadiazole 2.544



To a solution of **compound 1.994** (500 mg, 2.02 mmol) in THF (8 mL) was added DHP (510.34 mg, 6.07 mmol) followed by $TsOH.H_2O$ (38.47 mg, 202.24 μmol). The mixture was stirred at 60 °C for 0.5 h. The reaction mixture was added into saturated $NaHCO_3$ aqueous solution (15 mL) at 20 °C, and then extracted with EA (10 mL × 3). The combined organic layers were washed (brine, 15 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue. The residue was triturated with MeOH (3 mL), filtered and washed with MeOH (1 mL × 2). The filter cake was collected and dried under *vacuum* to afford **compound 2.544** (450 mg, 1.32 mmol, 65.14% yield) as a yellow solid.

LCMS (AM12): rt = 0.570 min, (332.0, $[M+H]^+$), 97.64% purity.

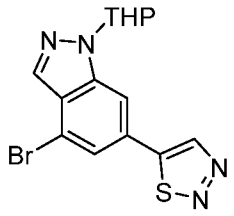
1-(tetrahydro-2H-pyran-2-yl)-6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-amine 2.5**45**



To a solution of **compound 2.544** (428 mg, 1.29 mmol) in MeOH (9 mL) was added NH_4Cl (552.75 mg, 10.33 mmol) in H_2O (3 mL) followed by Fe (432.81 mg, 7.75 mmol) at 60 °C. The mixture was stirred at 60 °C for 1.5 h. The mixture was filtered then the reaction mixture was added into water (30 mL) and extracted with EA (30 mL × 3). The combined organic phases were washed (brine, 20 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.545** (402 mg, 992.17 μmol, crude) as a yellow solid.

LCMS (AM12): rt = 0.467 min, (302.2, $[M+H]^+$), 74.38% purity.

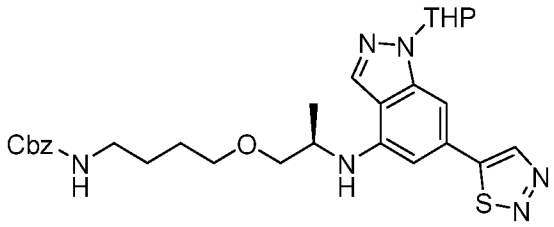
5-(4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-6-yl)-1,2,3-thiadiazole 2.546



To a solution of **compound 2.545** (400 mg, 987.2 μmol) in ACN (20 mL) was added *t*-BuONO (410.61 mg, 3.98 mmol) and CuBr (571.20 mg, 3.98 mmol). The mixture was heated to 60 °C and stirred for 0.5 h. The reaction mixture was poured into H_2O (30 mL) and extracted with EA (20 mL × 3). The combined organic phases were washed (brine, 10 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM58) to afford **compound 2.546** (100 mg, 180.12 μmol, 13.57% yield) as a yellow solid.

LCMS (AM12): rt = 0.606 min, (367.2, $[M+2+H]^+$), 65.78% purity.

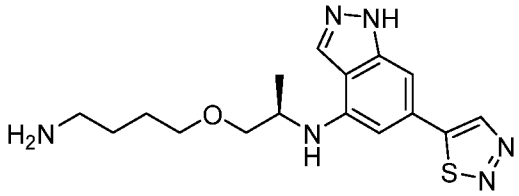
benzyl (4-((2R)-2-((1-(tetrahydro-2H-pyran-2-yl)-6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propoxy)butyl)carbamate 2.547



To a solution of **compound 2.546** (95 mg, 260.10 μmol) and (*R*)-benzyl (4-(2-aminopropoxy)butyl)carbamate (Ref: WO2022185041, 218.76 mg, 780.29 μmol) in dioxane (3 mL) was added Cs_2CO_3 (254.23 mg, 780.29 μmol), Xantphos (60.20 mg, 104.04 μmol) and $Pd_2(dba)_3$ (47.64 mg, 52.02 μmol). The mixture was degassed and purged with N_2 (x3), then the mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was cooled to 20 °C, diluted with EA (20 mL) and filtered. The filtrate was concentrated in *vacuo* to give a residue, which was purified by prep-TLC (PM2) to afford **compound 2.547** (70 mg, 115.04 μmol, 44.23% yield) as a yellow solid.

LCMS (AM12): rt = 0.611 min, (565.2, $[M+H]^+$), 92.85% purity.

(R)-N-(1-(4-aminobutoxy)propan-2-yl)-6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-amine 2.548

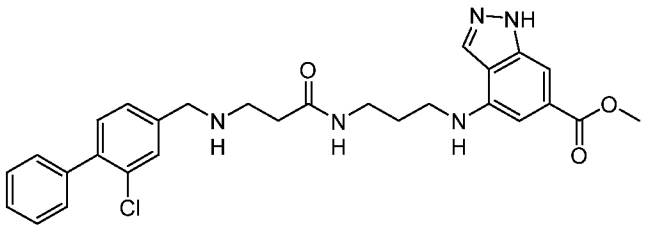


A solution of **compound 2.547** (65 mg, 115.11 μmol) in HCl (12 M, 8 mL) was heated to 80 °C and stirred for 0.5 h. The reaction mixture was concentrated in *vacuo* to afford **compound 2.548** (48 mg, crude, HCl salt) as a yellow gum.

LCMS (AM12): rt = 0.394 min, (347.2, $[M+H]^+$), 93.14% purity.

Synthesis of Intermediate 2.569

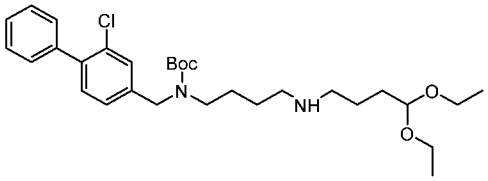
methyl 4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1H-indazole-6-carboxylate 2.569



A mixture of **compound 1.81** (144 mg, 204 μmol) in HCl/MeOH (4 M, 3 mL) was stirred at 25°C for 1 h. The solvent was removed under reduced pressure to afford **compound 2.569** (100 mg, 192.30 μmol, 96.73% yield) as a yellow oil, which was used for next step directly.
LCMS (AM3): rt = 0.817 min, (520.3 $[M+H]^+$), 82.34% purity.

Synthesis of Intermediate 2.574

tert-butyl ((2-chloro-[1,1'-biphenyl]-4-yl)methyl)(4-((4,4-diethoxybutyl)amino)butyl)carbamate 2.570

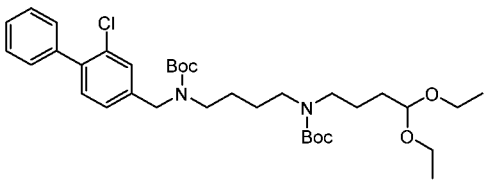


To a solution of **compound 1.7** (400 mg, 1.03 mmol), 4,4-diethoxybutan-1-amine (216 mg, 1.34 mmol, 231 μL) and AcOH (60.0 mg, 999 μmol) in MeOH (5 mL) was added $NaBH_3CN$

(130 mg, 2.07 mmol) and the mixture was stirred at 30°C for 30 min. The mixture was concentrated in *vacuo* to afford **compound 2.570** (500 mg, crude) as a yellow oil, which was used directly for the next step.

LCMS (AM21): rt = 2.441 min, (533.5 $[M+H]^+$), 37.09% purity.

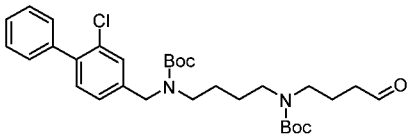
tert-butyl (4-((tert-butoxycarbonyl)(4,4-diethoxybutyl)amino)butyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)carbamate 2.571



To a solution of **compound 2.570** (500 mg, 937.84 μmol) and TEA (189.80 mg, 1.88 mmol) in DCM (3 mL) was added Boc_2O (204.68 mg, 937.84 μmol), and the mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water (20 mL) and extracted with DCM (10 mL × 3). The combined organic layer was washed (brine, 10 mL), dried (Na_2SO_4), filtered and concentrated to give a residue, which was purified (PM45) to afford **compound 2.571** (350 mg, 552.70 μmol, 58.93% yield) as a yellow oil.

LCMS (AM22): rt = 1.015 min, (655.5 $[M+Na]^+$), 51.03% purity

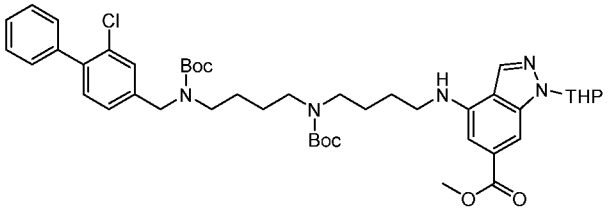
tert-butyl (4-((tert-butoxycarbonyl)(4-oxobutyl)amino)butyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)carbamate 2.572



A solution of **compound 2.571** (350 mg, 553 μmol) in H_2O (5 mL) and AcOH (4.59 g, 76.5 mmol, 4.38 mL) was stirred at 50°C for 1 h. The mixture was poured into water (30 mL) and extracted with EA (10 mL × 3). The combined organic layer was washed (brine, 20 mL), dried (Na_2SO_4), filtered and concentrated to afford **compound 2.572** (200 mg, 358 μmol, 64.7% yield) as a yellow oil.

LCMS (AM22): rt = 0.823 min, (559.5 $[M+H]^+$), 75.88% purity.

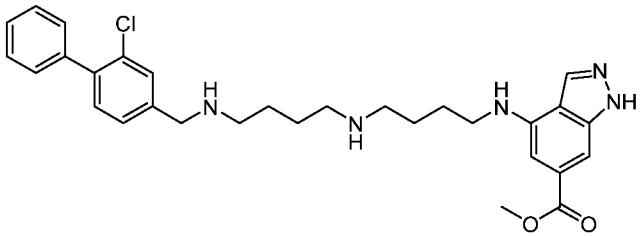
methyl 4-((4-((tert-butoxycarbonyl)(4-((tert-butoxycarbonyl)((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)butyl)amino)butyl)amino)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole-6-carboxylate 2.573



To a solution of **compound 2.572** (40.0 mg, 71.5 μmol) and **compound 1.80** (27.0 mg, 98.1 μmol) in MeOH (1.00 mL) was added AcOH (4.09 μL, 71.5 μmol) and the reaction was stirred at 20 °C for 0.5 h, then $NaBH_3CN$ (20.0 mg, 318 μmol) was added to the reaction mixture and stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified (PM183) to afford **compound 2.573** (35.0 mg, crude) as a white solid.

LCMS (AM3): rt = 1.278 min, (818.5 $[M+H]^+$), 35.18% purity.

methyl 4-((4-((4-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)butyl)amino)butyl)amino)-1H-indazole-6-carboxylate 2.574

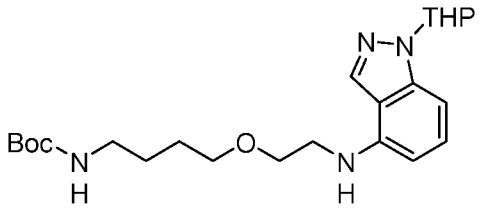


To a solution of **compound 2.573** (25.0 mg, 30.6 μmol) in DCM (2.00 mL) was added TFA (2.00 mL). The reaction was stirred at 30 °C for 12 h. The reaction mixture was concentrated under reduced pressure to afford **compound 2.574** (16.0 mg, crude), which was used in the next step directly.

LCMS (AM3): rt = 0.809 min, (534.3.5 $[M+H]^+$), 93.8 % purity.

Synthesis of Intermediate 2.576

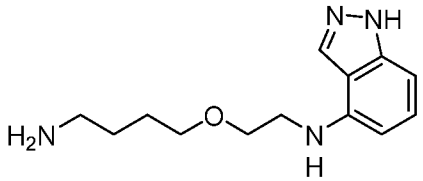
tert-butyl (4-(2-((1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)amino)ethoxy)butyl)carbamate 2.575



To a mixture of Pd/C (150 mg, 10% on carbon) in MeOH (30 mL) was added **compound 1.893** (200 mg, 391.04 μmol) and $NH_3 \cdot H_2O$ (146.83 mg, 1.17 mmol, 28% purity). The mixture was degassed and purged with N_2 (x3) and stirred at 20°C for 1 h under H_2 balloon (15 psi). The mixture was filtered. The filtrate was poured into water (50 mL) and extracted with EA (50 mL × 3). The combined organic phase was washed (brine, 20 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to afford **compound 2.575** (160 mg, 336.60 μmol, 86.08% yield) as a light-yellow solid.

LCMS (AM11): rt = 0.502 min, (433.6, $[M+H]^+$), 91.00% purity.

N-(2-(4-aminobutoxy)ethyl)-1H-indazol-4-amine 2.576



To a solution of **compound 2.575** (160 mg, 336.60 μmol) in MeOH (10 mL) was added HCl/dioxane (4 M, 10 mL), the mixture was stirred at 20°C for 1 h. The mixture was concentrated in *vacuo* to afford **compound 2.576** (130 mg, crude, HCl salt) as a yellow gum.

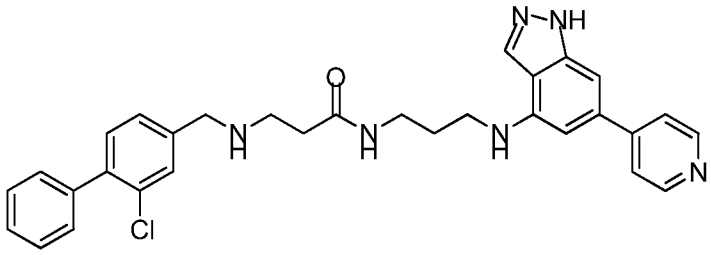
LCMS (AM11): rt = 0.234 min, (249.4, $[M+H]^+$), 87.08% purity.

Example compounds

[00665] 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.

Example 1

3-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



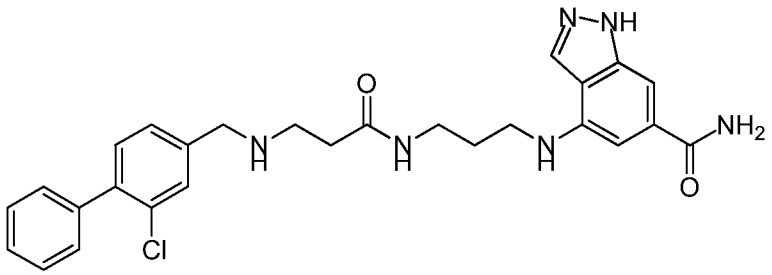
[00666] A mixture of **compound 1.323** (300 mg, 414.77 μmol) in aq. HCl (3 M, 30.0 mL) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated in *vacuo* and the residue purified (PM167) to afford **EXAMPLE 1** (256.95 mg, 389.50 μmol, 93.9% yield, TFA salt) as an orange solid.

[00667] LCMS (AM3): rt = 0.752 min, (539.0 $[M+H]^+$), 99.4% purity.

[00668] ^{1}H NMR (400 MHz, MeOH-d_4) δ: 8.81 (dd, *J* = 1.2 Hz, 6.0 Hz, 2H), 8.37 (d, *J* = 6.8 Hz, 2H), 8.25 (d, *J* = 1.2 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.50-7.35 (m, 8H), 7.33 (d, *J* = 0.8 Hz, 1H), 4.27 (s, 2H), 3.46-3.39 (m, 4H), 3.35-3.32 (m, 2H), 2.71 (t, *J* = 6.8 Hz, 2H), 1.98 (quin, *J* = 6.8 Hz, 2H) ppm.

EXAMPLE 2

4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1H-indazole-6-carboxamide



[00669] A solution of **compound 1.83** (50 mg, 0.07254 mmol) in aq. HCl (6 M, 5 mL) was stirred at 25 °C for 1 h. The reaction mixture was concentrated in *vacuo* and the residue was purified (PM206) to afford **EXAMPLE 2** (14.94 mg, 0.0276 mmol, 38% yield, HCl salt) as a green solid.

[00670] LCMS (AM4): rt = 0.781 min, (505.3 $[M+H]^+$), 100% purity.

[00671] **^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.25-8.18 (m, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.52-7.33 (m, 9H), 4.28 (s, 2H), 3.44-3.35 (m, 6H), 2.72 (t, J = 6.4 Hz, 2H), 1.99-1.91 (m, 2H) ppm.

[00672] The following examples in Table 6 were made with non-critical changes or substitutions to the exemplified procedure for Example 2, that would be understood by one skilled in the art

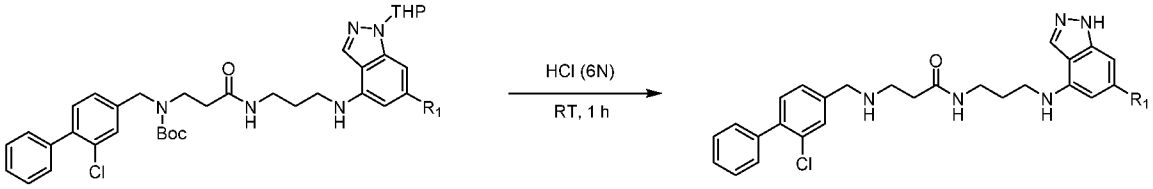
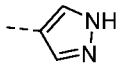
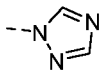
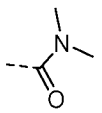


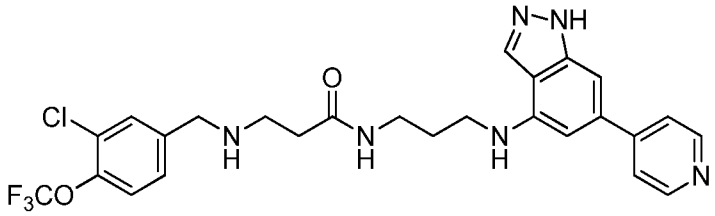
Table 6

Example No.	Chemical IUPAC name	R_1 structure/ Intermediate No	Analytical
Example 3	N-(3-((6-(1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide	 **(Intermediate 1.303)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 8.13 (s, 1H), 8.00 (s, 2H), 7.65 (d, J = 1.6 Hz, 1H), 7.48-7.36 (m, 9H), 4.24 (s, 2H), 3.41 (t, J = 6.8 Hz, 4H), 3.30-3.28 (m, 2H), 2.68 (t, J = 6.8 Hz, 2H), 2.00-1.92 (m, 2H) ppm. **LCMS** (AM2): rt = 0.714 min, (528.2 $[M+H]^+$), 92.4% purity. **Purification Method** PM207
Example 4	N-(3-((6-(1H-1,2,4-triazol-1-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide	 **(Intermediate 1.295)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.84 (s, 1H), 8.62 (s, 1H), 8.41 (s, 1H), 7.69 (d, J = 1.6 Hz, 1H), 7.53-7.49 (m, 1H), 7.46-7.38 (m, 8H), 4.29 (s, 2H), 3.45-3.39 (m, 4H), 3.36-3.33 (m, 2H), 2.73 (t, J = 6.6 Hz, 2H), 2.02-1.94 (quin, 2H) ppm. **LCMS** (AM3): rt = 0.802 min, (529.2 $[M+H]^+$), 100% purity. **Purification Method** PM211
Example 62	4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-N,N-dimethyl-1H-indazole-6-carboxamide	 **(Intermediate 2.362)**	**^{1}H NMR** (400 MHz,MeOH-d_4) δ 8.52 (s, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.54 (dd, J = 7.6, 1.6 Hz, 1H), 7.48 - 7.15 (m, 8H), 4.30 (s, 2H), 3.47 (t, J = 7.2 Hz, 2H), 3.40 - 3.33 (m, 4H), 3.13 (s, 3H), 3.03 (s, 3H), 2.76 (t, J = 6.8 Hz, 2H), 2.03 - 1.94 (m, 2H) ppm **LCMS** (AM2): rt = 0.798 min, (533.3 $[M+H]^+$), 99.57% purity. **Purification Method** PM212

Example 63	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(hydroxymethyl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.360)**	**^{1}H NMR** (400 MHz,MeOH-d_4) δ 8.12 (s, 1H), 7.68 (d, *J* = 1.6 Hz, 1H), 7.51 - 7.37 (m, 9H), 4.65 (s, 2H), 4.27 (s, 2H), 3.41 - 3.32 (m, 6H), 2.69 (t, *J* = 6.8 Hz, 2H), 1.97 - 1.90 (m, 2H) ppm **LCMS** (AM2): rt = 0.699 min, (492.2 $[M+H]^+$), 90.45% purity **Purification Method** PM207

EXAMPLE 5

3-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



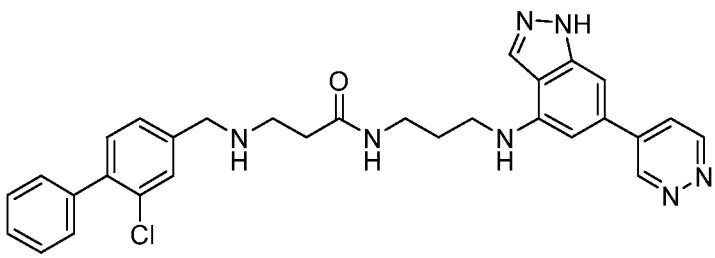
[00673] A solution of **compound 1.326** (240 mg, 308.79 μmol) in aq. HCl (6 M, 5 mL) was stirred at 20 °C for 0.5 h. The mixture was concentrated in *vacuo* and the residue was purified (PM213) to afford **EXAMPLE 5** (123.48 mg, 186.81 μmol, 60.5% yield, TFA salt) as a yellow solid.

[00674] LCMS (AM3): rt = 0.742 min, (547.2 $[M+H]^+$), 100% purity.

[00675] ^{1}H NMR (400 MHz, MeOH-d_4) δ: 8.80 (d, *J* = 6.8 Hz, 2H), 8.33 (d, *J* = 6.8 Hz, 2H), 8.24 (s, 1H), 7.77 (d, *J* = 2 Hz, 1H), 7.57-7.51 (m, 2H), 7.32 (s, 1H), 6.56 (d, *J* = 1.3 Hz, 1H), 4.27 (s, 2H), 3.48-3.43 (t, 2H), 3.43-3.38 (t, 2H), 3.33-3.28 (m, 2H), 2.69 (t, *J* = 6.8 Hz, 2H), 2.03-1.94 (m, 2H) ppm.

EXAMPLE 6

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



[00676] To a mixture of **compound 1.924** (90 mg, 124.26 μmol) in H_2O (5 mL) was added HCl (12 M, 11.66 mL) in one portion under N_2. The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM214) to afford **EXAMPLE 6** (65.24 mg, 96.75 μmol, 77.86% yield, TFA) as a red solid.

[00677] LCMS (AM3): rt = 0.771 min, (540.2 $[M+H]^+$), 97.1% purity.

[00678] ^{1}H NMR (400 MHz, DMSO-d_4) δ 9.64 (br s, 1H), 9.26 (d, *J* = 5.2 Hz, 1H), 8.22 - 8.20 (m, 2H), 7.67 (s, 1H), 7.38 - 7.16 (m, 7H), 7.25 (s, 1H), 6.52 (s, 1H), 4.27 (s, 2H), 3.43 (q, *J* = 6.8 Hz, 4H), 3.39 - 3.31 (m, 2H), 2.70 (t, *J* = 6.8 Hz, 2H), 1.98 (t, *J* = 6.8 Hz, 2H) ppm.

[00679] The following examples in Table 7 were made with non-critical changes or substitutions to the exemplified procedure for Example 6, that would be understood by one skilled in the art, wherein R may or may not contain a THP protecting group.

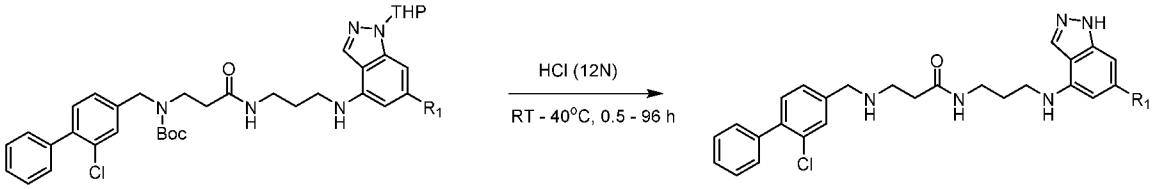
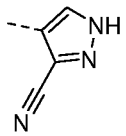
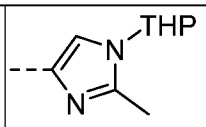
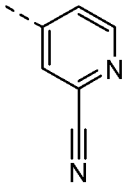
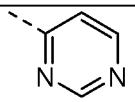
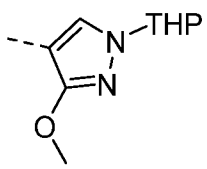


Table 7

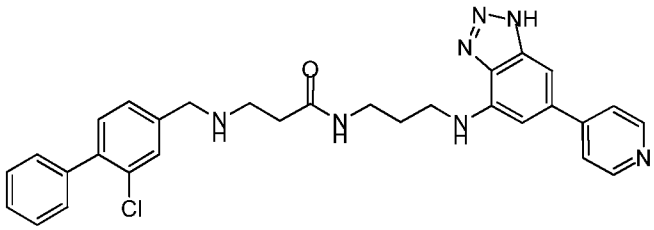
Example No.	Chemical IUPAC name	R_1 (Intermediate)	Analytical
Example 7	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-cyano-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 1.928)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.95 (br s, 2H), 8.44 (s, 1H), 8.24 - 8.22 (m, 1H), 8.16 (s, 1H), 7.74 (s, 1H), 7.72 - 7.42 (m, 8H), 6.99 (s, 1H), 6.33 (s, 1H), 4.22 (t, *J* = 4.8 Hz, 2H), 3.28 - 3.24 (m, 4H), 3.23 - 3.14 (m, 2H), 2.54 (t, *J* = 6.8 Hz, 2H) 1.83 (t, *J* = 6.8 Hz, 2H) ppm. **LCMS** (AM3): rt = 0.818 min, (553.2 $[M+H]^+$), 99.5% purity. **Purification Method** PM215

Example 9	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methyl-1H-imidazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 1.918)**	**^{1}H NMR**: (400 MHz, MeOH-d_4) δ: 8.19 (s, 1H), 7.76 (s, 1H), 7.69 - 7.68 (m, 1H), 7.49 - 7.40 (m, 7 H), 7.09 (m, 1H), 7.42 (s, 1H), 4.28 (s, 2H), 3.42 - 3.39 (m, 4H), 3.36 - 3.34 (m, 2H), 2.73 - 2.70 (m, 5H), 2.01 - 1.94 (m, 2H) ppm. **LCMS** (AM3): rt = 0.591 min, (542.2 $[M+H]^+$), 100% purity. **Purification Method** PM76
Example 74	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-cyanopyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.096)**	**^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.92 - 8.76 (m, 2H), 8.75 (d, *J* = 5.2 Hz, 1H), 8.41 (s, 1H), 8.23 (s, 2H), 7.74 d, *J* = 7.2 Hz,, 1H), 7.51 (s, 1H), 7.49 - 7.47 (m, 7H), 7.14 (s, 1H), 6.42 (s, 1H), 4.22 (t, *J* = 4.8 Hz, 2H), 3.34 (t, *J* = 4.8 Hz, 2H), 3.28 – 3.24 (m, 2H), 3.16 (t, *J* = 5.2 Hz, 2H), 2.54 (t, *J* = 6.8 Hz, 2H) 1.83 (t, *J* = 6.8 Hz, 2H) ppm **LCMS** (AM3): rt = 0.851 min, (564.3 $[M+H]^+$), 100.00% purity **Purification Method** PM217
Example 75	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyrimidin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.099)**	**^{1}H NMR** (DMSO-d_6, 400 MHz) δ 9.21 (s, 1H), 8.93 (s, 2H), 8.81 (d, *J* = 5.2 Hz, 1H), 8.26 - 8.23 (m, 2H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.53 (s, 1H), 7.49 - 7.40 (m, 8H), 6.86 (s, 1H), 4.22 (t, *J* = 4.8 Hz, 2H), 3.34 (t, *J* = 4.8 Hz, 2H), 3.28 – 3.24 (m, 2H), 3.16 (t, *J* = 5.2 Hz, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 1.83 (t, *J* = 6.8 Hz, 2H) ppm **LCMS** (AM3): rt = 0.825 min, (540.2 $[M+H]^+$), 100.00% purity **Purification Method** PM208

Example 76	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-methoxy-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.101)**	**^{1}H NMR** (DMSO-d_6, 400 MHz) δ 8.98 (s, 2H), 8.35 - 8.25 (m, 1H), 8.10 s, 1H), 8.00 (s, 1H), 7.76 (s, 1H), 7.50 - 7.45 (m, 8H), 7.14 (s, 1H), 6.34 (s, 1H), 4.22 (t, J = 4.8 Hz, 2H), 3.92 (s, 3H), 3.34 (t, J = 4.8 Hz, 2H), 3.28 – 3.24 (m, 2H), 3.16 (t, *J* = 5.2 Hz, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 1.83 (t, *J* = 6.8 Hz, 2H) ppm **LCMS** (AM3): rt = 0.827 min, (558.2 $[M+H]^+$), 98.31% purity **Purification Method** PM214

EXAMPLE 8

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)propyl)propanamide



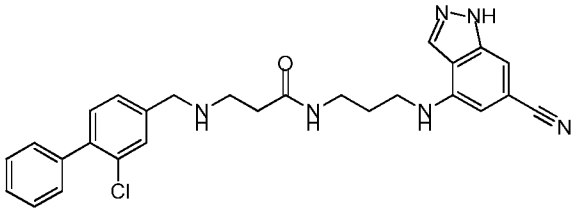
To a solution of **compound 1.900** (40 mg, 0.053 mmol) in H_2O (2 mL) was added HCl (2.04 g, 20.70 mmol, 37% purity). The mixture was stirred at 25 °C for 0.5 hour. The resultant mixture was then concentrated in *vacuo* and the residue was purified (PM216) to afford **EXAMPLE 8** (28.91 mg, 92.9% yield, HCl salt) as an orange solid.

LCMS (AM3): rt = 0.689 min, (540.2 $[M+H]^+$), 99.2% purity.

^{1}H NMR: (400 MHz, CD_3OD) δ: 8.88 (d, *J* = 6.8 Hz, 2H), 8.46 (d, *J* = 6.8 Hz, 2H), 7.71 (s, 1H), 7.53 - 7.52 (m, 2H), 7.46 - 7.41 (m, 6H), 6.86 (s, 1H), 4.32 (s, 2H), 3.60 (t, *J* = 6.8 Hz, 2H), 3.45 (t, *J* = 6.8 Hz, 2H),, 3.36 (t, *J* = 6.8 Hz, 2H), 2.76 (t, *J* = 6.8 Hz, 2H), 2.04 - 1.98 (m, 2H) ppm

EXAMPLE 10

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-cyano-1H-indazol-4-yl)amino)propyl)propanamide



[00680] To a mixture of **compound 1.88** (180 mg, 0.252 mmol) in DCM (15 mL) was added TFA (4.62 g, 40.52 mmol, 3 mL) at 0 °C. The reaction mixture was warmed to 25 °C and stirred for 1 h. The mixture was concentrated in *vacuo* and the residue was purified (PM209) to afford **EXAMPLE 10** (124 mg, 0.206 mmol, 81.8% yield, TFA salt) as a yellow solid.

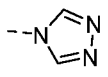
[00681] LCMS (AM3): rt = 0.836 min, (487.2 $[M+H]^+$), 100% purity.

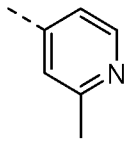
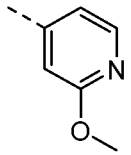
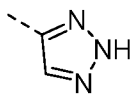
[00682] ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.22 (d, *J* = 0.8 Hz, 1H), 7.68 (d, *J* = 1.6 Hz, 1H), 7.51-7.38 (m, 7H), 7.14 (s, 1H), 6.29 (s, 1H), 4.29 (s, 2H), 3.40-3.32 (m, 6H), 2.70 (t, *J* = 6.4 Hz, 2H), 1.98-1.89 (m, 2H) ppm.

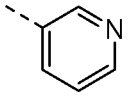
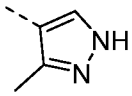
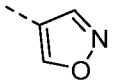
[00683] The following examples in Table 8 were made with non-critical changes or substitutions to the exemplified procedure for Example 10 that would be understood by one skilled in the art

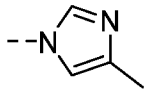
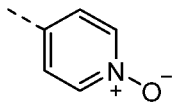
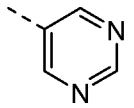


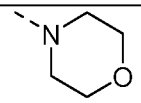
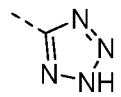
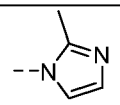
Table 8

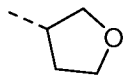
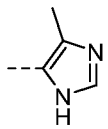
Example No.	Chemical IUPAC name	R_1 (Intermediate)	Analytical
Example 11	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide	 **(Intermediate 1.274)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ: 9.12 (s, 2H), 8.89 (br s, 2H), 8.24-8.18 (m, 2H), 7.74 (d, *J* = 1.6 Hz, 1H), 7.54-7.41 (m, 7H), 6.90 (s, 1H), 6.25 (d, *J* = 1.6 Hz, 1H), 4.23 (t, *J* = 5.2 Hz, 2H), 3.31-3.25 (t, 2H), 3.25-3.20 (q, 2H), 3.20-3.11 (m, 2H), 2.57-2.54 (t, 2H), 1.84-1.76 (quin, 2H) ppm. **LCMS** (AM3): rt = 0.791 min, (529.2 $[M+H]^+$), 100% purity. **Purification Method** PM218

Example 21	3-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methylpyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 1.383)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 8.61 (d, *J* = 6.4 Hz, 1H), 8.21-8.20 (m, 2H), 8.13 (dd, *J* = 6.0, 1.6 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.47-7.36 (m, 7H), 7.27 (s, 1H), 6.52 (d, *J* = 1.2 Hz, 1H), 4.25 (s, 2H), 3.43-3.40 (m, 2H), 3.40-3.37 (m, 2H), 3.32-3.30 (m, 2H), 2.80 (s, 3H), 2.67 (d, *J* = 6.4 Hz, 2H), 1.99-1.92 (quin, 2H) ppm **LCMS** (AM3): rt = 0.767 min, (553.3 $[M+H]^+$), 99.7% purity. **Purification Method** PM220
Example 22	3-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methoxypyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 1.384)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 8.18 (d, *J* = 4.4 Hz, 2H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.48-7.37 (m, 7H), 7.32 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.13 (s, 1H), 7.08 (s, 1H), 6.42 (s, 1H), 4.26 (s, 2H), 4.00 (s, 3H), 3.42 (t, *J* = 6.8 Hz, 4H), 3.32-3.28 (m, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.01-1.94 (quin, 2H) ppm. **LCMS** (AM3): rt =0.830 min, (569.3 $[M+H]^+$), 99.4% purity. **Purification Method** PM154
Example 25	N-(3-((6-(2H-1,2,3-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamid	 **(Intermediate 1.931)**	**^{1}H NMR** (400MHz, DMSO-d_6) δ 8.89 (s, 2H), 8.34 - 8.21 (m, 2H), 8.16 (s, 1H), 7.74 (s, 1H), 7.59 - 7.34 (m, 8H), 7.15 (s, 1H), 6.57 (s, 1H), 4.23 (br s, 2H), 3.31 - 3.16 (m, 6H), 2.61 - 2.55 (m, 2H), 1.90 - 1.79 (m, 2H) ppm **LCMS** (AM3): rt = 0.824min, (529.2 $[M+H]^+$), 100% purity. **Purification Method** PM221

Example 26	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridin-3-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 1.888)**	**^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 9.04 - 9.00 (m, 3H), 6.68 (d, *J* = 4.0 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 8.28 - 8.22 (m, 2H), 7.75 - 7.70 (m, 2H), 7.53 - 7.46 (m, 7H), 7.04 (s, 1H), 7.00 (s, 1H), 4.22 (s, 2H), 3.32 (t, *J* = 6.8 Hz, 2H), 3.26 - 3.23 (m, 2H), 3.15 (s, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.87-1.81 (m, 2H) ppm. **LCMS** (AM3): rt = 0.767 min, (539.4 $[M+H]^+$), 99.41% purity. **Purification Method** PM222
Example 27	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-methyl-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 1.889)**	**^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 8.95 (s, 2H), 8.27 - 8.24 (m, 1H), 8.12 (s, 1H), 7.79 (s, 1H), 7.75 (s, 1H), 7.55 - 7.41 (m, 7H), 6.69 (s, 1H), 6.13 (s, 1H), 4.22 (s, 2H), 3.27 - 3.22 (m, 4H), 3.16 - 3.13 (m, 2H), 2.57 - 2.53 (m, 2H), 2.39 (s, 3H), 1.85 - 1.79 (m, 2H) ppm. **LCMS** (AM3): rt = 0.787 min, (542.3 $[M+H]^+$), 99.8% purity. **Purification Method** PM214
Example 28	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(isoxazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 1.890)**	**^{1}H NMR**: (400 MHz, DMSO-d_6) δ: 9.43 (s, 1H), 9.17 (s, 1H), 8.92 (s, 2H), 8.25 (t, *J* = 6.0Hz, 1H), 8.16 (s, 1H), 7.75 (s, 1H), 7.53 - 7.42 (m, 7H), 6.97 (s, 1H), 6.32 (s, 1H), 4.23 (t, *J* = 5.2 Hz, 2H), 3.31 - 3.24 (m, 4H), 3.22 - 3.14 (m, 2H), 2.58 - 2.54 (m, 2H), 1.86 - 1.81 (m, 2H) ppm. **LCMS** (AM3): rt = 0.828 min, (529.3 $[M+H]^+$), 99.0% purity. **Purification Method** PM223

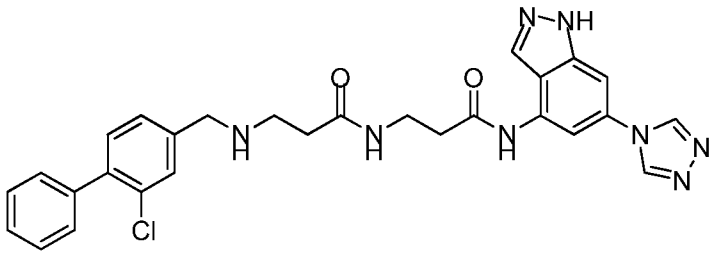
Example 29	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(4-methyl-1H-imidazol-1-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 1.904)**	**^{1}H NMR**: (400 MHz, MeOH-d_4) δ: 9.28 (s, 1H), 8.22 (s, 1H), 7.76 (s, 1H), 7.66 (m, 1H), 7.43 - 7.37 (m, 7H), 6.95 (s, 1H), 6.29 (s, 1H), 4.25 (s, 2H), 3.38 - 3.34 (m, 4H), 3.33 - 3.30 (m, 2H), 2.68 (t, *J* = 4.8 Hz, 2H), 2.42 (s, 3H), 1.96 - 1.89 (m, 2H) ppm **LCMS** (AM3): rt = 0.780 min, (542.2 $[M+H]^+$), 100% purity. **Purification Method** PM220
Example 30	4-(4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1H-indazol-6-yl)pyridine 1-oxide	 **(Intermediate 1.915)**	**^{1}H NMR**: (400 MHz, MeOH-d_4) δ: 8.39 - 8.37 (m, 2H), 8.18 (s, 1H), 7.90 - 7.88 (m, 2H), 7.65 (s, 1 H), 7.46 - 7.38 (m, 8H), 7.11 (s, 1H), 4.26 (s, 2H), 3.42 - 3.38 (m, 4H), 3.33 - 3.31 (m, 2H), 2.70 - 2.67 (m, 2H), 1.98 - 1.94 (m, 2H) ppm **LCMS** (AM3): rt = 0.706 min, (555.1 $[M+H]^+$), 97.3% purity. **Purification Method** PM214
Example 73	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyrimidin-5-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.265)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.17 (s, 1H), 9.13 (s, 2H), 8.95 (s, 2H), 8.26 - 8.23 (m, 1H), 8.22 (s, 1H), 7.74 (s, 1H), 7.53 - 7.01 (m, 7H), 7.01 (s, 1H), 6.34 (s, 1H), 4.25 - 4.21 (m, 2H), 3.32 (t, *J* = 9.8 Hz, 2H), 3.26 - 3.23 (m, 2H), 3.23 - 3.16 (m, 2H), 2.56 (t, *J* = 7.2 Hz, 2H),1.87 - 1.81 (m, 2H) ppm **LCMS** (AM3): rt = 0.806 min, (540.1 $[M+H]^+$), 100% purity **Purification Method** PM214

Example 78	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-morpholino-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.268)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.28 (d, *J* = 5.6 Hz, 1H), 7.69 - 7.68 (m, 1H), 7.49 - 7.39 (m, 9H), 4.29 (s, 2H), 3.84 - 3.82 (m, 4H), 3.75 - 3.72 (m, 4H), 3.61 - 3.59 (m, 2H), 3.36 - 3.32 (m, 4H), 2.73 - 2.69 (m, 2H), 2.00 - 1.94 (m, 2H) ppm **LCMS** (AM3): rt = 0.766 min, (547.4 $[M+H]^+$), 99.82% purity **Purification Method** PM231
Example 79	N-(3-((6-(2H-tetrazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide	 **(Intermediate 2.014)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 8.11 (s, 1H), 7.58 (s, 1H), 7.45 - 7.34 (m, 8H), 6.91 (s, 1H), 4.12 (s, 2H), 3.44 - 3.37 (m, 4H), 3.23 - 3.20 (m, 2H), 2.72 - 2.69 (m, 2H), 1.98 -1.29 (m, 2H) ppm **LCMS** (AM3): rt = 0.807 min, (530.5 $[M+H]^+$), 100% purity. **Purification Method** PM242
Example 80	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methyl-1H-imidazol-1-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.271)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.19 (s, 1H), 7.59 (s, 1H), 7.55 - 7.54 (m, 1H), 7.48 - 7.47 (m, 1 H), 7.35 - 7.34 (m, 1H), 7.33 - 7.30 (m, 6H), 6.79 (s, 1H), 6.08 (s, 1H), 4.19 (s, 2H), 3.27 - 3.21 (m, 6H), 2.64 - 2.60 (m, 2H), 2.52 (s, 3H),1.86 - 1.82 (m, 2H) ppm **LCMS** (AM3): rt = 0.735 min, (542.2 $[M+H]^+$), 99.86% purity **Purification Method** PM243

Example 82	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(tetrahydrofuran-3-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.009)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 8.10 (s, 1H), 7.67 (s, 1H), 7.47-7.39 (mz, 9H), 4.26 (s, 2 H), 4.09-4.07 (m, 2H), 3.89-3.87 (m, 2H), 3.78-3.76 (m, 2H), 3.39-3.37 (m, 1H), 3.35-3.31 (m, 6H), 2.70-2.67 (m, 2H), 2.39-2.36 (m, 1H), 2.08-2.05 (m, 1H), 1.94-1.90 (m, 2H) ppm **LCMS** (AM3): rt = 0.730 min, (532.1 $[M+H]^+$), 99.6% purity. **Purification Method** PM245
Example 91	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(4-methyl-1H-imidazol-5-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.006)**	**^{1}H NMR**: (400 MHz, MeOH-d_4) δ: 8.83 (s, 1H), 8.20 (s, 1H), 7.67 (m, 1H), 7.47 - 7.46 (m, 1 H), 7.44 - 7.37 (m, 6H), 6.91 (s, 1H), 6.26 (s, 1H), 4.26 (s, 2H), 3.40 - 3.38 (m, 4H), 3.37 - 3.32 (m, 2H), 2.72 - 2.68 (m, 2H), 2.51 (s, 3H), 1.98 - 1.93 (m, 2H) ppm **LCMS** (AM3): rt = 0.611 min, (542.1 $[M+H]^+$), 100% purity. **Purification Method** PM214

EXAMPLE 12

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propanamide



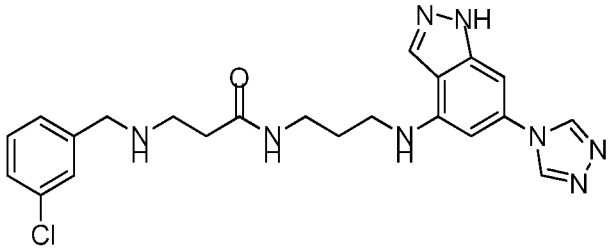
[00684] To a solution of **compound 1.328** (60 mg, 86.76 μmol) in DCM (2 mL) was added TFA (0.65 mL, 8.7 mmol) at 30 °C and the mixture was stirred for 2 h. The mixture was concentrated in *vacuo* and the residue was purified (PM224) to afford **EXAMPLE 12** (14.76 mg, 27.18 μmol, 31.3% yield, FA salt) as a yellow solid.

[00685] LCMS (AM3): rt = 0.792 min, (543.1 $[M+H]^+$), 100% purity.

[00686] **^{1}H NMR** (400 MHz, MeOH-d_4) δ: 8.98 (s, 2H), 8.44 (br s, 1H), 8.37 (s, 1H), 8.00 (d, *J* = 1.5 Hz, 1H), 7.57 (s, 1H), 7.53 (s, 1H), 7.45-7.33 (m, 7H), 4.08 (s, 2H), 3.63 (t, *J* = 6.2 Hz, 2H), 3.19-3.13 (m, 2H), 2.78 (t, *J* = 6.4 Hz, 2H), 2.58 (t, *J* = 5.6 Hz, 2H) ppm.

EXAMPLE 13

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chlorobenzyl)amino)propanamide



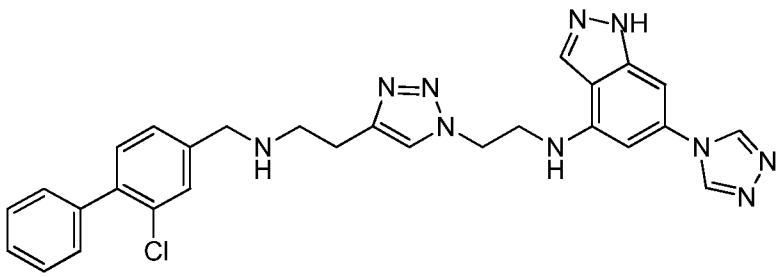
[00687] To a mixture of **compound 1.280** (20 mg, 0.0372 mmol) in DCM (0.5 mL) was added TFA (770 mg, 6.75 mmol) at 35 °C. The mixture was stirred at 35 °C for 1 h. The mixture was concentrated in *vacuo* and the residue was purified (PM226) to afford **EXAMPLE 13** (7.62 mg, 0.0133 mmol, 35.7% yield, TFA salt) as a yellow solid.

[00688] **LCMS** (AM3): rt = 0.736 min, (453.1 $[M+H]^+$), 99.2% purity.

[00689] **^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.02 (s, 2H), 8.20 (s, 1H), 7.56 (s, 1H), 7.48-7.42 (m, 3H), 6.93 (s, 1H), 6.27 (d, *J* = 1.6 Hz, 1H), 4.24 (s, 2H), 3.39-3.35 (t, 4H), 3.30-3.26 (t, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 1.98-1.91 (quin, 2H) ppm.

EXAMPLE 14

N-(2-(4-(2-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)-1H-1,2,3-triazol-1-yl)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine



[00690] To a solution of **compound 1.320** (215 mg, 181.33 μmol) in DCM (8 mL) was added TFA (12.32 g, 108.05 mmol, 8 mL) slowly at 20 °C. The reaction mixture was stirred at 20 °C

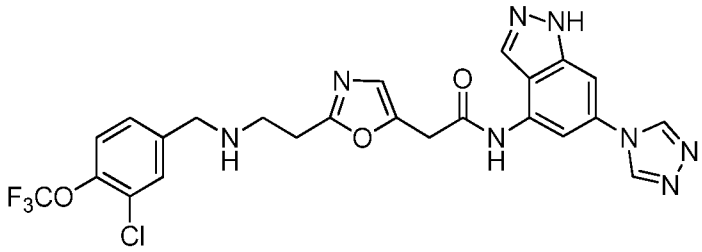
for 0.5 h. The mixture was concentrated in *vacuo* and the crude product was purified (PM228) to afford **EXAMPLE 14** (39.78 mg, 60.91 μmol, 33.6% yield, TFA salt) as a yellow solid.

[00691] LCMS (AM3): rt = 0.802 min, (539.1 $[M+H]^+$), 100% purity.

[00692] ^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.04 (br s, 2H), 8.12 (s, 1H), 7.84 (s, 1H), 7.67 (s, 1H), 7.47-7.37 (m, 7H), 6.98 (s, 1H), 6.21 (s, 1H), 4.71 (t, *J* = 5.8 Hz, 2H), 4.27 (s, 2H), 3.90 (t, *J* = 5.8 Hz, 2H), 3.31-3.28 (m, 2H), 3.06 (t, *J* = 7.6 Hz, 2H) ppm.

EXAMPLE 15

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-(2-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)oxazol-5-yl)acetamide



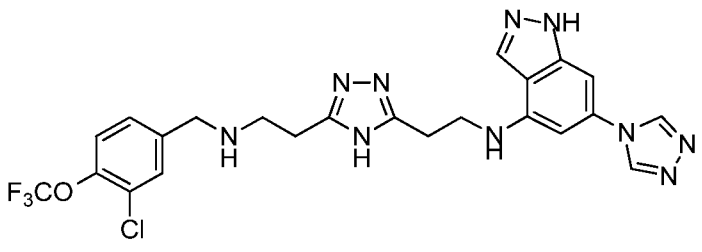
[00693] To a mixture of **compound 1.296** (80 mg, 107.36 μmol) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol) at 20 °C. The mixture was stirred at 20 °C for 1 h. The mixture was concentrated in *vacuo* and the residue was purified (PM77) to afford **EXAMPLE 15** (26.95 mg, 39.93 μmol, 37.2% yield, TFA salt) as a yellow solid.

[00694] LCMS (AM3): rt = 0.782 min, (561.1 $[M+H]^+$), 100% purity.

[00695] ^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.00 (s, 2H), 8.37 (d, *J* = 1.2 Hz, 1H), 7.97 (d, *J* = 1.6 Hz, 1H), 7.79 (d, *J* = 1.6 Hz, 1H), 7.60 (s, 1H), 7.58-7.53 (m, 2H), 7.06 (s, 1H), 4.33 (s, 2H), 4.08 (s, 2H), 3.54 (t, *J* = 6.8 Hz, 2H), 3.25 (t, *J* = 6.8 Hz, 2H) ppm.

EXAMPLE 16

N-(2-(5-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)-4H-1,2,4-triazol-3-yl)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine



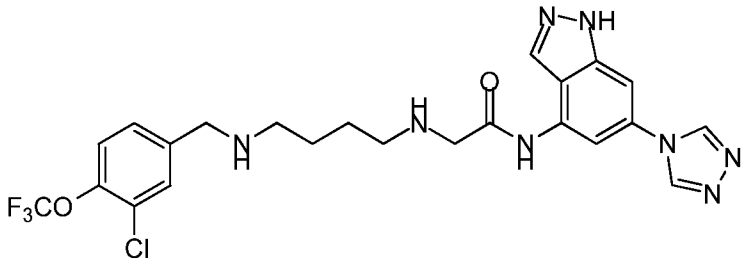
[00696] To a mixture of **compound 1.300** (50 mg, 68.38 μmol) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol) at 20 °C. The mixture was stirred at 20 °C for 1 h. The mixture was concentrated in *vacuo* and the residue was purified (PM207) to afford **EXAMPLE 16** (21.48 mg, 31.85 μmol, 46.6% yield, TFA salt) as a red gum.

[00697] LCMS (AM3): rt = 0.772 min, (547.1 $[M+H]^+$), 97.8% purity.

[00698] ^{1}H NMR (400 MHz,MeOH-d_4) δ: 9.08 (s, 2H), 8.16 (s, 1H), 7.78 (d, *J* = 1.6 Hz, 1H), 7.57-7.52 (m, 2H), 6.98 (s, 1H), 6.30 (d, *J* = 1.6 Hz, 1H), 4.30 (s, 2H), 3.75 (t, *J* = 7.0 Hz, 2H), 3.43 (t, *J* = 8.0 Hz, 2H), 3.18 (t, *J* = 8.0 Hz, 2 H), 3.12 (t, *J* = 7.2 Hz, 2H) ppm.

EXAMPLE 17

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-((4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butyl)amino)acetamide



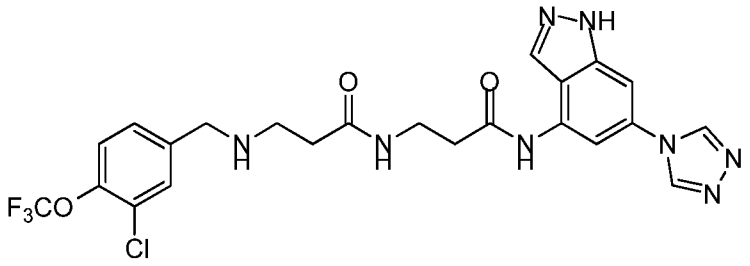
[00699] To a mixture of **compound 1.289** (50 mg, 0.078 mmol) in DCM (5 mL) was added TFA (5.00 mL, 67.53 mmol) at rt for 1 h. The reaction mixture was concentrated in *vacuo* and the residue was purified (PM229) to afford **EXAMPLE 17** (32.95 mg, 54.8% yield, 2 × TFA salt) as a white solid.

[00700] LCMS (AM3): rt = 0.723 min, (537.1 $[M+H]^+$), 100% purity.

[00701] ^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.01 (s, 2H), 8.37 (d, *J* = 0.8 Hz, 1H), 8.04 (d, *J* = 1.6 Hz, 1H), 7.78 (d, *J* = 0.8 Hz, 1H), 7.63 (s, 1H), 7.58-7.53 (m, 2H), 4.27 (s, 2H), 4.21 (s, 2H), 3.22 (t, *J* = 7.2 Hz, 2H), 3.16 (t, *J* = 7.2 Hz, 2H), 1.93-1.81 (m, 4H) ppm.

EXAMPLE 18

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-(3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamido)propanamide



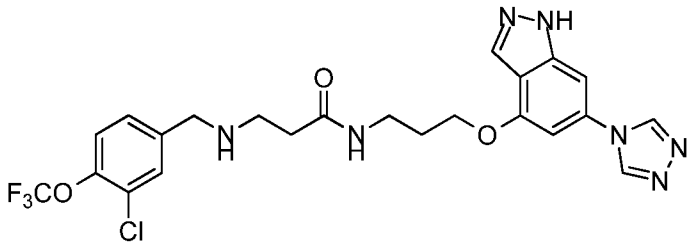
[00702] To a mixture of **compound 1.286** (35 mg, 0.054 mmol) in DCM (5 mL) was added TFA (5 mL, 67.53 mmol) and the mixture stirred at rt for 1 h. The reaction mixture was concentrated in *vacuo* and the residue was purified (PM230) to afford **EXAMPLE 18** (22.0 mg, 61.6% yield, TFA salt) as a white solid.

[00703] **LCMS** (AM3): rt = 0.770 min, (551.1 $[M+H]^+$), 100% purity.

[00704] **^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.04 (s, 2H), 8.37 (d, *J* = 0.8 Hz, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 7.75 (s, 1H), 7.57 (t, *J* = 1.2 Hz, 1H), 7.53 (s, 2H), 4.26 (s, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 3.35-3.32 (m, 2H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H) ppm.

EXAMPLE 19

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide



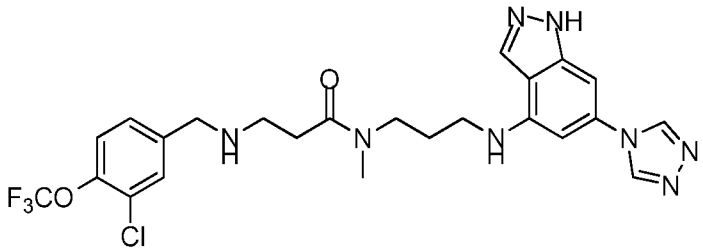
[00705] To a mixture of **compound 1.363** (0.3 g, 470.19 μmol) in DCM (5 mL) was added TFA (7.70 g, 67.53 mmol) at 25 °C. The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated in *vacuo* and the residue was purified (PM231) to afford **EXAMPLE 19** (113.08 mg, 171.72 μmol, 36.5% yield, TFA salt) as a white solid.

[00706] **LCMS** (AM3): rt = 0.792 min, (538.1 $[M+H]^+$), 99.1% purity.

[00707] **^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.08 (s, 2H), 8.15 (s, 1H), 7.76 (s, 1H), 7.54 (s, 2H), 7.38 (d, *J* = 1.2 Hz, 1H), 6.81 (d, *J* = 1.2 Hz, 1H), 4.32 (t, *J* = 7.2 Hz, 2H), 4.26 (s, 2H), 3.49 (t, *J* = 7.2 Hz, 2H), 3.30-3.28 (m, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.17-2.07 (quin, 2H) ppm.

EXAMPLE 20

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-methylpropanamide



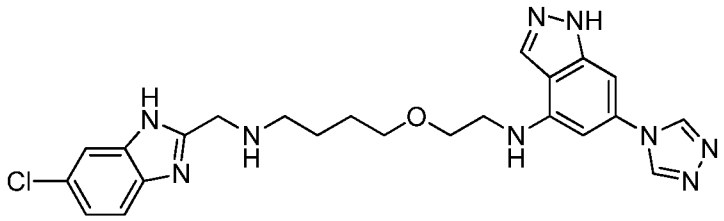
[00708] To a solution of **compound 1.283** (70 mg, 107.51 μmol) in DCM (4 mL) was added TFA (54.02 mmol, 4 mL) at 20°C. The resulting mixture was stirred at 20°C for 0.5 h. The mixture was concentrated in *vacuo* and the crude product was purified (PM232) to afford **EXAMPLE 20** (68.72 mg, 102.72 μmol, 95.5% yield, TFA salt) as a brown gum.

[00709] LCMS (AM3): rt = 0.716 min, (551.0 $[M+H]^+$), 95.1% purity.

[00710] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 2H), 8.22 (s, 1H), 7.85 (s, 1H), 7.61 (s, 2H), 6.91 (s, 1H), 6.26 (s, 1H), 4.25 (s, 2H), 3.47 (t, J = 7.2 Hz, 2H), 3.31 (t, J = 6.4 Hz, 2H), 3.19 (s, 2H), 3.01 - 2.89 (m, 3H), 2.78 (t, J = 6.4 Hz, 2H), 1.93 - 1.93 (dd, J = 2.0, 5.6 Hz, 2H) ppm

EXAMPLE 23

N-(2-(4-(((6-chloro-1H-benzo[d]imidazol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine



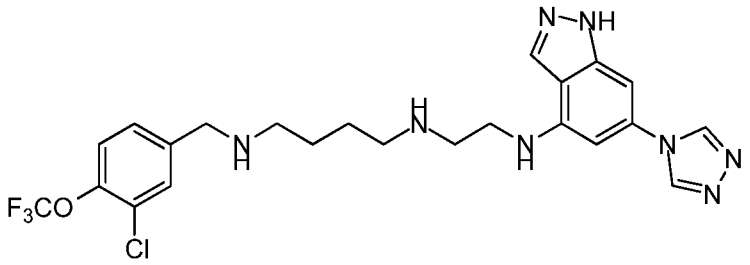
[00711] To a solution of **compound 1.371** (60 mg, 103.43 μmol) in DCM (10 mL) was added TFA (15.40 g, 135.06 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated in *vacuo* and the crude product purified (PM232) to afford **EXAMPLE 23** (21.49 mg, 35.27 μmol, 34.1% yield, TFA salt) as a brown gum.

[00712] LCMS (AM3): rt = 0.732 min, (480.4 $[M+H]^+$), 97.5% purity.

[00713] ^{1}H NMR (400 MHz, MeOH-d4) δ: 9.08 (s, 2H), 8.19 (s, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.94 (s, 1H), 6.29 (d, *J* = 1.6 Hz, 1H), 4.44 (s, 2H), 3.79 (t, *J* = 5.4 Hz, 2H), 3.62 (t, *J* = 5.8 Hz, 2H), 3.54 (t, *J* = 5.4 Hz, 2H), 3.25 (t, *J* = 7.4 Hz, 2H), 1.92-1.85 (quin, 2H), 1.77 (quin, *J* = 6.5 Hz, 2H) ppm.

EXAMPLE 24

N^1-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)-N^4-(3-chloro-4-(trifluoromethoxy)benzyl)butane-1,4-diamine



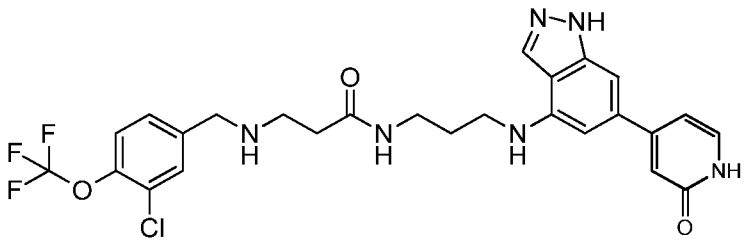
[00714] A mixture of **compound 1.292** (80 mg, 0.109 mmol, TFA salt) in DCM (1 mL) and TFA (1 mL, 13.51 mmol) was stirred at rt for 1 h. The reaction mixture was concentrated in *vacuo* and the residue purified (PM232) to afford **EXAMPLE 24** (50.57 mg, 62% yield, 2 × TFA salt) as a white solid.

[00715] LCMS (AM3): rt = 0.690 min, (523.1 $[M+H]^+$), 100% purity.

[00716] ^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.03 (s, 2H), 8.19 (d, *J* = 0.8 Hz, 1H), 7.77 (s, 1H), 7.54 (s, 2H), 7.07 (t, *J* = 1.2 Hz, 1H), 6.41 (d, *J* = 1.6 Hz, 1H), 4.24 (s, 2H), 3.73 (t, *J* = 6.0 Hz, 2H), 3.38 (t, *J* = 6.0 Hz, 2H), 3.16-3.07 (m, 4H), 1.87-1.76 (m, 4H) ppm.

EXAMPLE 31

3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(2-oxo-1,2-dihydropyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



[00717] To a solution of **compound 1.951** (40 mg, 53.53 μmol) in DCM (2 mL) was added TFA (0.4 mL, 5.40 mmol) at 20 °C and the mixture was stirred for 0.5 h. The mixture was added into saturated $NaHCO_3$ aqueous solution (30 mL) and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 15 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM234) to afford **EXAMPLE 31** (41.61 mg, 71.36 μmol, 63.65% yield) as a yellow solid.

[00718] LCMS (AM16): rt = 0.598 min, (563.3 $[M+H]^+$), 94.12% purity.

[00719] ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.17 (s, 1H), 7.53 (s, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.33 - 7.23 (m, 2H), 7.01 (s, 1H), 6.8 - 6.72 (m, 2H), 6.34 (s, 1H), 3.73 (s, 2H), 3.38 (q, J = 6.8 Hz, 4H), 2.82 (t, J = 6.8Hz, 2H), 2.41 (t, J = 6.8Hz, 2H), 2.0 - 1.84 (m, 2H) ppm.

[00720] The following examples in Table 9 were made with non-critical changes or substitutions to the exemplified procedure for Example 31, that would be understood by one skilled in the art

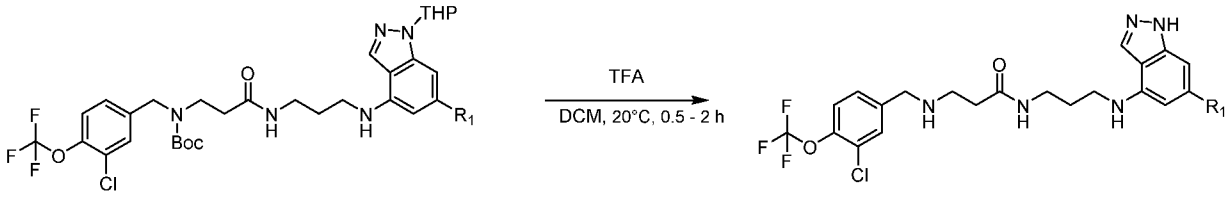
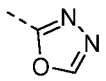
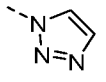
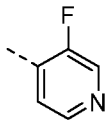
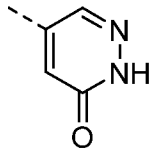
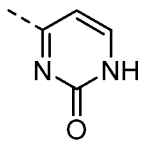
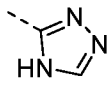
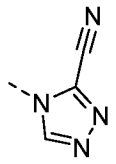
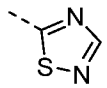


Table 9

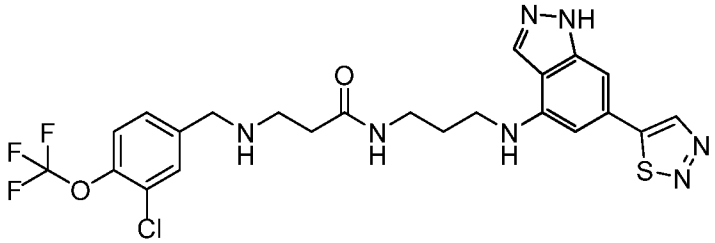
Example No.	Chemical IUPAC name	R_1 structure/intermediate No.	Analytical
Example 157	N-(3-((6-(1,3,4-oxadiazol-2-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide	 **(Intermediate 2.233)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.00 (s, 1H), 8.22 (s, 1H), 7.53 (s, 1H), 7.46 (s, 1H), 7.35 - 7.27 (m, 2H), 6.81 (s, 1H), 3.75 (s, 2H), 3.41 - 3.37 (m, 4H), 2.89 (t, J = 6.8 Hz, 2H), 2.44 (t, J = 6.8 Hz, 2H), 2.00 - 1.92 (m, 2H) ppm. **LCMS** (AM16): rt = 0.640 min, (538.2 $[M+H]^+$), 96.15% purity. **Purification Method** PM236
Example 161	N-(3-((6-(1H-1,2,3-triazol-1-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide	 **(Intermediate 2.236)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.54 (s, 1H), 8.23 (s, 1H), 7.90 (s, 1H), 7.55 (s, 1H), 7.33 (s, 2H), 7.16 (s, 1H), 6.61 (s, 1H), 3.76 (s, 2H), 3.40 (br d, J = 7.6 Hz, 4H), 2.85 (t, J = 6.8 Hz, 2H), 2.44 (t, J = 6.8 Hz, 2H),1.982 (br t, J = 6.8 Hz, 2H) ppm **LCMS** (AM16): rt = 0.640 min, (537.1 $[M+H]^+$), 99.24% purity **Purification Method** PM238

Example 162	3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-fluoropyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.239)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.50 (d, J = 2.8 Hz, 1H), 8.42 (d, J = 5.2 Hz, 1H), 8.16 (s, 1H), 7.64 (t, J = 5.2 Hz, 1H), 7.58 (s, 1H), 7.36 (s, 2H), 7.02 (s, 1H), 6.34 (s, 1H), 3.86 (s, 2H), 3.37 (t, J = 5.6 Hz, 4H), 2.93 (t, J = 6.8 Hz, 2H), 2.46 (t, J = 6.8 Hz, 2H), 1.96 - 1.90 (m, 2H) ppm **LCMS** (AM11): rt = 0.341 min, (565.2 $[M+H]^+$), 96.89% purity **Purification Method** PM177
Example 168	3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(6-oxo-1,6-dihydropyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.241)**	**^{1}H NMR** (400 MHz,MeOH-d_4) δ 8.35 (d, J = 2.0 Hz, 1H), 8.17 (s, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.57 - 7.52 (m, 2H), 7.16 (d, J = 2.0 Hz, 1H), 7.11 (s, 1H), 6.35 (s, 1H), 4.28 (s, 2H), 3.43 - 3.37 (m, 4H), 3.30 - 3.27 (m, 2H), 2.69 (t, J = 6.8 Hz, 2H), 2.00 - 1.92 (m,2H) ppm **LCMS** (AM12): rt = 0.421 min, (564.1 $[M+H]^+$), 97.03% purity **Purification Method** PM246
Example 170	3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(2-oxo-1,2-dihydropyrimidin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.247)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.4 (s, 1H), 8.01 (br d, J = 6.4 Hz, 1H), 7.52 (s, 1H), 7.46 (s, 1H), 7.34 - 7.26 (m, 2H), 7.06 (d, J = 6.4 Hz, 1H), 6.85 (s, 1H), 3.75 (s, 2H), 3.44 - 3.35 (m, 4H), 2.85 (t, J = 6.8 Hz, 2H), 2.44 (t, J = 6.8 Hz, 2H), 1.97 - 1.90 (m, 2H) ppm **LCMS** (AM11): rt = 0.376 min, (564.0 $[M+H]^+$), 94.73% purity **Purification Method** PM247
Example 174	N-(3-((6-(4H-1,2,4-triazol-3-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide	 **(Intermediate 2.021)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.29 (s, 1H), 8.16 (s,1H), 7.52 (s, 1H), 7.42 (s, 1H), 7.29 (s, 2H), 6.81 (s, 1H), 3.72 (s, 2H), 3.42 - 3.36 (m, 4H), 2.83 (t, J = 6.8 Hz, 2H), 2.42 (t, J = 6.8 Hz, 2H), 1.95 (t, J = 6.8 Hz, 2H) ppm **LCMS** (AM3) : rt = 0.779 min, (537.2 $[M+H]^+$), 96.24% purity. **Purification Method** PM249

Example 177	3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-cyano-4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.459)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.11 (s, 1H), 8.25 (s, 1H), 7.77 (s, 1H), 7.55 (s, 2H), 6.97 (s, 1H), 6.28 (d, *J* = 1.2 Hz, 1H), 4.27 (s, 2H), 3.41 - 3.33 (m, 4H), 3.29 (m, 2H), 2.66 (t, *J* = 6.4 Hz, 2H), 1.95 (t, *J* = 7.2 Hz, 2H) ppm **LCMS** (AM14): rt = 0.550 min, (562.3 $[M+H]^+$), 100.00% purity **Purification Method** SepaFlash SW040 spherical C18 20 - 45 μm, 100 A; [water (0.1%TFA) - ACN], %B: 50% - 60%, 10 min
Example 183	N-(3-((6-(1,2,4-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide	 **(Intermediate 2.374)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.73 (s, 1H), 8.21 (s, 1H), 7.52 (d, *J* = 1.6 Hz, 1H), 7.45 (s, 1H), 7.33 - 7.26 (m, 2H), 6.70 (d, *J* = 0.4 Hz, 1H), 3.74 (s, 2H), 3.39 (q, *J* = 6.4 Hz, 4H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.43 (t, *J* = 6.8 Hz, 2H), 1.96 (t, *J* = 6.8 Hz, 2H) ppm **LCMS** (AM14): rt = 0.573 min, (554.2 $[M+H]^+$), 100.00% purity **Purification Method** PM93

EXAMPLE 32

N-(3-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide



[00721] To a mixture of **compound 1.999** (20 mg, 26.04 μmol, TFA salt) in DCM (1 mL) was added TFA (308.00 mg, 2.70 mmol, 0.2 mL) in one portion. The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM251) to afford **EXAMPLE 32** (11.36 mg, 17.01 μmol, 65.31% yield, TFA salt) as a yellow gum.

[00722] LCMS (AM12): rt = 0.473 min, (554.2 $[M+H]^+$), 100% purity.

[00723] ^{1}H NMR (400 MHz, MeOH-d_4) δ 9.12 (s, 1H), 8.18 (s, 1H), 7.76 (s, 1H), 7.53 (s, 2H), 7.15 (s, 1H), 6.39 (s, 1H), 4.26 (s, 2H), 3.40 (td, *J* = 6.8 Hz, 2.0 Hz, 4H), 3.29 (br s, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 1.98 - 1.93 (m, 2H) ppm.

[00724] **^{19}F NMR** (400 MHz, MeOH-d_4) δ -59.53 (s, 3F), -77.07 (s, 6F).

[00725] The following examples in Table 10 were made with non-critical changes or substitutions to the exemplified procedure for Example 32, that would be understood by one skilled in the art

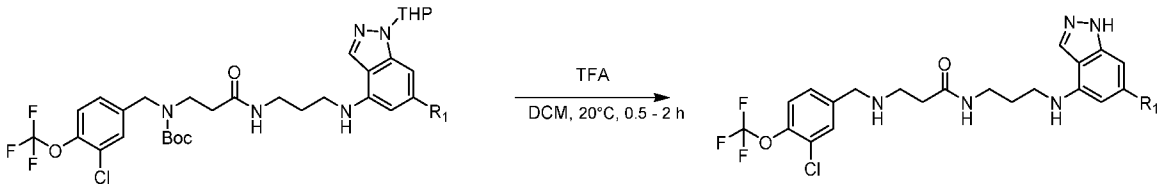
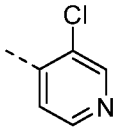
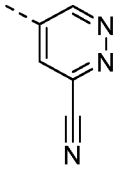


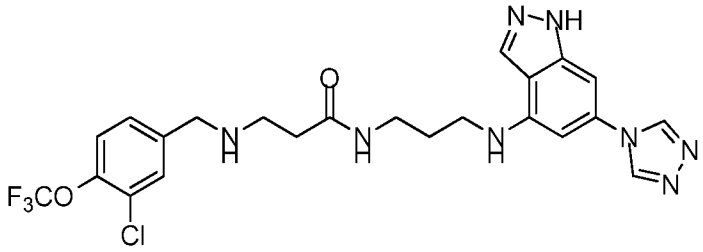
Table 10

Example No.	Chemical IUPAC name	R_1 structure/intermediate No.	Analytical
Example 160	3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-cyano-1H-indazol-4-yl)amino)propyl) propanamide	 **(Intermediate 2.253)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.22 (s, 1H), 7.77 (s, 1H), 7.55 (s, 2H), 7.14 (s, 1H), 6.28 (s, 1H), 4.28 (s, 2H), 3.39 - 3.33 (m, 6H), 2.69 (t, *J* = 6.4 Hz, 2H), 1.96 - 1.90 (m, 2H) ppm **LCMS** (AM11): rt = 0.367 min, (495.1 $[M+H]^+$), 97.4% purity **Purification Method** PM252
Example 169	3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-chloropyridin-4-yl)-1H-indazol-4-yl)amino)propyl) propanamide	 **(Intermediate 2.481)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.62 (s, 1H), 8.48 (d, *J* = 5.2 Hz, 1H), 8.19 (s, 1H), 7.54 (s, 1H), 7.49 (d, *J* = 5.2 Hz, 1H), 7.32 (s, 2H), 6.82 (s, 1H), 6.18 (s, 1H), 3.73 (s, 2H), 3.32 - 3.31 (m, 4H), 2.81 (t, *J* = 6.4 Hz, 2H), 2.39 (t, *J* = 6.4 Hz, 2H), 1.92 (q, *J* = 6.4 Hz, 2H) ppm **LCMS** (AM11): rt =0.390 min, (581.1 $[M+H]^+$), 98.39% purity **Purification Method** PM256

Example 187	**3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(6-cyanopyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide**	 **(Intermediate 2.326)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.76 (d, *J* = 2.0 Hz, 1H), 8.49 (d, *J* = 2.4 Hz, 1H), 8.21 (s, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.35 - 7.30 (m, 2H), 7.26 (s, 1H), 6.51 (s, 1H), 3.75 (s, 2H), 3.33 - 3.37 (m, 4H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.43 (t, *J* = 6.8 Hz, 2H), 1.96 (t, *J* = 6.8 Hz, 2H) ppm **LCMS** (AM11): rt =0.389 min, (573.1 $[M+H]^+$), 100% purity **Purification Method** PM257

EXAMPLE 33

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide

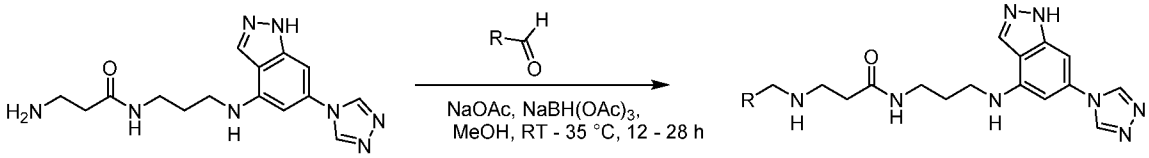


[00726] A mixture of **Intermediate N** (50 mg, 0.137 mmol, HCl salt), NaOAc (33.7 mg, 0.411 mmol) and 3-chloro-4-(trifluoromethoxy)benzaldehyde (CAS 83279-39-4, 31 mg, 0.138 mmol) in MeOH (2 mL) was stirred at 35 °C for 16.5 h, then $NaBH(AcO)_3$ (116 mg, 0.548 mmol) was added. The mixture was stirred at 35 °C for 3 h. The mixture was concentrated in *vacuo* and the residue was purified (PM77) to afford **EXAMPLE 33** (41.67 mg, 0.0640 mmol, 46.7% yield, TFA salt) as an off-white solid.

[00727] LCMS (AM3): rt = 0.784 min, (537.1 $[M+H]^+$), 100% purity.

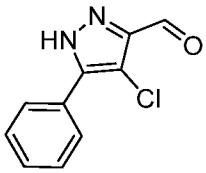
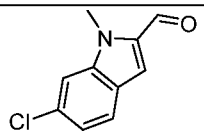
[00728] ^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.09 (s, 2H), 8.20 (d, *J* = 0.8 Hz, 1H), 7.77 (s, 1H), 7.55 (s, 2H), 6.95 (s, 1H), 6.28 (d, *J* = 1.6 Hz, 1H), 4.28 (s, 2H), 3.38 (t, *J* = 6.0 Hz, 4H), 3.30-3.26 (m, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 1.98-1.91 (quin, 2H) ppm.

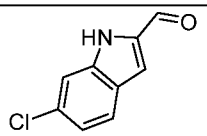
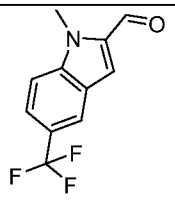
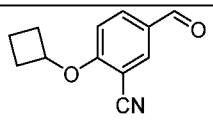
[00729] The following examples in Table 11 were made with non-critical changes or substitutions to the exemplified procedure for Example 33, that would be understood by one skilled in the art using Intermediate N

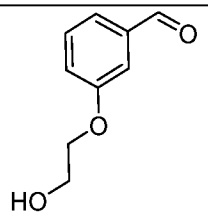
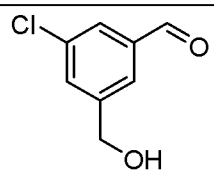
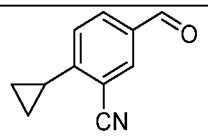


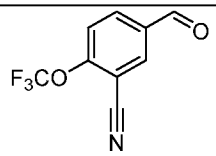
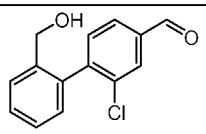
Intermediate N

Table 11

Example No.	Chemical IUPAC name	Aldehyde/ Intermediate No./ CAS	Analytical
Example 34	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((4-chloro-5-phenyl-1H-pyrazol-3-yl)methyl)amino)propanamide	 **1.67**	**^{1}H NMR** (400 MHz, MeOH-d4) δ: 9.04 (s, 2H), 8.21 (s, 1H), 7.74 (d, *J* = 1.6 Hz, 1H), 7.72 (d, *J* = 1.0 Hz, 1H), 7.53-7.44 (m, 3H), 6.94 (s, 1H), 6.28 (d, *J* = 1.6 Hz, 1H), 4.34 (s, 2H), 3.43-3.35 (m, 6H), 2.71 (t, *J* = 6.6 Hz, 2H), 1.95 (quin, *J* = 6.8 Hz, 2H) ppm. **LCMS** (AM3): rt = 0.755 min, (519.2 $[M+H]^+$), 100% purity. **Purification Method** PM258
Example 36	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((6-chloro-1-methyl-1H-indol-2-yl)methyl)amino)propanamide	 CAS 1781757-70-7	**^{1}H NMR** (400 MHz, MeOH-d4) δ: 9.05 (s, 2H), 8.20 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.48 (s, 1H), 7.06 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.94 (d, *J* = 0.7 Hz, 1H), 6.72 (s, 1H), 6.27 (d, *J* = 1.6 Hz, 1H), 4.52 (s, 2H), 3.80 (s, 3H), 3.37 (t, *J* = 6.4 Hz, 6H), 2.68 (t, *J* = 6.5 Hz, 2H), 1.94 (quin, *J* = 6.8 Hz, 2H) ppm. **LCMS** (AM3): rt = 0.780 min, (506.4 $[M+H]^+$), 98.0% purity. **Purification Method** PM207

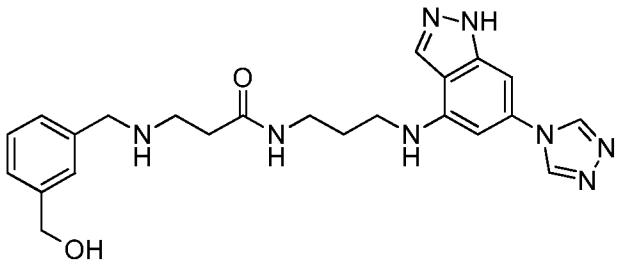
Example 37	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((6-chloro-1H-indol-2-yl)methyl)amino)propanamide	 CAS 53590-59-3	**^{1}H NMR** (400 MHz, MeOH-d4) δ: 9.04 (s, 2H), 8.20 (s, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.41 (s, 1H), 7.03 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.94 (s, 1H), 6.66 (s, 1H), 6.26 (d, *J* = 1.6 Hz, 1H), 4.40 (s, 2H), 3.36 (t, *J* = 6.9 Hz, 4H), 3.32-3.28 (m, 2H), 2.65 (t, *J* = 6.5 Hz, 2H), 1.93 (quin, *J* = 6.8 Hz, 2H) ppm. **LCMS** (AM3): rt = 0.773 min, (492.2 $[M+H]^+$), 99.3 % purity. **Purification Method** PM167
Example 38	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((1-methyl-5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)propanamide	 CAS 2090356-65-1	**^{1}H NMR** (400 MHz, MeOH-d4) δ: 9.04 (s, 2H), 8.20 (s, 1H), 7.91 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 1.6, 8.8 Hz, 1H), 6.94 (s, 1H), 6.87 (s, 1H), 6.27 (d, *J* = 1.2 Hz, 1H), 4.58 (s, 2H), 3.88 (s, 3H), 3.42-3.36 (m, 6H), 2.69 (t, *J* = 6.4 Hz, 2H), 1.98 - 1.91 (quin, 2H) ppm. **LCMS** (AM3): rt = 0.787 min, (540.4 $[M+H]^+$), 97.8% purity. **Purification Method** PM259
Example 39	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-cyano-4-cyclobutoxybenzyl)amino)propanamide	 2-cyclobutoxy-5-formylbenzonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, DMSO-d_6) δ: 9.10 (s, 2H), 8.20 (s, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.71-7.67 (m, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 6.95 (s, 1H), 6.28 (d, *J* = 1.2 Hz, 1H), 4.85-4.82 (m, 1H), 4.20 (s, 2H), 3.39-3.35 (t, 4H), 3.26 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 2.55-2.47 (m, 2H), 2.24-2.15 (m, 2H), 1.97-1.86 (m, 3H), 1.83-1.71 (m, 1H) ppm. **LCMS** (AM3): rt = 0.778 min, (514.3 $[M+H]^+$), 100% purity. **Purification Method** PM258

Example 42	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(2-hydroxyethoxy)benzyl)amino)propanamide	 CAS 60345-97-3	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.04 (s, 2H), 8.20 (d, *J* = 0.9 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.08-7.07 (m, 1H), 7.05-7.03 (m, 2H), 6.94 (d, *J* = 0.6 Hz, 1H), 6.28 (d, *J* = 1.6 Hz, 1H), 4.19 (s, 2H), 4.07 (t, *J* = 4.8 Hz, 2H), 3.87 (t, *J* = 4.8 Hz, 2H), 3.37 (t, *J* = 6.2 Hz, 4H), 3.27 (t, *J* = 6.6 Hz, 2H), 2.64 (t, *J* = 6.6 Hz, 2H), 1.94 (quin, *J* = 6.9 Hz, 2H) ppm. **LCMS** (AM3): rt = 0.674 min, (479.4 [M+H]+), 97.6 % purity. **Purification Method** PM220
Example 43	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-5-(hydroxymethyl)benzyl)amino)propanamide	 3-chloro-5-(hydroxymethyl)benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.11 (s, 2H), 8.21 (s, 1H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.40 (s, 1H), 6.95 (s, 1H), 6.28 (s, 1H), 4.63 (s, 2H), 4.23 (s, 2H), 3.37 (t, *J* = 6.5 Hz, 4H), 3.30-3.26 (m, 2H), 2.67 (t, *J* = 6.6 Hz, 2H), 1.94 (quin, *J* = 6.8 Hz, 2H) ppm. **LCMS** (AM3): rt = 0.696 min, (483.4 $[M+H]^+$), 100% purity. **Purification Method** PM220
Example 45	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-cyano-4-cyclopropylbenzyl)amino)propanamide	 2-cyclopropyl-5-formylbenzonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.00 (s, 2H), 8.20 (s, 1H), 7.78 (d, *J* = 2.0 Hz, 1H), 7.66 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.93 (s, 1H), 6.27 (d, *J* = 1.6 Hz, 1H), 4.24 (s, 2H), 3.37 (t, *J* = 6.8 Hz, 4H), 3.28 (t, *J* = 6.8 Hz, 2H), 2.67 (t, *J* = 6.8 Hz, 2H), 2.28-2.22 (m, 1H), 1.94 (quin, *J* = 6.8 Hz, 2H), 1.21-1.16 (m, 2H), 0.87-0.84 (m, 2H) ppm. **LCMS** (AM3): rt = 0.738 min, (484.5 $[M+H]^+$), 99.2% purity. **Purification Method** PM98

Example 46	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-cyano-4-(trifluoromethoxy)benzyl)amino)propanamide	 5-Formyl-2-(trifluoromethoxy)benzonitrile, (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.03 (br s, 2H), 8.22 (br s, 1H), 8.05 (d, *J* = 2.4 Hz, 1H), 7.96 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.67 (dd, *J* = 1.6, 8.8 Hz, 1H), 6.95 (s, 1H), 6.29 (s, 1H), 4.35 (s, 2H), 3.41-3.32 (m, 6H), 2.71 (t, *J* = 6.8 Hz, 2H), 1.96 (quin, *J* = 6.8 Hz, 2H) ppm. **LCMS** (AM3): rt = 0.755 min, (528.2 $[M+H]^+$),100.00% purity. **Purification Method** PM98
Example 58	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide	 CAS 2830620-64-7	**^{1}H NMR** (400 MHz, MeOH-d4) δ: 9.04 (s, 2H), 8.20 (s, 1H), 7.68 (d, *J* = 1.6 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.50-7.48 (m, 1H), 7.46-7.43 (m, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.37-7.33 (m, 1H), 7.09 (d, *J* = 6.4 Hz, 1H), 6.94 (s, 1H), 6.28 (d, *J* = 1.5 Hz, 1H), 4.43-4.26 (dd, 4H), 3.41-3.37 (t, 4H), 3.35-3.31 (m, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 1.96 (quin, *J* = 6.8 Hz, 2H) ppm. **LCMS** (AM3): rt = 0.757 min, (559.2 $[M+H]^+$), 95.7% purity. **Purification Method** PM167

EXAMPLE 35

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(hydroxymethyl)benzyl)amino)propanamide



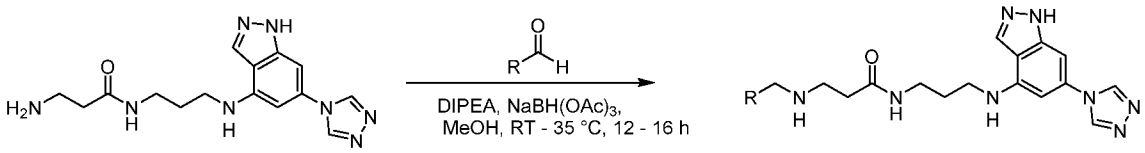
[00730] A mixture of 3-(hydroxymethyl)benzaldehyde (20 mg, 146.90 μmol), **Intermediate N** (53.59 mg, 146.90 μmol, HCl salt) and DIPEA (37.97 mg, 293.80 μmol) in MeOH (2 mL) was stirred at 25 °C for 1 h, then $NaBH(AcO)_3$ (155.67 mg, 734.50 μmol) was added. The mixture was stirred for 11 h. The reaction mixture was concentrated in *vacuo* and the residue was

purified (PM260) to afford **EXAMPLE 35** (51.64 mg, 89.96 μmol, 61.2% yield, TFA salt) as a purple gum.

[00731] LCMS (AM3): rt = 0.648 min, (449.1 $[M+H]^+$), 98.2% purity.

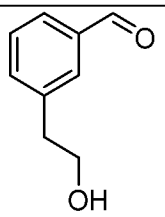
[00732] ^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.20 (br s, 2H), 8.22 (s, 1H), 7.47 (s, 1H), 7.44 (d, *J* = 4.2 Hz, 2H), 7.40-7.35 (m, 1H), 6.96 (s, 1H), 6.30 (s, 1H), 4.64 (s, 2H), 4.23 (s, 2H), 3.39-3.35 (m, 4H), 3.28 (t, *J* = 6.8 Hz, 2H), 2.67 (t, *J* = 6.8 Hz, 2H), 1.94 (quin, *J* = 6.8 Hz, 2H) ppm.

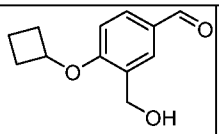
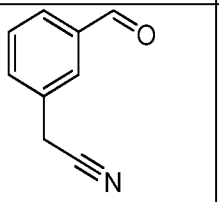
[00733] The following examples in Table 12 were made with non-critical changes or substitutions to the exemplified procedure for Example 35, that would be understood by one skilled in the art using Intermediate N



Intermediate N

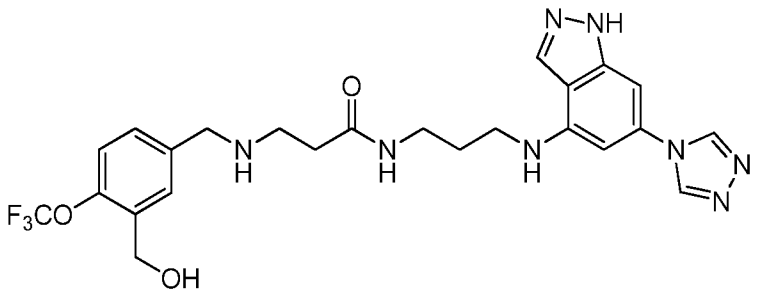
Table 12

Example No.	Chemical IUPAC name	Aldehyde	Analytical
Example 40	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(2-hydroxyethyl)benzyl)amino)propanamide	 CAS 212914-87-9	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.04 (s, 2H), 8.20 (d, *J* = 0.8 Hz, 1H), 7.39-7.30 (m, 4H), 6.94 (d, *J* = 1.2 Hz, 1H), 6.27 (d, *J* = 1.6 Hz, 1H), 4.20 (s, 2H), 3.78 (t, *J* = 6.8 Hz, 2H), 3.38-3.35 (m, 4H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 1.94 (quin, *J* = 6.8 Hz, 2H) ppm. **LCMS** (AM3): rt = 0.657 min, (463.2 $[M+H]^+$),100.00% purity. **Purification Method** PM261

Example 41	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((4-cyclobutoxy-3-(hydroxymethyl)benzyl)amino)propanamide	 4-cyclobutoxy-3-(hydroxymethyl) benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.15 (s, 2H), 8.23 (d, *J* = 0.8 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.32 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.97 (d, *J* = 0.8 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.31 (d, *J* = 1.6 Hz, 1H), 4.77-4.69 (sext, 1H), 4.66 (s, 2H), 4.18 (s, 2H), 3.41-3.37 (m, 4H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.53-2.43 (m, 2H), 2.20-2.09 (m, 2H), 1.98-1.91 (quin, 2H), 1.90-1.71 (m, 2H) ppm. **LCMS** (AM3): rt = 0.739 min, (519.3 $[M+H]^+$),100.00% purity. **Purification Method** PM262
Example 47	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(cyanomethyl) benzyl)amino) propanamide	 2-(3-formylphenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ: 9.21 (s, 2H), 8.22 (s, 1H), 7.50-7.44 (m, 4H), 6.96 (s, 1H), 6.30 (d, *J* = 1.2 Hz, 1H), 4.25 (s, 2H), 3.94 (s, 2H), 3.37 (t, *J* = 6.8 Hz, 4H), 3.32-3.27 (m, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 1.94 (quin, *J* = 6.8 Hz, 2H) ppm. **LCMS** (AM3): rt = 0.652 min, (458.2 $[M+H]^+$),91.5% purity. **Purification Method** PM263

EXAMPLE 44

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(hydroxymethyl)-4-(trifluoromethoxy)benzyl)amino)propanamide



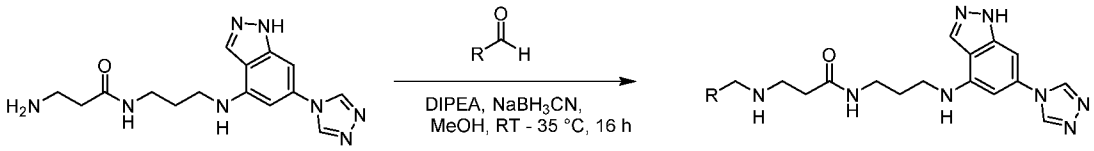
To a solution of **Intermediate N** (70 mg, 191.87 μmol, HCl salt) in MeOH (3 mL) was added DIPEA (49.60 mg, 383.74 μmol) and 3-(Hydroxymethyl)-4-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041, 42.24 mg, 191.87 μmol) at 20 °C. The reaction mixture was stirred at 20 °C for 12.5 h and then $NaBH_3CN$ (36.17 mg, 575.61 μmol) was added. The reaction mixture

was stirred at 20 °C for 3 h. The reaction mixture was filtered and the filtrate was purified (PM229) to afford **EXAMPLE 44** (39.59 mg, 61.23 μmol, 31.9% yield, TFA salt) as a brown solid.

[00734] LCMS (AM3): rt = 0.711 min, (533.4 $[M+H]^+$), 100% purity.

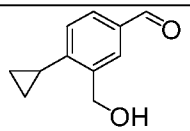
[00735] ^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.06 (s, 2H), 8.20 (s, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 7.50 (dd, *J* = 2.3, 8.5 Hz, 1H), 7.37 (dd, *J* = 1.7, 8.4 Hz, 1H), 6.95 (s, 1H), 6.28 (d, *J* = 1.6 Hz, 1H), 4.72 (s, 2H), 4.28 (s, 2H), 3.39-3.36 (m, 4H), 3.30-3.28 (m, 2H), 2.66 (t, *J* = 6.6 Hz, 2H), 1.94 (quin, *J* = 6.9 Hz, 2H) ppm.

[00736] The following examples in Table 13 were made with non-critical changes or substitutions to the exemplified procedure for Example 44, that would be understood by one skilled in the art using intermediate N



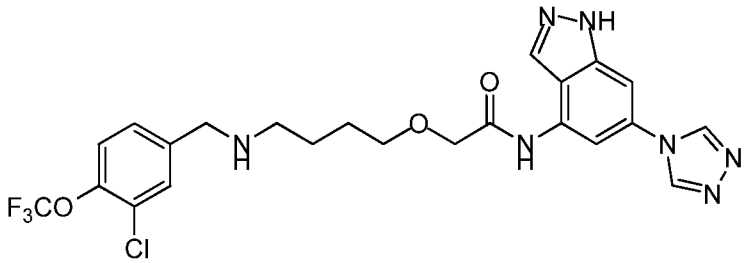
Intermediate N

Table 13

Example No.	Chemical IUPAC name	Aldehyde	Analytical
Example 77	N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((4-cyclopropyl-3-(hydroxymethyl)benzyl)amino)propanamide	 CAS 2830620-94-3	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.00 (s, 2H), 8.20 (s, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.28 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.94 (s, 1H), 6.27 (d, *J* = 1.6 Hz, 1H), 4.19 (s, 2H), 3.40 - 3.35 (m, 4H), 3.33 - 3.32 (m, 2H), 3.29 - 3.19 (m, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.00 - 1.95 (m, 1H), 1.95 - 1.90 (m, 2H), 1.00 - 0.96 (m, 2H), 0.66 - 0.64 (m, 2H) ppm **LCMS** (AM3): rt = 0.726 min, (489.2 $[M+H]^+$), 100% purity **Purification Method** PM265

EXAMPLE 48

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)acetamide



[00737] A mixture of **compound 1.307** (64 mg, 0.175 mmol, HCl salt), 3-chloro-4-(trifluoromethoxy)benzaldehyde (CAS 83279-39-4, 40 mg, 0.178 mmol) and DIPEA (0.07 mL, 0.402 mmol) in MeOH (10 mL) was stirred at RT for 20 h, then $NaBH_3CN$ (44 mg, 0.7 mmol) was added. The reaction was stirred at RT for 2 h. The reaction mixture was concentrated in *vacuo* and the residue was purified (PM266) to afford **EXAMPLE 48** (28.41 mg, 24.9% yield, TFA salt) as a yellow gum.

[00738] LCMS (AM3): rt = 0.790 min, (538.1 $[M+H]^+$), 100% purity.

[00739] ^{1}H NMR (400 MHz, MeOH-d_4) δ: 9.01 (s, 2H), 8.31 (d, *J* = 0.8 Hz, 1H), 7.94 (d, *J* = 1.6 Hz, 1H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.61 (t, *J* = 1.6 Hz, 1H), 7.54-7.52 (m, 1H), 7.47-7.45 (m, 1H), 4.34 (s, 2H), 4.28 (s, 2H), 3.72 (t, *J* = 5.6 Hz, 2H), 3.21 (t, *J* = 7.2 Hz, 2H), 1.96-1.90 (quin, 2H), 1.87-1.80 (quin, 2H) ppm.

[00740] The following examples in Table 14 were made with non-critical changes or substitutions to the exemplified procedure for Example 48, that would be understood by one skilled in the art using 3-chloro-4-(trifluoromethoxy)benzaldehyde (CAS 83279-39-4)

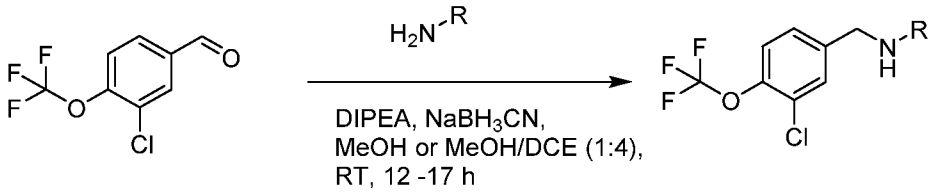
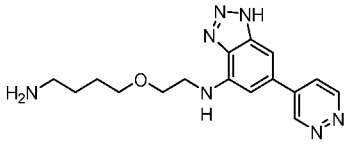
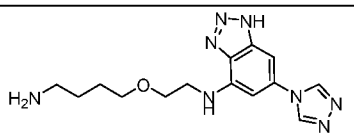
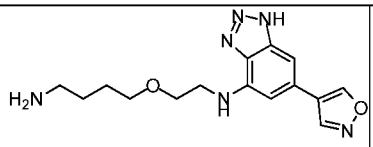
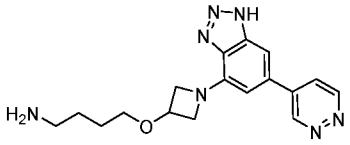


Table 14

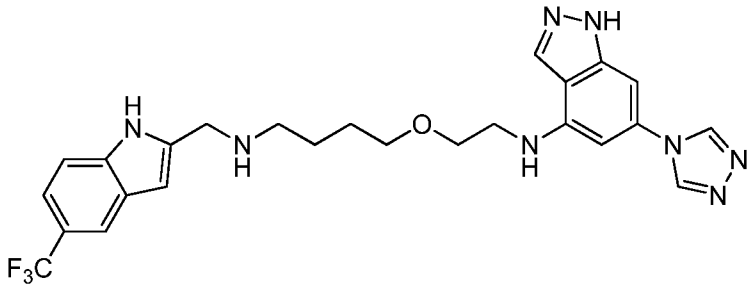
Example No.	Chemical IUPAC name	H_2NR	Analytical

Example 99	N-(2-(4-((3-chloro-4-(trifluoromethoxy) benzyl)amino)butoxy)ethyl)-6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine	 **(Intermediate 2.067)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.58 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.20 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.04 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.57 (s, 1H), 7.43 (d, *J* = 1.2 Hz, 1H), 7.36 (s, 2H), 6.73 (d, *J* = 1.2 Hz, 1H), 3.82 (s, 2H), 3.80 (t, *J* = 5.2 Hz, 2H), 3.63 (t, *J* = 5.2 Hz, 2H), 3.58 (br t, *J* = 5.6 Hz, 2H), 2.73 (br t, *J* = 7.2 Hz, 2H), 1.75 – 1.64 (m, 4H) ppm **LCMS** (AM3): rt = 0.787 min, (536.1 $[M+H]^+$), 95.6% purity **Purification Method** PM267
Example 126	N-(2-(4-((3-chloro-4-(trifluoromethoxy) benzyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine	 **(Intermediate 2.045)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.01 (s, 2H), 7.59 (s, 1H), 7.37 (s, 2H), 7.18 (d, *J* = 1.6 Hz, 1H), 6.50 (d, *J* = 1.6 Hz, 1H), 3.82 (s, 2H), 3.78 (t, *J* = 5.2 Hz, 2H), 3.58 (dt, *J* = 5.2, 2.4 Hz, 4H), 2.72 (t, *J* = 7.2 Hz, 2H), 1.73 – 1.66 (m, 4H). **LCMS** (AM3): rt = 0.765 min, (525.1 $[M+H]^+$), 96.7% purity **Purification Method** PM268

Example 127	N-(2-(4-((3-chloro-4-(trifluoromethoxy) benzyl)amino)butoxy)ethyl)-6-(azetidine-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine	 **(Intermediate 2.064)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.16 (s, 1H), 8.92 (s, 1H), 8.52 (s, 1H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.19 (d, *J* = 1.2 Hz, 1H), 6.68 (d, *J* = 1.2 Hz, 1H), 4.15 (s, 2H), 3.84 – 3.80 (m, 2H), 3.67 – 3.60 (m, 4H), 3.13 – 3.06 (m, 2H), 1.92 – 1.82 (m, 2H), 1.79 – 1.70 (m, 2H) ppm **LCMS** (AM3): rt = 0.793 min, (525.1 $[M+H]^+$), 99.57% purity **Purification Method** PM269 **then 2)** PM270
Example 150	N-(3-chloro-4-(trifluoromethoxy) benzyl)-4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butan-1-amine	 **(Intermediate 2.285)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.57 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.20 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.04 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.58 (d, *J* = 0.8 Hz, 1H), 7.45 (s, 1H), 7.37 (s, 2H), 6.48 (s, 1H), 4.64 – 4.59 (m, 2H), 4.59 – 4.54 (m, 1H), 4.17 (dd, *J* = 3.8, 8.9 Hz, 2H), 3.83 (s, 2H), 3.61 – 3.53 (m, 2H), 2.75 – 2.65 (m, 2H), 1.70 – 1.66 (m, 4H) ppm **LCMS** (AM3): rt = 0.775 min, (548.1 $[M+H]^+$), 98.00% purity **Purification method 1)** PM271 then 2) PM272

EXAMPLE 49

6-(4H-1,2,4-triazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine

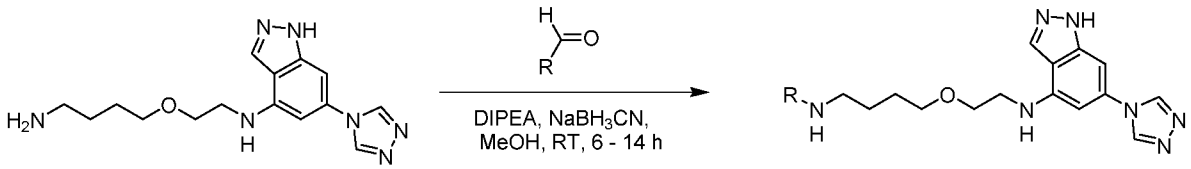


[00741] A solution of **compound 1.306** (80 mg, 227.38 μmol, HCl salt), DIPEA (58.77 mg, 454.76 μmol) and 5-(trifluoromethyl)-1H-indole-2-carbaldehyde (48.47 mg, 227.38 μmol) in MeOH (10 mL) was stirred at 30 °C for 3.5 h, then $NaBH_3CN$ (42.87 mg, 682.14 μmol) was added. The reaction mixture was stirred at 30 °C for 3 h. The reaction mixture was filtered and the filtrate was purified (PM273) to afford **EXAMPLE 49** (30.39 mg, 48.07 μmol, 21% yield, TFA salt) as a white solid.

[00742] **LCMS** (AM3): rt = 0.800 min, (513.4 $[M+H]^+$), 99.1% purity.

[00743] **^{1}H NMR** (400 MHz, MeOH-d4) δ: 9.01 (s, 2H), 8.19 (s, 1H), 7.88 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 1.6, 8.8 Hz, 1H), 6.95 (s, 1H), 6.74 (s, 1H), 6.33 (d, *J* = 1.6 Hz, 1H), 4.34 (s, 2H), 3.74 (t, *J* = 5.6 Hz, 2H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.52 (t, *J* = 5.4 Hz, 2H), 3.11 (t, *J* = 7.6 Hz, 2H), 1.86-1.78 (quin, 2H), 1.74-1.67 (quin, 2H) ppm.

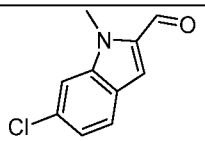
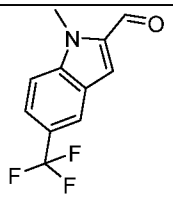
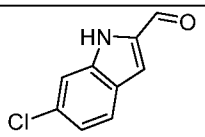
[00744] The following examples in Table 15 were made with non-critical changes or substitutions to the exemplified procedure for Example 49, that would be understood by one skilled in the art using intermediate 1.306



Intermediate 1.306

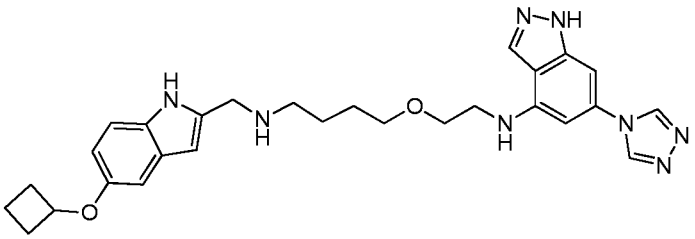
Table 15

Example No.	Chemical IUPAC name	Aldehyde (RCHO) Intermediate No./ CAS	Analytical

Example 50	N-(2-(4-(((6-chloro-1-methyl-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine	 CAS 1781757-70-7	**^{1}H NMR** (400 MHz, MeOH-d4) δ: 9.01 (s, 2H), 8.20 (s, 1H), 7.49-7.45 (m, 2H), 7.04 (dd, *J* = 1.6, 8.4 Hz, 1H), 6.93 (s, 1H), 6.64 (s, 1H), 6.32 (s, 1H), 4.38 (s, 2H), 3.76 (t, *J* = 5.6 Hz, 2H), 3.72 (s, 3H), 3.60 (t, *J* = 5.8 Hz, 2H), 3.52 (t, *J* = 5.6 Hz, 2H), 3.16 (t, *J* = 7.6 Hz, 2H), 1.87-1.80 (quin, 2H), 1.76-1.69 (quin, 2H) ppm. **LCMS** (AM3): rt = 0.786 min, (493.3 $[M+H]^+$), 99.5% purity. **Purification Method** PM230
Example 51	N-(2-(4-(((1-methyl-5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine	 CAS 2090356-65-1	**^{1}H NMR** (400 MHz, MeOH-d4) δ: 9.04 (s, 2H), 8.21 (s, 1H), 7.87 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.46 (dd, *J* = 1.6, 8.8 Hz, 1H), 6.94 (s, 1H), 6.79 (s, 1H), 6.32 (s, 1H), 4.44 (s, 2H), 3.81 (s, 3H), 3.77 (t, *J* = 5.2 Hz, 2H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.53 (t, *J* = 5.6 Hz, 2H), 3.18 (t, *J* = 8.0 Hz, 2H), 1.89-1.82 (quin, 2H), 1.78-1.70 (quin, 2H) ppm. **LCMS** (AM3): rt = 0.802 min, (527.4 $[M+H]^+$), 99.6% purity. **Purification Method** PM255
Example 52	N-(2-(4-(((6-chloro-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine	 CAS 53590-59-3	**^{1}H NMR** (400 MHz, MeOH-d4) δ: 8.98 (s, 2H), 8.20 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.29 (s, 1H), 6.94-6.91 (m, 2H), 6.33-6.32 (m, 2H), 3.85 (s, 2H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.53-3.49 (m, 4H), 2.62 (t, *J* = 6.8 Hz, 2H), 1.65-1.56 (m, 4H) ppm. **LCMS** (AM3): rt = 0.777 min, (479.4 $[M+H]^+$), 100% purity. **Purification Method** PM62

EXAMPLE 53

N-(2-(4-(((5-cyclobutoxy-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine

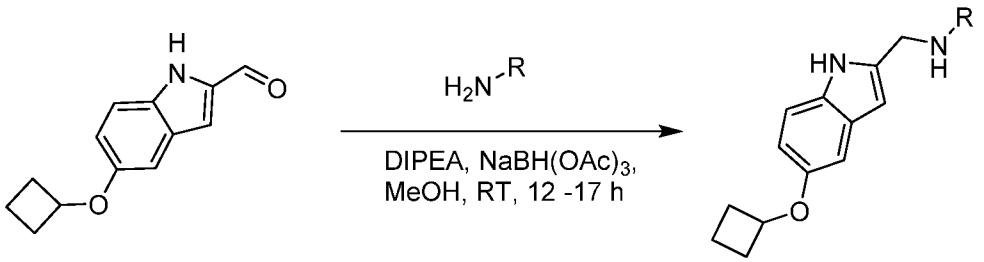


[00745] A mixture of **compound 1.420** (110 mg, 0.511 mmol), **compound 1.306** (200 mg, 0.515 mmol, HCl salt) and DIPEA (1.55 mmol, 0.27 mL) in MeOH (10 mL) was stirred at 16°C for 15 h before $NaBH(OAc)_3$ (0.44 g, 2.08 mmol) was added, then the reaction mixture was stirred for 2 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM274) then (PM134) to afford **EXAMPLE 53** (79.97 mg, 30.41% yield) as an off-white solid.

[00746] LCMS (AM3): rt = 0.806 min, (515.5 $[M+H]^+$), 100% purity.

[00747] ^{1}H NMR: (400 MHz, MeOH-d_4) δ 8.96 (s, 2H), 8.20 (d, *J* = 1.2 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 6.92 (s, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.67 (d, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.32 - 6.28 (m, 2H), 4.64 - 4.54 (m, 1H), 3.96 (s, 2H), 3.70 (t, *J* = 5.6 Hz, 2H), 3.56 - 3.45 (m, 4H), 2.74 (t, *J* = 6.8 Hz, 2H), 2.47 - 2.36 (m, 2H), 2.16 - 2.02 (m, 2H), 1.87 - 1.76 (m, 1H), 1.73 - 1.67 (m, 1H), 1.67 - 1.60 (m, 4H) ppm.

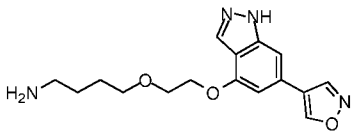
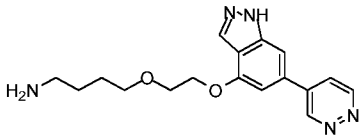
[00748] The following examples in Table 16 were made with non-critical changes or substitutions to the exemplified procedure for Example 53, that would be understood by one skilled in the art using Intermediate 1.420

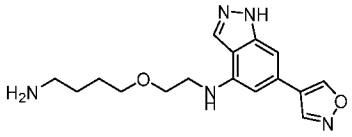
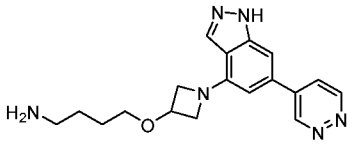


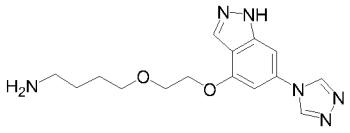
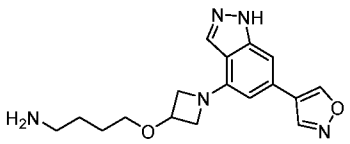
Intermediate 1.420

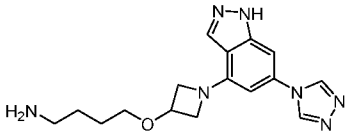
Table 16

Example No.	Chemical IUPAC name	H_2NR	Analytical

Example 54	N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-(2-((6-(isoxazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butan-1-amine	 **(Intermediate 1.910)**	**^{1}H NMR**: (400 MHz, MeOH-d_4) δ: 9.13 (s, 1H), 8.90 (s, 1H), 8.56 (s, 1H), 8.06 (s, 1H), 7.36 (s, 1H), 7.23 - 7.21 (m, 1H), 6.87 - 6.86 (m, 1H), 7.78 (s, 1H), 6.74 - 6.71 (m, 1H), 6.40 (s, 1H), 4.61 - 4.60 (m, 1H), 4.34 - 4.32 (m, 2H), 4.16 (s, 2H), 3.90 - 3.88 (m, 2H), 3.65 - 3.63 (m, 2H), 3.30 - 2.97 (m, 2H), 2.41 - 2.40 (m, 2H), 2.10 - 2.12 (m, 2H), 1.80 - 1.69 (m, 6H) ppm. **LCMS** (AM3): rt = 0.874 min, (516.5 $[M+H]^+$), 100% purity. **Purification Method** PM275
Example 55	N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-(2-((6-(pyridazin-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butan-1-amine	 **(Intermediate 1.913)**	**^{1}H NMR**: (400 MHz, MeOH-d_4) δ: 9.58 - 9.57 (m, 1H), 9.20 - 9.19 (m, 1H), 8.15 - 8.14 (m, 1H), 8.02 - 8.00 (m, 1H), 7.56 (s, 1H), 7.15 - 7.13 (m, 1H), 6.92 (d, J = 0.8 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H), 6.64 - 6.61 (m, 1H), 6.20 (s, 1H), 4.60 - 4.58 (m, 1H), 4.39 - 4.37 (m, 2H), 3.90 - 3.87 (m, 2H), 3.82 (s, 2H), 3.60 - 3.58 (m, 2H), 2.65 - 2.63 (m, 2H), 2.41 - 2.39 (m, 2H), 2.14 - 2.04 (m, 2H), 1.85 - 1.75 (m, 1H), 1.68 - 1.57 (m, 5H) ppm. **LCMS** (AM3): rt = 0.781 min, (527.1 $[M+H]^+$), 97.1% purity. **Purification Method** PM276

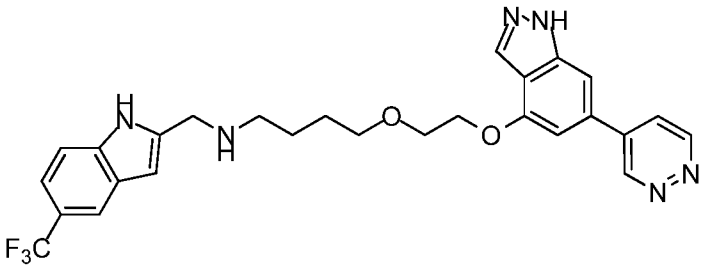
Example 98	N-(2-(4-(((5-cyclobutoxy-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(isoxazol-4-yl)-1H-indazol-4-amine	 **(Intermediate 1.895)**	**^{1}H NMR** (400 MHz,MeOH-d_4) δ 9.04 (s, 1H), 8.82 (s, 1H), 8.11 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.99 (s, 1H), 6.87 - 6.80 (m, 1H), 6.69 - 6.62 (m, 1H), 6.39 (s, 1H), 6.23 (s, 1H), 4.65 - 4.55 (m, 1H), 3.84 (s, 2H), 3.70 (t, *J* = 5.6 Hz, 2H), 3.52 - 3.46 (m, 4H), 2.67 - 2.58 (m, 2H), 2.55 - 2.46 (m, 2H), 2.13 - 2.05 (m, 2H), 1.92-1.85 (m, 1H), 1.71 - 1.65 (m, 1H), 1.46 - 1.39 (m, 4H) ppm **LCMS** (AM3): rt = 0.851 min, (515.3 $[M+H]^+$),100% purity **Purification Method** PM278
Example 109	N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine	 **(Intermediate 2.113)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.55 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.19 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 8.01 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.27 (s, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.64 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.29 – 6.21 (m, 2H), 4.60 (d, *J* = 7.6 Hz, 1H), 4.50 – 4.45 (m, 1H), 4.45 – 4.40 (m, 2H), 4.01 (dd, *J* = 3.6, 8.4 Hz, 2H), 3.87 (s, 2H), 3.53 – 3.46 (m, 2H), 2.65 (t, *J* = 6.8 Hz, 2H), 2.46 – 2.37 (m, 2H), 2.15 – 2.03 (m, 2H), 1.86 – 1.74 (m, 1H), 1.73 – 1.66 (m, 1H), 1.66 – 1.59 (m, 4H) ppm **LCMS** (AM3): rt = 0.819 min, 538.3 $[M+H]^+$), 100.00% purity **Purification method 1)** PM279 **then 2)** PM280

Example 118	4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-cyclobutoxy-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 1.374)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.02 (s, 2H), 8.16 (s, 1H), 7.35 (s, 1H), 7.14 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.79 (s, 1H), 6.65 - 6.60 (m, 1H), 6.20 (s, 1H), 4.62 - 4.57 (m, 1H), 4.36 - 4.32 (m, 2H), 3.89 - 3.85 (m, 2H), 3.83 (s, 2H), 3.62 - 3.57 (m, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.46 - 2.38 (m, 2H), 2.15 - 2.05 (m, 2H), 1.85 - 1.77 (m, 1H), 1.74 - 1.67 (m, 1H), 1.67 - 1.61 (m, 4H) ppm **LCMS** (AM3): rt = 0.822 min, (516.1 $[M+H]^+$), 100% purity **Purification Method** PM282
Example 119	N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine	 **(Intermediate 2.115)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.08 (s, 1H), 8.86 (s, 1H), 8.52 (s, 1H), 7.97 (d, J = 0.4 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.09 (s, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.75 (dd, J = 2.4, 9.2 Hz, 1H), 6.51 (s, 1H), 6.15 (d, J = 1.2 Hz, 1H), 4.62 (t, J = 7.2 Hz, 1H), 4.50 – 4.47 (m, 1H), 4.39 (t, J = 6.8 Hz, 2H), 4.29 (s, 2H), 3.96 (dd, J = 8.4, 4.0 Hz, 2H), 3.54 (t, J = 6.0 Hz, 2H), 3.10 – 3.06 (m, 2H), 2.46 – 2.42 (m, 2H), 2.13 – 2.08 (m, 2H), 1.85 – 1.80 (m, 3H), 1.75 – 1.71 (m, 3H) ppm **LCMS** (AM3): rt = 0.874 min, (527.3 $[M+H]^+$), 100% purity **Purification Method** PM78

Example 124	4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-cyclobutoxy-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 2.221)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.99 (s, 2H), 8.07 (d, *J* = 0.8 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.00 (s, 1H), 6.85 (d, *J* = 2.0 Hz, 1H), 6.64 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.25 (s, 1H), 6.07 (d, *J* = 1.6 Hz, 1H), 4.65 - 4.55 (m, 1H), 4.48 - 4.38 (m, 3H), 4.01 (dd, *J* = 8.4 Hz, 3.6 Hz, 2H), 3.88 (s, 2H), 3.51 - 3.45 (m, 2H), 2.65 (t, *J* = 6.8 Hz, 2H), 2.45 - 2.37 (m, 2H), 2.15 - 2.04 (m, 2H), 1.85 - 1.75 (m, 1H), 1.74 - 1.66 (m, 1H), 1.66 - 1.61 (m, 4H) ppm **LCMS** (AM3): rt = 0.821 min, (527.3 $[M+H]^+$), 100% purity **Purification method 1)** PM283 **then 2)** PM280

EXAMPLE 56

4-(2-((6-(pyridazin-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine



[00749] To a solution of **compound 1.913** (255 mg, 0.54 mmol, HCl salt) in MeOH (2 mL) at 25 °C was added DIPEA (139.96 mg, 1.08 mmol) and 5-(trifluoromethyl)-1H-indole-2-carbaldehyde(Intermediate (CAS 1367793-79-0, 126.96 mg, 0.54 mmol). The reaction mixture was stirred for 11h. $NaBH(OAc)_3$ (1.15 g, 5.41 mmol) was added then the mixture stirred for 1 h. The mixture was then concentrated in *vacuo* to give a residue, which was purified (PM284) to afford **EXAMPLE 56** (138.20 mg, 47.9% yield) as a yellow solid.

[00750] LCMS (AM3): rt = 0.779 min, (525.0 $[M+H]^+$), 98.5% purity.

[00751] **^{1}H NMR**: (400 MHz, MeOH-d_4) δ: 9.57 (m, 1H), 9.21 - 9.20 (m, 1H), 8.14 (m, 1H), 8.04 - 8.02 (m, 1H), 7.78 - 7.77 (m, 1H), 7.57 - 7.56 (m, 1H), 7.47 - 7.45 (m, 1H), 7.34 - 7.31 (m, 1H), 6.93 (s, 1H), 6.57 (s, 1H), 4.41 - 4.39 (m, 2H), 4.12 - 4.10 (m, 2H), 3.93 - 3.91 (m, 2H), 3.66 - 3.63 (m, 2H), 2.90 (s, 2H), 1.78 - 1.69 (m, 4H) ppm.

[00752] The following examples in Table 17 were made with non-critical changes or substitutions to the exemplified procedure for Example 56, that would be understood by one skilled in the art using 5-(trifluoromethyl)-1H-indole-2-carbaldehyde (CAS 1367793-79-0)

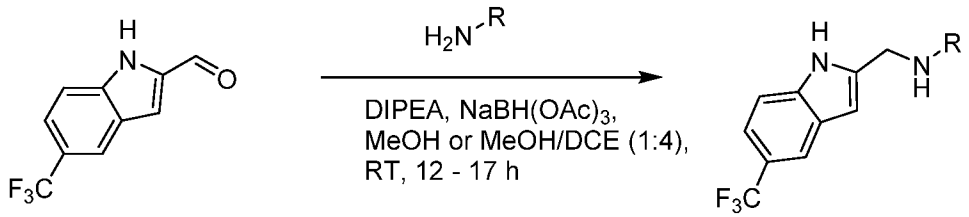
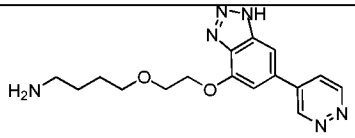
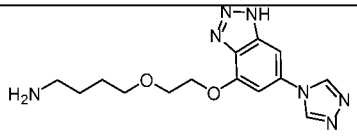
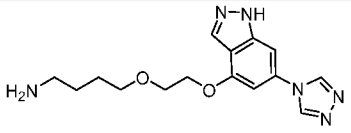
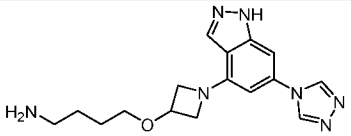
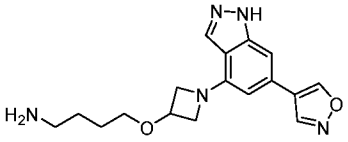
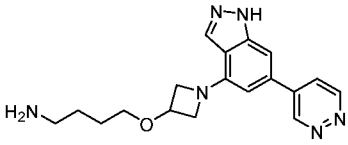
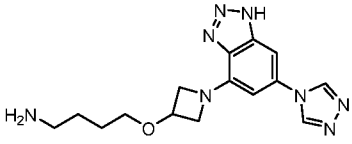


Table 17

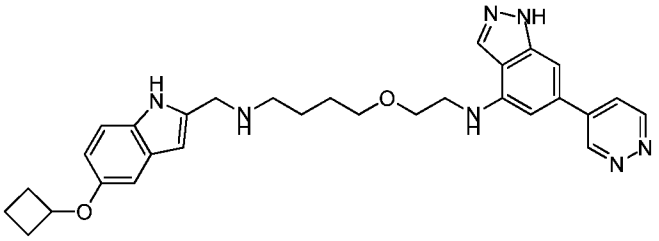
Example No.	Chemical IUPAC name	H_2NR	Analytical
Example 101	4-(2-((6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 2.367)**	**^{1}H NMR** (400 MHz,MeOH-d_4) δ 9.60 (d, *J* = 1.2 Hz, 1H), 9.16 (dd, *J* = 5.6, 1.2 Hz, 1H), 8.03 (dd, J = 5.2, 2.4 Hz, 1H), 7.92 (s, 1H), 7.80 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 1.2 Hz, 1H), 6.61 (s, 1H), 4.45 - 4.38 (m, 2H), 4.31 (s, 2H), 3.98 - 3.89 (m, 2H), 3.66 (t, *J* = 5.2 Hz, 2H), 3.11 (t, *J* = 7.2 Hz, 2H), 1.99 - 1.88 (m, 2H), 1.83 - 1.72 (m, 2H) ppm **LCMS** (AM3): rt = 0.820 min, (526.3 [M+H]+), 99% purity **Purification Method** PM285

Example 116	4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 2.347)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.99 (s, 2H), 7.82 (s, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.82 (d, *J* = 1.6 Hz, 1H), 6.66 (s, 1H), 4.39 - 4.35 (m, 4H), 3.94 - 3.91 (m, 2H), 3.67 (t, *J* = 5.6 Hz, 2H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.00 - 1.93 (m, 2H), 1.81 - 1.75 (m, 2H) ppm **LCMS** (AM3): rt = 0.794 min, (515.2 $[M+H]^+$), 100.00% purity **Purification Method** PM286
Example 117	4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 1.374)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.04 (s, 2H), 8.16 (s, 1H), 7.75 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.36 (s, 1H), 7.30 - 7.27 (m, 1H), 6.82 (s, 1H), 6.44 (s, 1H), 4.39 - 4.36 (m, 2H), 3.91 - 3.88 (m, 4H), 3.61 (t, *J* = 5.6 Hz, 2H), 2.66 (t, *J* = 7.2 Hz, 2H), 1.67 - 1.62 (m, 4H) ppm **LCMS** (AM3): rt = 0.817 min, (514.0 $[M+H]^+$), 99.8% purity **Purification Method** PM287
Example 128	4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 2.221)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.99 (s, 2H), 8.08 (s, 1H), 7.76 (s, 1H), 7.43 (d, *J* = 8.0 Hz,1H), 7.29 (dd, *J* = 1.6 Hz, *J* = 8.8 Hz, 1H), 7.01 (s, 1H), 6.48 (s, 1H), 6.09 (d, *J* = 1.6 Hz, 1H), 4.50 - 4.43 (m, 3H), 4.06 - 4.02 (m, 2H), 3.94 (s, 2H), 3.53 - 3.50 (m, 2H), 2.70 - 2.66 (m, 2H), 1.68-1.64 (m, 4H) ppm **LCMS** (AM3) :rt = 0.766 min, (525.2 $[M+H]^+$), 100% purity **Purification Method** PM288

Example 139	4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 2.115)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.07 (s, 1H), 8.85 (s, 1H), 8.50 (s, 1H), 7.98 (s, 1H), 7.87 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.09 (s, 1H), 6.74 (s, 1H), 6.17 (s, 1H), 4.52 - 4.49 (m, 1H), 4.43 (t, *J* = 7.2 Hz, 2H), 4.36 (s, 2H), 3.99 (dd, *J* = 8.4, 4.0 Hz, 2H), 3.56 (t, *J* = 5.6 Hz, 2H), 3.10 (t, *J* = 7.6 Hz, 2H), 1.87 - 1.83 (m, 2H), 1.75-1.71 (m, 2H) ppm **LCMS** (AM3): rt = 0.835 min, (525.3 $[M+H]^+$), 99.1% purity **Purification Method** PM289
Example 140	4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 2.113)**	**^{1}H NMR** (400 MHz, MeOH-d_4-d4) δ 9.55 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.19 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.07 (s, 1H), 8.01 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.76 (s, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.33 - 7.25 (m, 2H), 6.48 (s, 1H), 6.28 (d, *J* = 1.2 Hz, 1H), 4.53 - 4.40 (m, 3H), 4.03 (dd, *J* = 3.6, 8.4 Hz, 2H), 3.93 (s, 2H), 3.51 (t, *J* = 5.6 Hz, 2H), 2.67 (br t, *J* = 6.8 Hz, 2H), 1.70 - 1.61 (m, 4H) ppm **LCMS** (AM3): rt = 0.630 min, (536.1 $[M+H]^+$), 96.88% purity **Purification Method** PM277
Example 152	4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 2.304)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.00 (s, 2H), 7.79 (s, 1H), 7.50 - 7.41 (m ,1H), 7.35 - 7.26 (m, 1H), 7.17 (s, 1H), 6.55 (s, 1H), 6.23 (s, 1H), 4.60 - 4.50 (m, 3H), 4.20 - 4.10 (m, 2H), 4.04 (s, 2H), 3.52 (t, *J* = 6.0 Hz, 2H), 2.79 (t, *J* = 6.8 Hz, 2H), 1.78 - 1.60 (m, 4H) ppm **LCMS** (AM3): rt = 0.821 min, (526.2 $[M+H]^+$), 100% purity. **Purification Method** PM293

EXAMPLE 57

N-(2-(4-(((5-cyclobutoxy-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(pyridazin-4-yl)-1H-indazol-4-amine



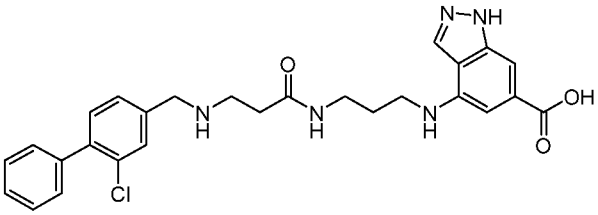
[00753] To a solution of **compound 1.921** (300 mg, 826.77 μmol) and **compound 1.420** (160.16 mg, 744.10 μmol) in MeOH (10 mL) was added DIPEA (320.56 mg, 2.48 mmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (519.56 mg, 8.27 mmol) was added and the reaction was stirred at 20 °C for 1 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM294) to afford **EXAMPLE 57** (92.33mg, 169.50 μmol, 20.5% yield) as a yellow solid.

[00754] **LCMS** (AM3): rt = 0.814 min, (526.2 $[M+H]^+$), 96.4% purity.

[00755] **^{1}H NMR**: (400 MHz, MeOH-d_4) δ: 9.53 (dd, *J* = 2.8, 1.2 Hz, 1H), 9.16 (dd, *J* = 5.6, 1.2 Hz, 1H), 8.19 (d, *J* = 0.8 Hz, 1H), 7.97 (dd, *J* = 5.6, 2.4 Hz, 1H), 7.19 - 7.14 (m, 2H), 6.83 (d, *J* = 2.4Hz, 1H), 6.64 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.52 (d, *J* = 1.2 Hz, 1H), 6.23 (s, 1H), 4.62 - 4.55 (m, 1H), 3.84 (s, 2H), 3.72 (t, *J* = 5.6 Hz, 2H), 3.53 (q, *J* = 5.6 Hz, 4H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.45 - 2.37 (m, 2H), 2.14 - 2.04 (m, 2H), 1.82 - 1.66 (m, 2H), 1.63 - 1.61 (m, 4H) ppm

EXAMPLE 59

4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1H-indazole-6-carboxylic acid



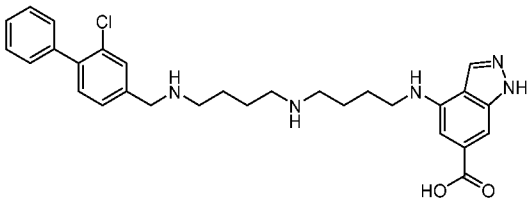
A mixture of **compound 2.569** (100 mg, 192.30 μmol) in MeOH (2.0 mL) and NaOH (2.0 M in water, 3.50 mL) was stirred at 25°C for 4 h. The solvent was removed under reduced pressure to give a residue, which was purified (PM295) to obtain 70 mg of crude product, then the crude product was further purified (PM296) to afford **EXAMPLE 59** (20 mg, 37.5 μmol, 13.9% yield) as a white solid.

LCMS (AM21): rt = 1.825 min, (506.2 $[M+H]^+$), 95.47% purity.

^{1}H NMR (400 MHz, DMSO) δ 8.21 (s, 1H), 8.03 - 8.02 (m, 1H), 7.50 (s, 1H),7.44 - 7.30 (m, 8H), 6.60 (s, 1H), 6.34 (s, 1H), 3.73 (s, 2H), 3.20 - 3.16 (m, 4H), 2.74 - 2.70 (m, 2H), 2.30 - 2.27 (m, 2H), 1.81 - 1.77(m, 2H) ppm.

EXAMPLE 60

4-((4-((4-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)butyl)amino)butyl)amino)-1H-indazole-6-carboxylic acid



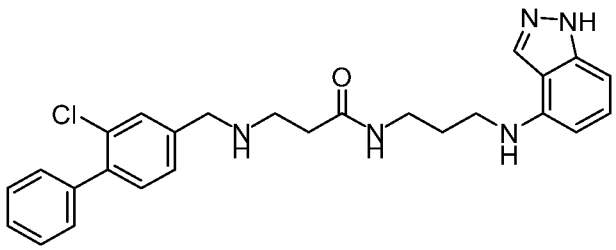
To a solution of **compound 2.574** (16.0 mg, 30.0 μmol) in AcOH (1.50 mL) was added HCl (1.50 mL) and the reaction was stirred at 90°C for 2 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM297) to afford **EXAMPLE 60** (10 mg, 18.27 μmol, 60.98% yield) as a grey solid.

LCMS (AM3): rt = 0.742 min, (520.3 $[M+H]^+$), 100 % purity.

^{1}H NMR (400 MHz, D_2O) δ 8.10 (s, 1H), 7.68 (s, 1H), 7.50 (s, 1H), 7.40 - 7.33 (m, 8H), 4.13 (s, 2H), 3.30 - 3.27 (t, *J* = 6.4 Hz, 2H), 2.99 - 2.90 (m, 6H), 1.68 - 1.62 (m, 8H) ppm.

EXAMPLE 61

N-(3-((1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propenamide



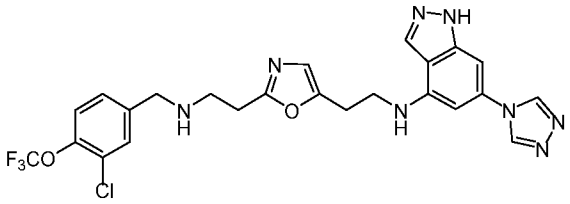
[00756] A mixture of **compound 2.357** (50 mg, 88.95 μmol) in HCl (2 M, 5 mL) was stirred at 25 °C for 16 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM298) to afford **EXAMPLE 61** (21.9 mg, 43.94 μmol, 49.39% yield, HCl salt) as a white solid.

[00757] **LCMS** (AM3): rt = 0.806 min, (462.2 $[M+H]^+$), 100.00% purity.

[00758] **^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.49 (s, 1H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.58 - 7.33 (m, 10H), 4.30 (s, 2H), 3.56 (t, *J* = 7.2 Hz, 2H), 3.40 - 3.34 (m, 4H), 2.74 (t, *J* = 6.8 Hz, 2H), 2.05 - 1.98 (m, 2H) ppm

EXAMPLE 64

N-(2-(2-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)oxazol-5-yl)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine



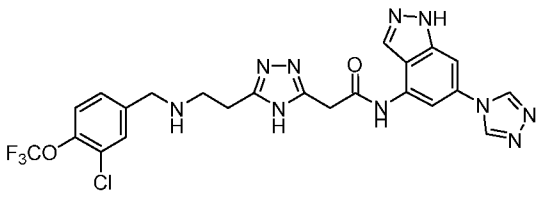
To a mixture of **compound 2.069** (50 mg, 68.38 μmol) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM77) to afford **EXAMPLE 64** (15.88 mg, 23.31 μmol, 34.08% yield, TFA salt) as a yellow oil.

LCMS (AM3): rt = 0.792 min, (547.1 $[M+H]^+$), 96.9% purity.

^{1}H NMR (400MHz,MeOH-d_4) δ 9.00 (s, 2H), 8.15 (m, 1H), 7.77 (s, 1H), 7.55 (s, 2H), 6.95 (d, *J* = 1.2 Hz, 1H), 6.90 (s, 1H), 6.28 (s, 1H), 4.29 (s, 2H), 3.65 (t, *J* = 6.8 Hz, 2 H), 3.43 (t, *J* = 7.2 Hz, 2 H), 3.30 - 3.12 (m, 4 H) ppm

EXAMPLE 65

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-(5-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)-4H-1,2,4-triazol-3-yl)acetamide



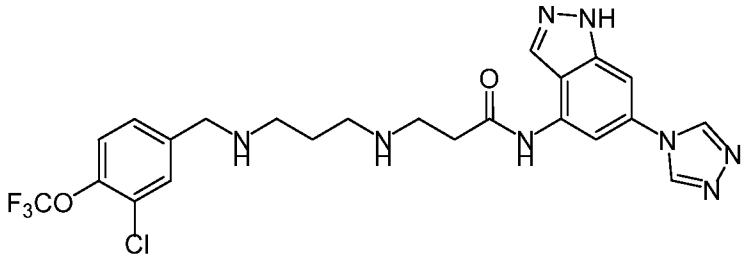
To a mixture of **compound 1.299** (50 mg, 67.10 μmol) in DCM (1 mL) was added TFA (1.54 g, 13.51 mmol, 1.00 mL). The mixture was stirred at 20 °C for 1 h. The solvent was removed to give a residue, which was purified (PM77) to afford **EXAMPLE 65** (16.44 mg, 24.11 μmol, 35.94% yield, TFA salt) as a green solid.

LCMS (AM3): rt = 0.763 min, (561.1[M+H]+), 99.27% purity

^{1}H NMR (400 MHz,MeOH-d_4) δ 9.05 (s, 2H), 8.40 (d, J = 1.2 Hz, 1H), 8.02 (d, J = 1.6 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.58 - 7.55 (m, 1H), 7.53 - 7.48 (m, 1H), 4.33 (s, 2H), 4.21 - 4.10 (m, 2H), 3.51 (t, J = 6.8 Hz, 2H), 3.20 (t, J = 6.8 Hz, 2H) ppm

EXAMPLE 66

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-((3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propyl)amino)propanamide



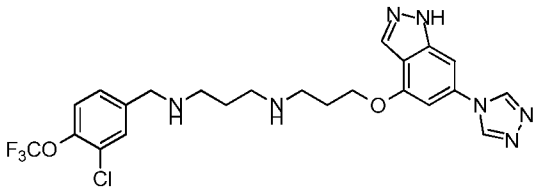
A mixture of **compound 2.294** (30 mg, 39.94 μmol, TFA salt) and TFA (67.53 mmol, 5 mL) in DCM (5 mL) was stirred at 25 °C for 2 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM219) to afford **EXAMPLE 66** (17.29 mg, 56.59% yield, TFA salt) as a white solid.

LCMS (AM3): rt = 0.712 min, (537.1 $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.01 (s, 2H), 8.39 (s, 1H), 8.07 (d, J = 1.6 Hz, 1H), 7.78 (s, 1H), 7.59 (s, 1H), 7.55 (s, 2H), 4.28 (s, 2H), 3.45 (t, J = 5.6 Hz, 2H), 3.27 - 3.20 (m, 4H), 3.08 (t, J = 6.8 Hz, 2H), 2.26 - 2.14 (m, 2H) ppm

EXAMPLE 67

N1-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propyl)-N3-(3-chloro-4-(trifluoromethoxy)benzyl)propane-1,3-diamine



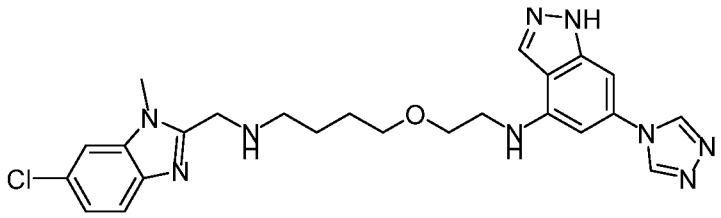
To a mixture of **compound 2.363** (40 mg, 64.10 μmol) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol). The mixture was stirred at 25 °C for 0.5 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM299) to afford **EXAMPLE 67** (27.33 mg, 36.34 μmol, 56.70% yield, TFA salt) as a white solid.

LCMS (AM3): rt = 0.746 min, (524.1 $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz,MeOH-d_4) δ 9.05 (s, 2H), 8.16 (d, *J* = 1.2 Hz, 1H), 7.78 (s, 1H), 7.60 - 7.51 (m, 2H), 7.42 (t, *J* = 1.6 Hz, 1H), 6.84 (d, *J* = 1.6 Hz, 1H), 4.39 (t, *J* = 6.0 Hz, 2H), 4.28 (s, 2H), 3.38 - 3.34 (m, 2H), 3.26 - 3.19 (m, 4H), 2.38 - 2.29 (m, 2H), 2.24 - 2.14 (s, 2H) ppm

EXAMPLE 68

N-(2-(4-(((6-chloro-1-methyl-1H-benzo[d]imidazol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine



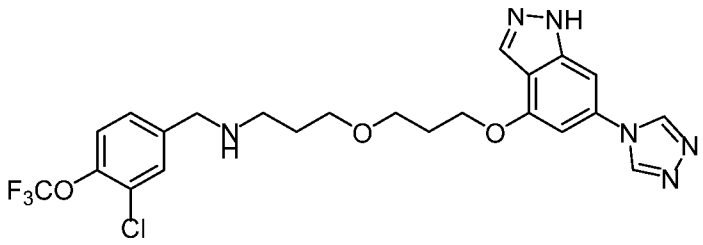
To a solution of **compound 1.306** (100 mg, 284.23 μmol, HCl salt) in DMF (15 mL) was added K_2CO_3 (117.84 mg, 852.68 μmol) and 6-chloro-2-(chloromethyl)-1-methyl-1H-1,3-benzimidazole (CAS 109047-39-4, 30.57 mg, 142.11 μmol). The reaction mixture was stirred at 50 °C for 3 h. To the reaction mixture was added H_2O (15 mL) and then extracted with EA (20 mL × 2). The combined organic phases were washed (brine, 30 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM229) to afford **EXAMPLE 68** (21.32 mg, 35.06 μmol, 12.34% yield, TFA salt) as a purple gum.

LCMS (AM3): rt = 0.737 min, (494.4 $[M+H]^+$), 100.00% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.16 (s, 2H), 8.21 (s, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.18 - 7.15 (m, 1H), 6.94 (s, 1H), 6.19 (s, 1H), 4.50 (s, 2H), 3.81 (t, *J* = 5.2 Hz, 2H), 3.67 (t, *J* = 5.6 Hz, 2H), 3.61 (s, 3H), 3.53 (t, *J* = 5.6 Hz, 2H), 3.33 - 3.30 (m, 2H), 1.97 - 1.91 (m, 2H), 1.86 - 1.80 (m, 2H) ppm

EXAMPLE 69

3-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propoxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)propan-1-amine

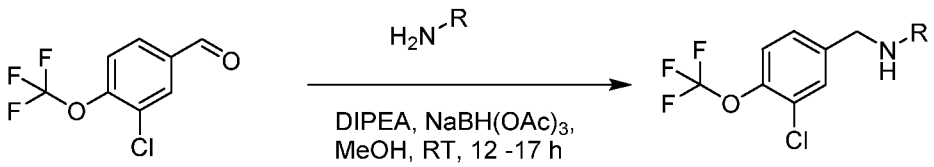


A mixture of **compound 2.289** (94.27 mg, 267.18 μmol, HCl), 3-chloro-4-(trifluoromethoxy)benzaldehyde (CAS 83279-39-4, 60 mg, 267.18 μmol) and DIPEA (69.06 mg, 534.37 μmol) in MeOH (1 mL) was stirred at 25°C for 1 h, then $NaBH(OAc)_3$ (283.14 mg, 1.34 mmol) was added. The mixture was stirred at 25°C for 11 h. The mixture was filtered and the filtrate was concentrated in *vacuo* to give a residue, which was purified (PM214) to afford **EXAMPLE 69** (68.53 mg, 107.25 μmol, 40.14% yield, TFA salt) as a brown gum.

LCMS (AM3): rt = 0.716 min, (525.2 $[M+H]^+$), 100.00% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.08 (s, 2H), 8.13 (d, *J* = 0.8 Hz, 1H), 7.73 (d, *J* = 2.0 Hz, 1H), 7.50 (t, *J* = 2.0 Hz, 2H), 7.38 (s, 1H), 6.81 (s, 1H), 4.34 (t, *J* = 6.0 Hz, 2H), 4.21 (s, 2H), 3.73 (t, *J* = 6.0 Hz, 2H), 3.62 (t, *J* = 5.6 Hz, 2H), 3.19 (t, *J* =7.2 Hz, 2H), 2.20 - 2.16 (m, 2H), 2.03 - 1.98 (m, 2H) ppm

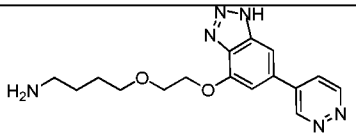
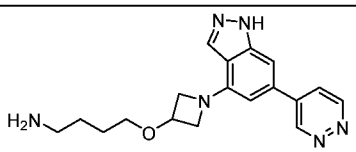
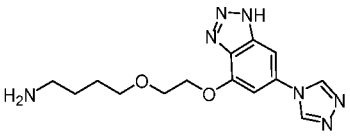
[00759] The following examples in Table 18 were made with non-critical changes or substitutions to the exemplified procedure for Example 69, that would be understood by one skilled in the art using 3-chloro-4-(trifluoromethoxy)benzaldehyde

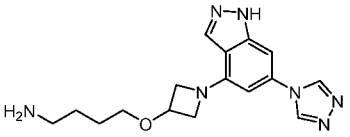
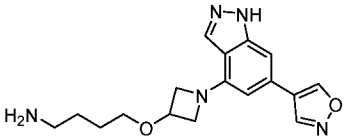
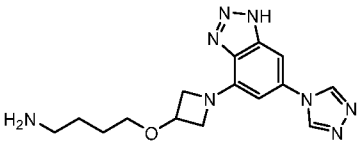


CAS 83279-39-4

Table 18

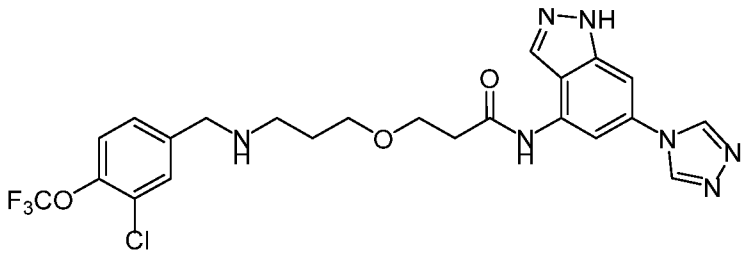
Example No.	Chemical IUPAC name	H_2NR	Analytical

Example 102	N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-(2-((6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butan-1-amine	 **(Intermediate 2.367)**	**^{1}H NMR** (400 MHz,MeOH-d_4) δ 9.62 (dd, *J* = 2.8, 1.2 Hz, 1H), 9.20 (dd, *J* = 5.2, 1.2 Hz, 1H), 8.07 (dd, *J* = 5.6, 2.8 Hz, 1H), 7.91 (d, *J* = 0.8 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.39 - 7.27 (m, 2H), 7.08 (d, *J* = 1.2 Hz, 1H), 4.50 - 4.41 (m, 2H), 4.08 (s, 2H), 3.99 - 3.92 (m, 2H), 3.68 (t, *J* = 5.2 Hz, 2H), 3.08 (t, *J* = 7.2 Hz, 2H), 1.94 - 1.85 (m, 2H), 1.83 - 1.73 (m, 2H) ppm **LCMS** (AM3): rt = 0.813 min, (537.0 [M+H]$^+$), 97.13% purity **Purification Method** PM300
Example 107	N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine	 **(Intermediate 2.113)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.53 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.17 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.06 (d, *J* = 1.2 Hz, 1H), 7.99 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.56 (s, 1H), 7.34 (s, 2H), 7.25 (s, 1H), 6.26 (d, *J* = 1.2 Hz, 1H), 4.54 - 4.42 (m, 3H), 4.03 (dd, *J* = 3.6, 8.4 Hz, 2H), 3.75 (s, 2H), 3.55 - 3.47 (m, 2H), 2.65 - 2.56 (m, 2H), 1.69 - 1.60 (m, 4H) ppm **LCMS** (AM3): rt = 0.813 min, (547.2 [M+H]$^+$), 100.00% purity **Purification Method** PM301
Example 123	4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)butan-1-amine	 **(Intermediate 2.347)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.15 (s, 2H), 7.67 (s, 2H), 7.51 - 7.45 (m, 2H), 7.00 (s, 1H), 4.50 - 4.46 (m, 2H), 3.85 - 3.81 (m, 2H), 3.78 (s, 2H), 3.55 - 3.49 (m, 2H), 2.58 - 2.54 (m, 2H), 2.58 - 2.54 (m, 2H), 1.60 - 1.53 (m, 4H) ppm **LCMS** (AM3): rt = 0.801 min, (526.0 [M+H]$^+$), 100.00% purity **Purification Method** PM229

Example 132	4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)butan-1-amine	 **(Intermediate 2.221)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.00 (s, 2H), 8.09 (d, *J* = 0.8 Hz, 1H), 7.57 (s, 1H), 7.38-7.33 (m, 2H), 7.04-6.98 (m, 1H), 6.11 (d, *J* = 1.6 Hz, 1H), 4.54-4.45 (m, 3H), 4.06 (dd, *J* = 8.4, 3.6 Hz, 2H), 3.76 (s, 2H), 3.55-3.49 (m, 2H), 2.66-2.57 (m, 2H), 1.69-1.62 (m, 4H) ppm **LCMS** (AM3): rt = 0.616 min, (536.1 [M+H]$^+$), 95% purity. **Purification Method** PM302
Example 137	N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine	 **(Intermediate 2.115)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.07 (s, 1H), 8.85 (s, 1H), 8.51 (s, 1H), 7.99 (s, 1H), 7.72 (s, 1H), 7.51 - 7.46 (m, 2H), 7.09 (s, 1H), 6.18 (s, 1H), 4.54-4.49 (m, 1H), 4.44 (t, *J* = 6.8 Hz, 2H), 4.15 (s, 2H), 4.00 (dd, *J* = 8.4, 4.0 Hz, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 1.84 - 1.79 (m, 2H), 1.74 - 1.70 (m, 2H) ppm **LCMS** (AM3): rt = 0.821 min, (536.3 [M+H]$^+$), 98.9% purity **Purification Method** PM289
Example 153	4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)butan-1-amine	 **(Intermediate 2.304)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.00 (s, 2H), 7.60 (s, 1H), 7.42 - 7.33 (m, 2H), 7.16 (d, *J* = 1.6 Hz, 1H), 6.25 (d, *J* = 1.6 Hz, 1H), 4.60 - 4.48 (m, 3H), 4.19 - 4.10 (m, 2H), 3.85 (s, 2H), 3.53 (t, *J* = 5.6 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 1.75 - 1.60 (m, 4H) ppm **LCMS** (AM3): rt = 0.824 min, (537.2 [M+H]$^+$), 100% purity. **Purification Method** PM304

EXAMPLE 70

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-(3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propoxy)propanamide



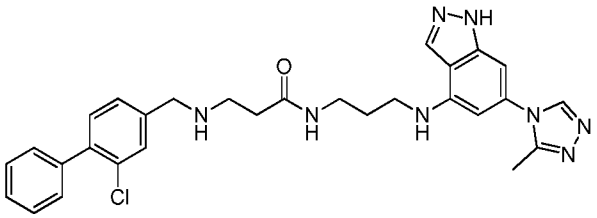
A mixture of **compound 2.298** (180 mg, 492.05 μmol, HCl salt), 3-chloro-4-(trifluoromethoxy)benzaldehyde (CAS 83279-39-4, 23 mg, 547.73 μmol) and DIPEA (1.15 mmol, 200 μL) in MeOH (10 mL) was stirred at 25 °C for 16 h, then $NaBH_3CN$ (137 mg, 2.18 mmol) was added and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM305) to afford **EXAMPLE 70** (76.72 mg, 23.92% yield, TFA salt) as a brown solid.

LCMS (AM3): rt = 0.749min, (538.1 $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.04 (s, 2H), 8.37 (s, 1H), 7.91 (s, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 1.2 Hz, 1H), 7.48 - 7.38 (m, 1H), 7.33 - 7.25 (m, 1H), 4.20 (s, 2H), 3.86 (t, *J* = 5.6 Hz, 2H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.24 (t, *J* = 5.6 Hz, 2H), 2.87 (t, *J* = 5.6 Hz, 2H), 2.10 - 1.98 (m, 2H) ppm

EXAMPLE 71

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-methyl-4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



To a mixture of **compound 2.072** (100 mg, 155.48 μmol) in DCM (3 mL) was added TFA (4.62 g, 40.52 mmol). The mixture was stirred at 30 °C for 0.5 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM220) to afford **EXAMPLE 71** (66.13 mg, 99.64 μmol, 64.08% yield, TFA salt) as a grey solid.

LCMS (AM3): rt = 0.785min, (543.4 $[M+H]^+$), 99% purity.

^{1}H NMR (400MHz, MeOH-d_4) δ 8.90 (s, 1H), 8.25 (d, J = 1.2 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 7.55 - 7.35 (m, 7H), 6.85 (s, 1H), 6.14 (d, J = 1.6 Hz, 1H), 4.29 (s, 2H), 3.41 - 3.32 (m, 6H), 2.68 (t, J = 6.4 Hz, 2H), 2.54 (s, 3H), 1.99 - 1.85 (m, 2H) ppm

[00760] The following examples in Table 19 were made with non-critical changes or substitutions to the exemplified procedure for Example 71 that would be understood by one skilled in the art

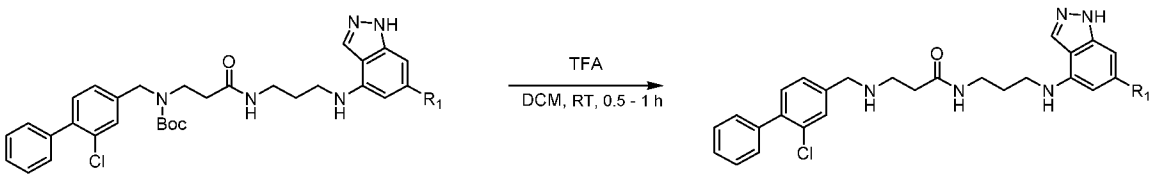
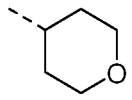
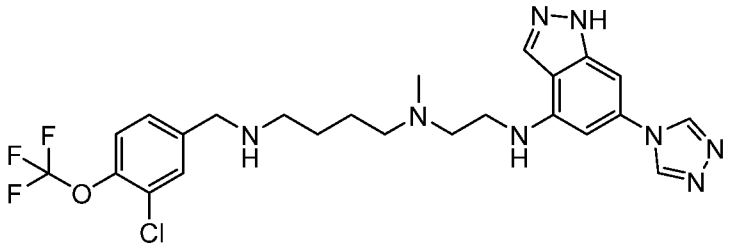


Table 19

Example No.	Chemical IUPAC name	R_1 (Intermediate)	Analytical
Example 90	3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(tetrahydro-2H-pyran-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.277)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.55 (br. s, 1H), 8.90 (br. s, 2H), 8.22 (s, 1H), 8.06 (s, 1 H), 7.75 (s, 1H), 7.55 -7.42 (m, 7H), 6.50 (s, 1H), 5.95 (s, 1H), 4.23 (s, 2H), 3.96 - 3.93 (m, 2H), 3.44 - 3.43 (m, 2H), 3.22 - 3.17 (m, 6H), 2.58 - 2.56 (m, 1H), 2.51 - 2.50 (m, 2H), 1.80 - 1.78 (m, 2H), 1.72 - 1.69 (m, 4H) ppm **LCMS** (AM3): rt = 0.847 min, (546.3 $[M+H]^+$), 98.28% purity **Purification Method** PM223

EXAMPLE 72

N1-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)-N4-(3-chloro-4-(trifluoromethoxy)benzyl)-N1-methylbutane-1,4-diamine



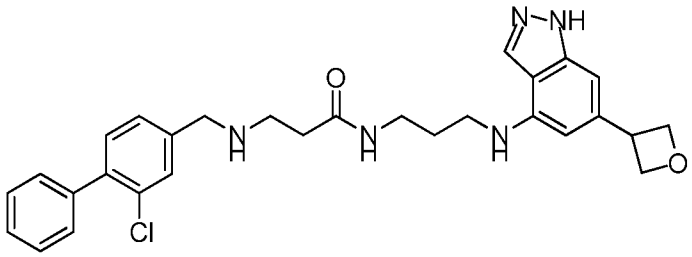
To a solution of **compound 2.225** (90 mg, 141.27 μmol) in DCM (8 mL) was added TFA (12.32 g, 108.05 mmol). The reaction mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM306) and then further purified (PM307) to afford **EXAMPLE 72** (31.77 mg, 59.16 μmol, 41.88% yield) as an off-white solid.

LCMS (AM3): rt = 0.729 min, (537.4 $[M+H]^+$), 100% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.08 (s, 2H), 8.19 (s, 1H), 7.76 (s, 1H), 7.54 (s, 2H), 7.10 (s, 1H), 6.46 (s, 1H), 4.23 (s, 2H), 3.81 (t, *J* = 6.0 Hz, 2H), 3.65 - 3.45 (m, 2H), 3.28 - 3.20 (m, 2H), 3.11 (t, *J* = 7.6 Hz, 2H), 2.99 (s, 3H), 1.90 - 1.78 (m, 4H) ppm

EXAMPLE 81

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(oxetan-3-yl)-1H-indazol-4-yl)amino)propyl)propanamide



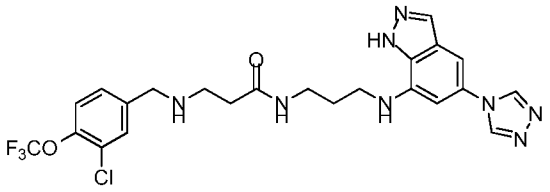
To a solution of **compound 2.011** (60 mg, 0.085 mmol) in DCM (3 mL) was added TFA (2.31 g, 20.26 mmol). The mixture was stirred at 25 °C for 0.5 h. The mixture was neutralized to pH=7 with formic acid. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM308) to afford **EXAMPLE 82** (21.01 mg, 47.4% yield) as a yellow oil.

LCMS (AM3): rt = 0.633 min, (518.1 $[M+H]^+$), 100% purity.

^{1}H NMR: (400 MHz, $CHCl_3$-d) δ: 7.92 (s, 1H), 7.61 - 7.59 (m, 1H), 7.28 - 7.24 (m, 3H), 7.14 - 7.12 (m, 1 H), 7.08 - 7.06 (m, 1H), 6.60 (s, 1H), 6.10 (s, 1H), 4.93 - 4.89 (m, 2H), 4.67 - 4.63 (m, 2H), 4.08 - 4.04 (m, 2H), 3.66 (s, 2H), 3.31 - 3.23 (m, 4H), 2.82 - 2.79 (m, 2H), 2.34 - 2.31 (m, 2H), 1.79 - 1.72 (m, 2H) ppm

EXAMPLE 83

N-(3-((5-(4H-1,2,4-triazol-4-yl)-1H-indazol-7-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide



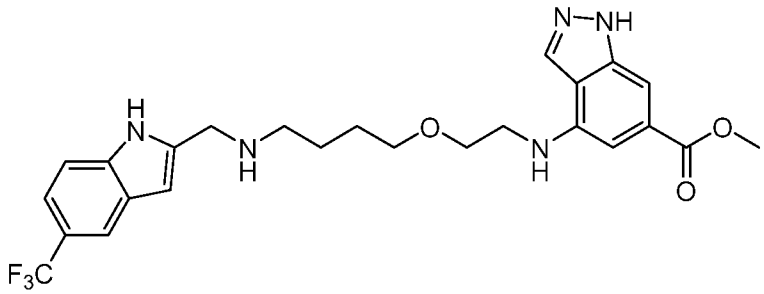
A mixture of **compound 2.081** (36 mg, 47.54 μmol) in TFA (4.62 g, 40.52 mmol) was stirred at 30 °C for 12 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM309) to afford **EXAMPLE 83** (13.98 mg, 20.40 μmol, 42.91% yield, TFA salt) as a yellow oil.

LCMS (AM3): rt = 0.790 min, (537.1 $[M+H]^+$), 95.4% purity.

^{1}H NMR (400MHz, MeOH-d_4) δ 9.05 (s, 2H), 8.07 (s, 1H), 7.77 (d, *J* = 1.2 Hz, 1H), 7.56 - 7.52 (M, 2H), 7.24 (d, *J* = 1.6 Hz, 1H), 6.55 (d, *J* = 1.6 Hz, 1H), 4.27 (s, 2H), 3.44 - 3.65 (m, 4H), 3.30 - 3.27 (m, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.05 - 1.89 (m, 2H) ppm

EXAMPLE 84

methyl4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxylate



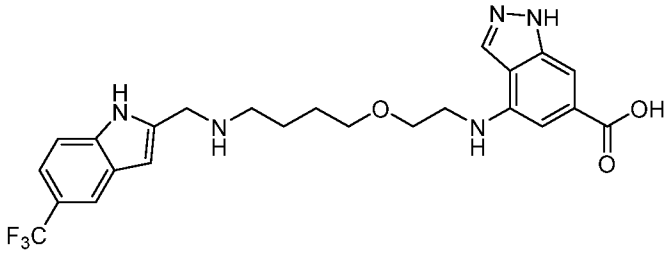
A mixture of 5-(trifluoromethyl)-1H-indole-2-carbaldehyde (CAS 1367793-79-0, 100 mg, 469.14 μmol), **compound 2.105** (250.71 mg, 469.14 μmol) and DIPEA (121.26 mg, 938.28 μmol) in MeOH (10 mL) was stirred at 25°C for 1 h, then $NaBH_3CN$ (294.82 mg, 4.69 mmol) was added. The mixture was stirred at 25°C for 11 h. The mixture concentrated in *vacuo* to give a residue, which was purified (PM310) to afford **EXAMPLE 84** (60 mg, 117.97 μmol, 25.15% yield) as a brown solid.

LCMS (AM3): rt = 0.870 min, (504.2 $[M+H]^+$), 94.60% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.20 (br s, 1H), 7.88 (s, 1H), 7.50 - 7.57 (m, 2H), 7.42 (dd, *J* = 8.8, 1.2 Hz, 1H), 6.65 - 6.94 (m, 2H), 4.34 (s, 2H), 3.90 (s, 3H), 3.73 (t, *J* = 5.6 Hz, 2H), 3.59 (t, *J* = 5.6 Hz, 2H), 3.49 (t, *J* = 5.6 Hz, 2H), 3.10 - 3.16 (m, 2H), 1.81 - 1.89 (m, 2H), 1.70 - 1.75 (m, 2H) ppm

EXAMPLE 85

4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxylic acid



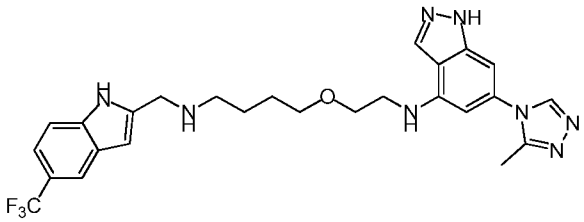
To a mixture of **EXAMPLE 84** (50 mg, 99.30 umol) in THF (1 mL) and MeOH (1 mL) and H_2O (1 mL) was added LiOH.H_2O (41.67 mg, 993.02 umol). The mixture was stirred at 25 °C for 12 h. The mixture concentrated in *vacuo* to give a residue, which was purified (PM208) to afford **EXAMPLE 85** (21.06 mg, 33.85 μmol, 34.09% yield) as a yellow solid.

LCMS (AM3): rt = 0.789 min, (490.2 $[M+H]^+$), 97.91% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.16 (d, *J* = 0.8 Hz, 1H), 7.87 (s, 1H), 7.57 - 7.48 (m, 2H), 7.41 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.84 (d, *J* = 0.8 Hz, 1H), 6.72 (s, 1H), 4.31 (s, 2H), 3.73 (t, *J* = 5.6 Hz, 2H), 3.58 (t, *J* = 5.6 Hz, 2H), 3.49 (t, *J* = 5.6 Hz, 2H), 3.14 - 3.08 (m, 2H), 1.87 - 1.78 (m, 2H), 1.76 - 1.68 (m, 2H) ppm

EXAMPLE 86

6-(3-methyl-4H-1,2,4-triazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine

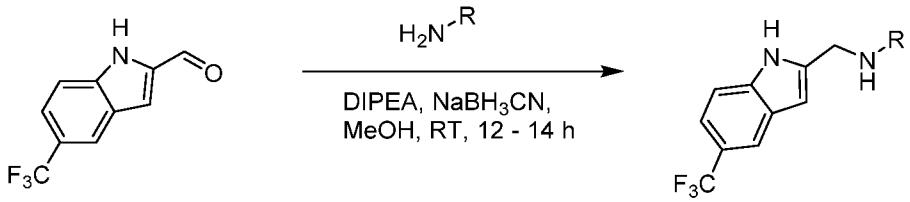


To a mixture of **compound 2.093** (50 mg, 136.66 μmol, HCl salt) and DIPEA (44.16 mg, 341.66 μmol) in MeOH (3 mL) was added 5-(trifluoromethyl)-1H-indole-2-carbaldehyde (CAS 1367793-79-0, 29.13 mg, 136.66 μmol). The mixture was stirred at 25 °C for 12 h. $NaBH_3CN$ (85.88 mg, 1.37 mmol) was added and the mixture was stirred at 25 °C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM309) to afford **EXAMPLE 86** (14.48 mg, 19.00 μmol, 13.90% yield, TFA salt) as a brown solid.

LCMS (AM3): rt = 0.811min, (527.2 $[M+H]^+$), 99% purity.

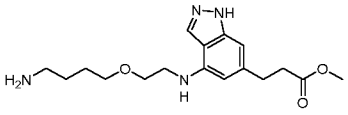
^{1}H NMR (400MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.23 (d, *J* = 0.8 Hz, 1H), 7.88 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 8.4,1.2 Hz, 1H), 6.84 (s, 1H), 6.75 (s, 1H), 6.15 (d, *J* = 1.6 Hz, 1H), 4.36 (s, 2H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.56 (d, *J* = 6.0 Hz, 1H), 3.46 (t, J = 5.2 Hz, 2H), 3.18 - 3.05 (m, 2H), 2.49 (s, 3H), 1.88 - 1.76 (m, 2H), 1.76 - 1.64 (m, 2H) ppm

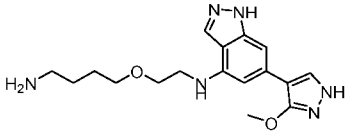
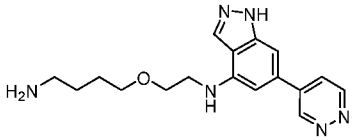
[00761] The following examples in Table 20 were made with non-critical changes or substitutions to the exemplified procedure for Example 86, that would be understood by one skilled in the art using 5-(trifluoromethyl)-1H-indole-2-carbaldehyde (CAS 1367793-79-0)

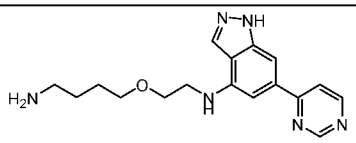
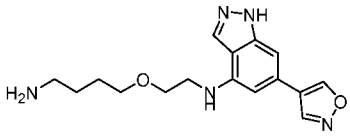
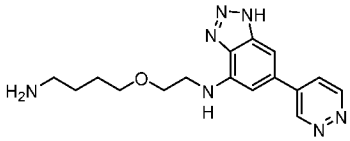


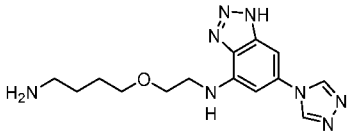
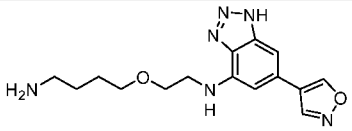
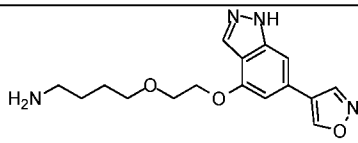
CAS 1367793-79-0

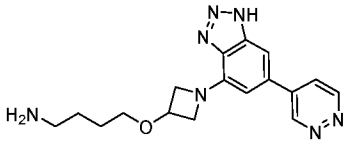
Table 20

Example No.	Chemical IUPAC name	H_2NR	Analytical
Example 88	methyl 3-(4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)propanoate	 **(Intermediate 2.352)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 10.73 (br s, 1H), 8.10 (s, 1H), 7.63 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.24 (dd, *J* = 0.8, 8.8 Hz, 1H), 6.20 (s, 1H), 5.93 (s, 1H), 4.39 (s, 2H), 3.75 (t, *J* = 5.6 Hz, 2H), 3.64 - 3.59 (m, 2H), 3.58 (s, 3H), 3.49 (t, *J* = 5.6 Hz, 2H), 3.06 - 2.93 (m, 4H), 2.49 (t, *J* = 7.6 Hz, 2H), 1.84 - 1.69 (m, 4H) ppm **LCMS** (AM3): rt = 0.863 min, (532.3 $[M+H]^+$), 97.66% purity **Purification Method** PM311

Example 92	6-(3-methoxy-1H-pyrazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine	 **(Intermediate 2.086)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 8.97 (s, 1H), 8.07 (s, 1H), 8.01 - 7.99 (m, 2H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.43 - 7.41 (m, 1H), 7.04 (s, 1H), 6.75 (s, 1H), 6.35 (s, 1H), 4.32 - 4.31 (m, 2H), 3.92 (s, 3H), 3.65 (t, *J* = 5.6 Hz, 2H), 3.47 (t, *J* = 6.4 Hz, 2H), 3.41 (t, *J* = 6.0 Hz, 2H), 2.98 (d, *J* = 2.8 Hz, 2H), 1.72 - 1.66 (m, 2H), 1.61 - 1.57 (m, 2H) ppm **LCMS** (AM3): rt = 0.827min, (542.4 $[M+H]^+$), 100% purity **Purification Method** PM312
Example 93	6-(pyridazin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine	 **(Intermediate 1.921)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.55 (d, *J* = 1.6 Hz, 1H), 9.20 (dd, *J* = 0.8, 5.6 Hz, 1H), 8.52 (br s, 1H), 8.21 (s, 1H), 8.01 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.86 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.40 (dd, *J* = 1.6, 8.5 Hz, 1H), 7.22 (s, 1H), 6.70 (s, 1H), 6.55 (d, *J* = 1.2 Hz, 1H), 4.29 (s, 2H), 3.78 (t, *J* = 5.6 Hz, 2H), 3.61 - 3.55 (m, 4H), 3.12 - 3.04 (m, 2H), 1.86 - 1.79 (m, 2H), 1.75 - 1.70 (m, 2H) ppm **LCMS** (AM3): rt = 0.780 min, (524.3 $[M+H]^+$), 95.811% purity **Purification Method** PM313

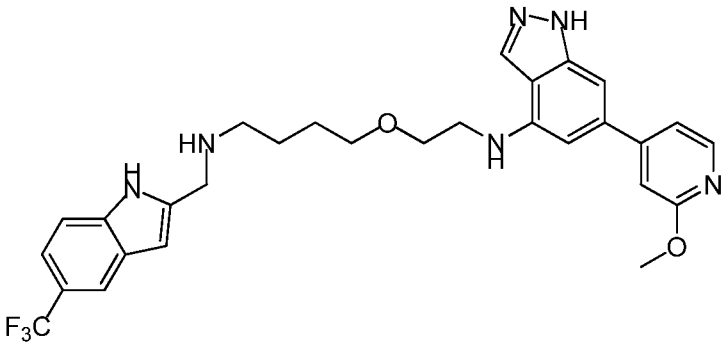
Example 95	6-(pyrimidin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine	 **(Intermediate 2.117)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 9.21 (s, 1H), 8.80 (d, *J* = 5.2 Hz, 1H), 8.25 (s, 1H), 8.21 (s, 1H), 8.08 (d, *J* = 4.4 Hz, 1H), 7.84 (s, 1H), 7.55 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.33 - 7.30 (m, 1H), 6.88 (s, 1H), 6.48 - 6.43 (m, 2H), 3.94 (s, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.48 - 3.44 (m, 4H), 2.61 (t, *J* = 6.4 Hz, 2H),1.55 (s, 4H) ppm **LCMS** (AM3): rt = 0.835min, (524.2 $[M+H]^+$), 98.8% purity **Purification method 1)** PM78 **then 2)** PM79
Example 97	6-(isoxazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine	 **(Intermediate 1.895)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.71 (s, 1H), 9.42 (s, 1H), 9.15 (s, 1H), 9.04 (s, 1H), 8.18 (s, 1H), 7.98 (s, 1H), 7.63 - 7.61 (m, 1H), 7.43 - 7.41 (m, 1H), 6.98 (s, 1H), 6.75 (s, 1H), 6.36 (s, 1H), 4.33 (s, 2H), 3.67 - 3.64 (m, 2H), 3.48 - 3.44 (m, 4H), 2.99 (s, 2H), 1.72 - 1.68 (m, 2H), 1.61 - 1.57 (m, 2H) ppm **LCMS** (AM3): rt = 0.759 min, (513.2 $[M+H]^+$), 97.52% purity. **Purification Method** PM314
Example 100	6-(pyridazin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-benzo[d][1,2,3]triazol-4-amine	 **(Intermediate 2.067)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.58 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.20 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.03 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.85 - 7.79 (m, 1H), 7.50 - 7.43 (m, 2H), 7.33 (dd, *J* = 1.2, 8.4 Hz, 1H), 6.73 (d, *J* = 1.2 Hz, 1H), 6.54 (s, 1H), 4.06 (s, 2H), 3.82 - 3.76 (m, 2H), 3.60 (td, *J* = 5.4, 13.6 Hz, 4H), 2.82 (t, *J* = 7.2 Hz, 2H), 1.83 - 1.66 (m, 4H) ppm **LCMS** (AM3): rt = 0.792 min, (525.1 $[M+H]^+$), 97.7% purity **Purification Method** PM210

Example 142	6-(4H-1,2,4-triazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-benzo[d][1,2,3]triazol-4-amine	 **(Intermediate 2.045)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.00 (s, 2H), 7.81 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.34 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.18 (d, *J* = 1.6 Hz, 1H), 6.57 (s, 1H), 6.49 (d, *J* = 1.6 Hz, 1H), 4.09 (s, 2H), 3.77 (t, *J* = 5.2 Hz, 2H), 3.61 - 3.53 (m, 4H), 2.84 (t, *J* = 7.2 Hz, 2H), 1.80 - 1.67 (m, 4H) ppm **LCMS** (AM3): rt = 0.753 min, (514.2 $[M+H]^+$), 100% purity **Purification method 1)** PM97 **then 2)** PM225
Example 143	6-(isoxazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-benzo[d][1,2,3]triazol-4-amine	 **(Intermediate 2.064)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.14 (s, 1H), 8.91 (s, 1H), 8.53 (s, 1H), 7.85 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.44 - 7.37 (m, 1H), 7.18 (d, *J* = 1.2 Hz, 1H), 6.70 (s, 1H), 6.66 (d, *J* = 1.2 Hz, 1H), 4.32 (s, 2H), 3.80 (t, *J* = 5.2 Hz, 2H), 3.65 - 3.58 (m, 4H), 3.12 - 3.06 (m, 2H), 1.90 - 1.82 (m, 2H), 1.79 - 1.71 (m, 2H) ppm **LCMS** (AM3): rt = 0.810 min, (514.1 $[M+H]^+$), 100% purity **Purification method 1)** PM88 then 2) PM290
Example 144	4-(2-((6-(isoxazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 1.910)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.14 (s, 1H), 8.90 (s, 1H), 8.50 (s, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 7.85 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.41 - 7.34 (m, 2H), 6.80 (d, *J* = 0.8 Hz, 1H), 6.68 (s, 1H), 4.39 - 4.35 (m, 2H), 4.27 (s, 2H), 3.95 - 3.90 (m, 2H), 3.67 (t, *J* = 5.6 Hz, 2H), 3.08 (t, *J* = 7.6 Hz, 2H), 1.88 - 1.79 (m, 2H), 1.78 - 1.72 (m, 2H) ppm **LCMS** (AM3): rt = 0.867 min, (514.2 $[M+H]^+$), 100% purity **Purification Method** PM291

Example 149	4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine	 **(Intermediate 2.285)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.58 (d, *J* = 2.4 Hz, 1H), 9.22 - 9.16 (m, 1H), 8.06 - 8.03 (m, 1H), 7.79 (s, 1H), 7.56 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.35 - 7.28 (m, 1H), 6.51 (s, 1H), 6.42 (s, 1H), 4.60 - 4.58 (m, 2H), 4.57- . 4.53 (m, 1H), 4.15 - 4.07 (m, 2H), 3.97 (s, 2H), 3.57 - 3.52 (m, 2H), 2.76 - 2.69 (m, 2H), 1.71 - 1.66 (m, 4H) ppm **LCMS** (AM3): rt = 0.785 min, (537.2 $[M+H]^+$), 97.95% purity **Purification Method** PM292

EXAMPLE 87

6-(2-methoxypyridin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine

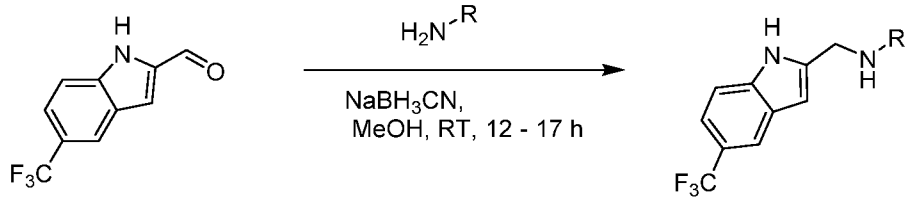


To a solution of **compound 2.001** (100 mg, 281.35 μmol) in MeOH (1 mL) was added 5-(trifluoromethyl)-1H-indole-2-carbaldehyde (CAS 1367793-79-0, 53.97 mg, 0.25 mmol). After 11 h, $NaBH_3CN$ (176.80 mg, 2.81 mmol) was added. The mixture was stirred at 25 °C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM315) to afford **EXAMPLE 87** (44.03 mg, 23.4% yield, TFA salt) as a yellow solid.

LCMS (AM3): rt = 0.849 min, (553.3 $[M+H]^+$), 99.7% purity.

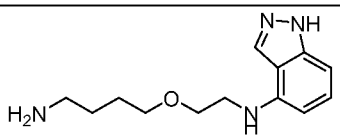
^{1}H NMR: (400 MHz, MeOH-d_4) δ: 8.17-8.15 (m, 2H), 7.84 (s, 1H), 7.52 - 7.50 (m, 1H), 7.40 - 7.39 (m, 1H), 7.33 - 7.32 (m, 1H), 7.14 (s, 1H), 7.10 (s, 1H), 6.68 (s, 1H), 6.46 (s, 1H), 4.26 (s, 2H), 3.99 (s, 3H), 3.77 - 3.74 (m, 2H), 3.59 - 3.53 (m, 4H), 3.10 - 3.06 (m, 2H), 1.85 - 1.77 (m, 2H), 1.74 - 1.68 (m, 2H) ppm

[00762] The following examples in Table 21 were made with non-critical changes or substitutions to the exemplified procedure in Example 87, that would be understood by one skilled in the art using 5-(trifluoromethyl)-1H-indole-2-carbaldehyde (CAS 1367793-79-0)



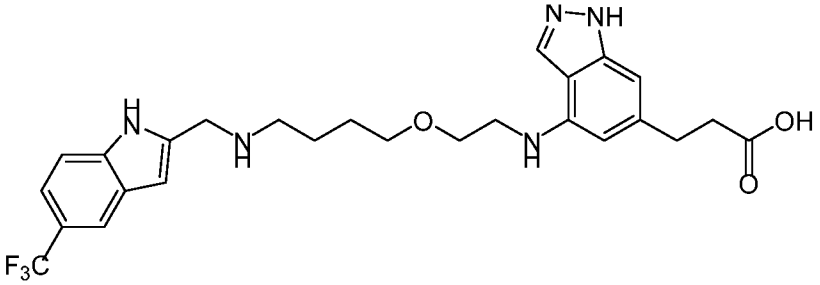
CAS 1367793-79-0

Table 21

Example No.	Chemical IUPAC name	H_2NR	Analytical
Example 94	N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino) butoxy)ethyl)-1H-indazol-4-amine	 **(Intermediate 2.356)**	**H NMR** (400 MHz, MeOH-d_4) δ 8.58 (s, 1H), 8.12 (s, 1H), 7.86 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.45 - 7.35 (m, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.63 (s, 1H), 6.20 (d, *J* = 7.6 Hz, 1H), 4.17 (s, 2H), 3.72 (t, *J* = 9.2 Hz, 2H), 3.56 (t, *J* = 8.8 Hz, 2H), 3.45 (t, *J* = 8.8 Hz, 2H), 3.00 - 2.91 (m, 2H), 1.84 - 1.62 (m, 4H) ppm **LCMS** (AM3): rt = 0.832 min, (446.3 $[M+H]^+$), 100.00% purity **Purification Method** PM316

EXAMPLE 89

3-(4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)propanoic acid



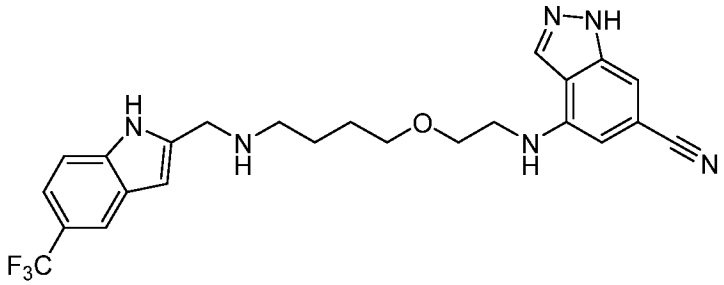
To a solution of **EXAMPLE 88** (50 mg, 94.06 μmol) in THF (1 mL) and water (1 mL) was added LiOH (5.63 mg, 235.15 μmol). The reaction was stirred at 20 °C for 1 h. The reaction mixture was acidified to pH = 7 by HCl (1N) and concentrated in *vacuo* to give a residue, which was purified (PM317) to afford **EXAMPLE 89** (13.69 mg, 26.45 μmol, 28.12% yield, 100% purity) as a red oil.

LCMS (AM3): rt = 0.838 min, (518.2 $[M+H]^+$), 100.00% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 10.74 (s, 1H), 8.13 (s, 1H), 7.64 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.24 (dd, *J* = 1.2, 8.4 Hz, 1H), 6.31 (s, 1H), 5.95 (s, 1H), 4.41 (s, 2H), 3.75 (t, *J* = 5.6 Hz, 2H), 3.59 (t, *J* = 5.6 Hz, 2H), 3.54 - 3.49 (m, 2H), 3.04 - 2.93 (m, 4H), 2.51 (t, *J* = 7.8 Hz, 2H), 1.82 - 1.67 (m, 4H) ppm

EXAMPLE 96

4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carbonitrile



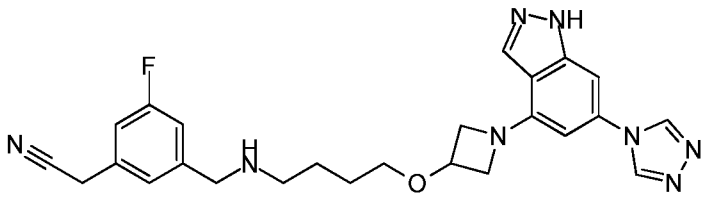
To a mixture of **compound 2.108** (30 mg, 45.28 μmol) in MeOH (2 mL) was added K_2CO_3 (12.52 mg, 90.57 μmol). The mixture was stirred at 60 °C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM318) to afford **EXAMPLE 96** (6.05 mg, 11.48 μmol, 25.35% yield, FA salt) as a yellow solid.

LCMS (AM3): rt = 0.854 min, (471.2 $[M+H]^+$), 98.1% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.51 (br s, 1H), 8.21 (d, *J* = 0.8 Hz, 1H), 7.86 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.40 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.14 (s, 1H), 6.70 (s, 1H), 6.35 (s, 1H), 4.28 (s, 2H), 3.70 (t, *J* = 5.6 Hz, 2H), 3.56 (t, *J* = 6.0 Hz, 2H), 3.49 - 3.44 (m, 2H), 3.09 - 3.03 (m, 2H), 1.83 - 1.77 (m, 2H), 1.71 - 1.68 (m, 2H) ppm

EXAMPLE 103

2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-fluorophenyl)acetonitrile

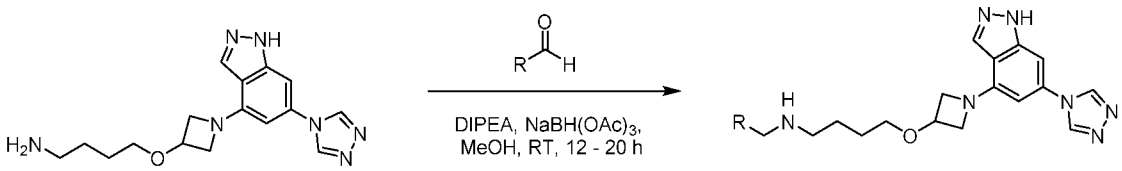


To a solution of **compound 2.221** (200 mg, 535.61 μmol) and 2-(3-Fluoro-5-formylphenyl)acetonitrile (Ref: WO2022185041, 87.38 mg, 535.61 μmol) in MeOH (2 mL) was added DIPEA (222.89 mg, 1.72 mmol). The mixture was stirred at 20 °C for 12 h, then $NaBH(OAc)_3$ (454.07 mg, 2.14 mmol) was added and the mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM319) to afford **EXAMPLE 103** (77.47 mg, 162.60 μmol, 30.36% yield) as a yellow gum.

LCMS (AM3): rt = 0.682 min, (475.2 $[M+H]^+$), 99.6% purity.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 9.13 (s, 2H), 8.08 (s, 1H), 7.16 (s, 1H), 7.13 (d, *J* = 9.6 Hz, 1H), 7.02 - 7.01 (m, 2H), 6.13 (d, *J* = 1.6 Hz, 1H), 4.48 - 4.44 (m, 1H), 4.41 (t, *J* = 6.8 Hz, 2H), 4.04 (s, 2H), 3.97 (dd, *J* = 8.8, 3.6 Hz, 2H), 3.69 (s, 2H), 3.43 - 3.41 (m, 2H), 2.47 - 2.46 (m, 2H), 1.59 - 1.54 (m, 2H), 1.51 - 1.46 (m, 2H) ppm

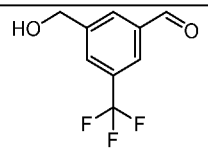
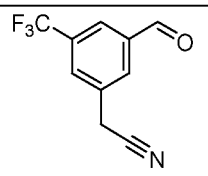
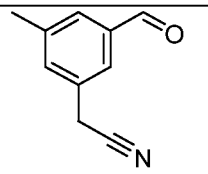
[00763] The following examples in Table 22 were made with non-critical changes or substitutions to the exemplified procedure for Example 103, that would be understood by one skilled in the art, using Intermediate 2.221

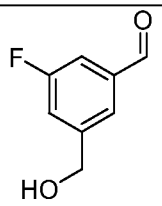
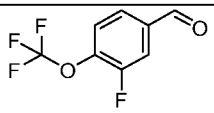
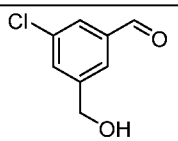


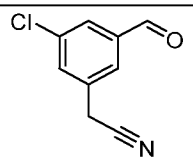
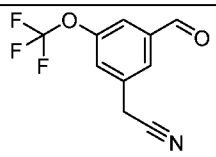
Intermediate 2.221

Table 22

Example No.	Chemical IUPAC name	Aldehyde Intermediate No./ CAS	Analytical

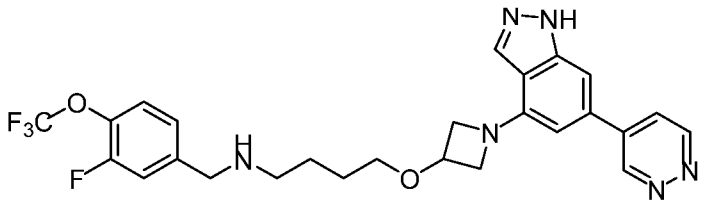
Example 104	(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)methanol	 3-(Hydroxymethyl)-5-(trifluoromethyl) benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.00 (s, 2H), 8.08 (d, *J* = 0.4 Hz, 1H), 7.58 - 7.55 (m, 3H), 7.01 - 6.99 (m, 1H), 6.11 (d, *J* = 1.6 Hz, 1H), 4.66 (s, 2H), 4.54 - 4.50 (m, 1H), 4.49 - 4.45 (m, 2H), 4.07 - 4.02 m, 2H), 3.83 (s, 2H), 3.54 - 3.49 (m, 2H), 2.63 (t, *J* = 6.8 Hz, 2H), 1.68 - 1.63 (m, 4H) **LCMS** (AM3): rt = 0.750 min, (516.2 $[M+H]^+$), 99.2% purity **Purification Method** PM320
Example 105	2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)acetonitrile	 2-(3-Formyl-5-(trifluoromethyl) phenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.99 (s, 2H), 8.08 (d, *J* = 0.8 Hz, 1H), 7.66 (s, 1H), 7.62 (s, 1H), 7.56 (s, 1H), 7.00 (s, 1H), 6.10 (d, *J* = 1.6 Hz, 1H), 4.52 - 4.50 (m, 1H), 4.47 (t, *J* = 7.2 Hz, 2H), 4.05 (dd, *J* = 8.4, 3.6 Hz, 2H), 3.85 (s, 2H), 3.52 (t, *J* = 5.6 Hz, 2H), 3.34 (s, 2H), 2.63 (t, *J* = 7.2 Hz, 2H), 1.68 - 1.65 (m, 4H) ppm **LCMS** (AM3): rt = 0.714 min, (525.3 $[M+H]^+$), 98.9% purity **Purification Method** PM321
Example 106	2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-methylphenyl)acetonitrile	 2-(3-Formyl-5-methylphenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.99 (s, 2H), 8.07 (d, *J* = 0.8 Hz, 1H), 7.12 (s, 2H), 7.04 (s, 1H), 7.01 - 6.99 (m, 1H), 6.10 (d, *J* = 1.6 Hz, 1H), 4.52 - 4.49 (m, 1H), 4.48 - 4.44 (m, 2H), 4.05 - 4.01 (m, 2H), 3.81 (s, 2H), 3.72 (s, 2H), 3.51 (t, *J* = 5.6 Hz, 2H), 2.62 (t, *J* = 6.8 Hz, 2H), 2.31 (s, 3H), 1.67 - 1.62 (m, 4H) ppm **LCMS** (AM3): rt = 0.694 min, (471.2 $[M+H]^+$), 100% purity **Purification Method** PM253

Example 125	(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-fluorophenyl)methanol	 3-Fluoro-5-(hydroxymethyl) benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.00 (s, 2H), 8.08 (s, 1H), 7.12 (s, 1H), 7.01 – 6.93 (m, 3H), 6.11 (d, *J* = 1.6 Hz, 1H), 4.58 (s, 2H), 4.54 – 4.42 (m, 3H), 4.09 – 4.01 (m, 2H), 3.76 (s, 2H), 3.52 (t, *J* = 5.6 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.70 – 1.60 (m, 4H) ppm **LCMS** (AM3): rt = 0.729 min, (466.2 $[M+H]^+$), 100% purity. **Purification method 1)** PM254 then **2)** PM255
Example 129	4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl) azetidine-3-yl)oxy)-N-(3-fluoro-4-(trifluoromethoxy) benzyl)butan-1-amine	 CAS 473917-15-6	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.00 (s, 2H), 8.08 (d, *J* = 0.8 Hz, 1H), 7.35 - 7.31 (m, 2H), 7.32 - 7.23 (m, 1H), 7.01 (s, 1H), 6.11 (d, *J* = 1.6 Hz, 1H), 4.53 - 4.46 (m, 3H), 4.06 (dd, *J* = 3.6Hz, J= 8.6 Hz, 2H), 3.77 (s, 2H), 3.54 - 3.50 (m, 2H), 2.63 - 2.59 (m, 2H), 1.67 - 1.63 (m, 4H) ppm **LCMS** (AM3): rt = 0.751 min, (520.2 $[M+H]^+$), 99.80% purity **Purification Method** PM280
Example 130	(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-chlorophenyl)methanol	 3-chloro-5-(hydroxymethyl) benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.00 (s, 2H), 8.08 - 8.07 (m, 1H), 7.27 - 7.22 (m, 3H), 7.01 - 6.99 (m, 1H), 6.11 - 6.09 (m, 1H), 4.56 (s, 2H), 4.51 - 4.44 (m, 3H), 4.06 - 4.02 (m, 2H), 3.74 (s, 2H), 3.51 (s, 2H), 2.63 - 2.59 (m, 2H), 1.65 (quin, *J* = 3.2 Hz, 4H) ppm **LCMS** (AM3): rt = 0.690 min, (482.1 $[M+H]^+$), 99.39% purity **Purification method 1)** PM322 **then 2)** PM323

Example 131	2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-chlorophenyl)acetonitrile	 2-(3-chloro-5-formylphenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz,MeOH-d_4) δ 9.00 (s, 2H), 8.08 (d, *J* = 1.2 Hz, 1H), 7.36 (t, *J* = 1.6 Hz, 1H), 7.29 - 7.26 (m, 1H), 7.26 - 7.23 (m, 1H), 7.03 - 6.98 (m, 1H), 6.11 (d, *J* = 1.6 Hz, 1H), 4.53 - 4.45 (m, 3H), 4.04 (dd, *J* = 8.4, 3.6 Hz, 2H), 3.76 (s, 2H), 3.54 - 3.49 (m, 2H), 3.34 - 3.32 (m, 2H), 2.64 - 2.58 (m, 2H), 1.68 - 1.61 (m, 4H) ppm **LCMS** (AM3): rt = 0.553 min, (491.1 $[M+H]^+$), 100% purity. **Purification Method** PM324
Example 147	2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile	 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400MHz, DMSO-d_6) δ 9.11 (s, 2H), 8.08 (s, 1H), 7.36 (s, 1H), 7.29 (s, 1H), 7.19 (s, 1H), 7.02 (s, 1H), 6.13 (s, 1H), 4.46 - 4.43 (m ,1H), 4.43 - 4.39 (m, 2H), 4.09 (s, 2H), 3.99 - 3.95 (m, 2H), 3.73 (s, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 2.49 (t, *J* = 6.4 Hz, 2H), 1.60 - 1.54 (m, 2H), 1.52 - 1.46 (m, 2H) ppm **LCMS** (AM3): rt = 0.767 min, (541.5 $[M+H]^+$), 98.6% purity **Purification Method** PM321

EXAMPLE 108

N-(3-fluoro-4-(trifluoromethoxy) benzyl)-4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl) azetidin-3-yl) oxy) butan-1-amine

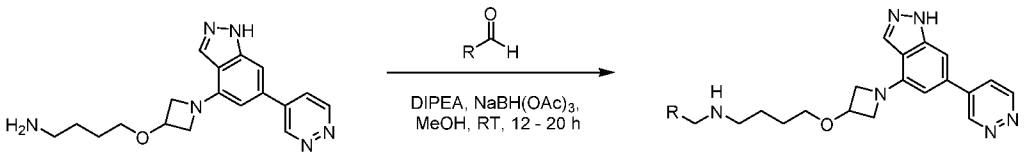


A mixture of compound **2.113** (200 mg, 591.01 μmol), 3-fluoro-4-(trifluoromethoxy)benzaldehyde (CAS 473917-15-6, 122.99 mg, 591.01 μmol) and DIPEA (229.14 mg, 1.77 mmol) in MeOH (3 mL) was stirred at 25°C for 1 h, then sodium triacetoxyborhydride (375.77 mg, 1.77 mmol) was added. The mixture was stirred at 25°C for 11 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM325) to afford **EXAMPLE 108** (20.82 mg, 38.46 μmol, 6.51% yield) as a yellow gum.

LCMS (AM3): rt = 0.612 min, (531.1 $[M+H]^+$), 98.8% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.53 (dd, *J* = 2.4, 1.2 Hz, 1H), 9.17 (dd, *J* = 5.6, 1.2 Hz, 1H), 8.06 (d, *J* = 1.2 Hz, 1H), 7.99 (dd, *J* = 5.6, 2.4 Hz, 1H), 7.38 - 7.29 (m, 2H), 7.28 - 7.17 (m, 2H), 6.26 (d, *J* = 1.2 Hz, 1H), 4.56 - 4.43 (m, 3H), 4.03 (dd, *J* = 8.4, 3.6 Hz, 2H), 3.78 (s, 2H), 3.55 - 3.48 (m, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.70 - 1.60 (m, 4H) ppm

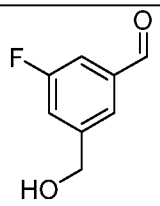
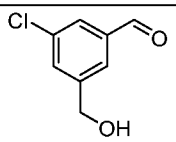
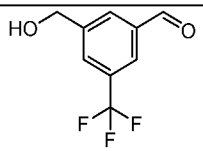
[00764] The following examples in Table 23 were made with non-critical changes or substitutions to the exemplified procedure for Example 108, that would be understood by one skilled in the art, using Intermediate 2.113

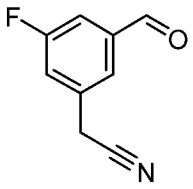
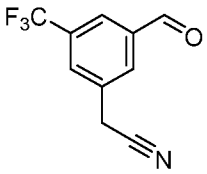
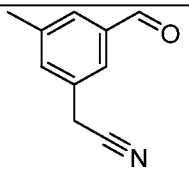


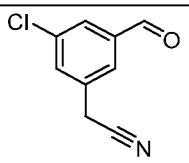
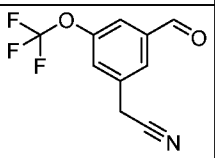
Intermediate 2.113

Table 23

Example No.	Chemical IUPAC name	Aldehyde Intermediate No./ CAS	Analytical

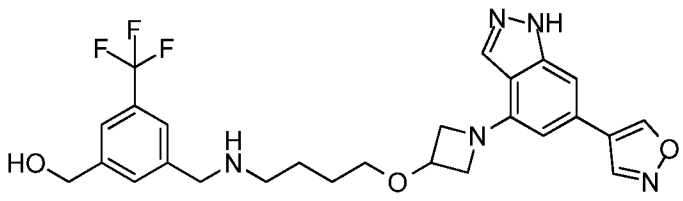
Example 110	(3-fluoro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol	 3-Fluoro-5-(hydroxymethyl)benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.55 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.19 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.07 (d, *J* = 0.8 Hz, 1H), 8.02 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.28 (s, 1H), 7.12 (s, 1H), 6.99 (t, *J* = 8.8 Hz, 2H), 6.29 (d, *J* = 1.2 Hz, 1H), 4.58 (s, 2H), 4.51 (s, 1H), 4.50 - 4.44 (m, 2H), 4.03 (dd, *J* = 3.6, 8.4 Hz, 2H), 3.79 (s, 2H), 3.56 - 3.49 (m, 2H), 2.70 - 2.61 (m, 2H), 1.69 - 1.61 (m, 4H) ppm **LCMS** (AM3): rt = 0.730 min, (477.3 $[M+H]^+$), 99.25% purity **Purification method 1)** PM303 **then 2)** PM326
Example 111	(3-chloro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol	 3-chloro-5-(hydroxymethyl)benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.53 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.18 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.55 (s, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 8.00 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.33 - 7.27 (m, 3H), 6.26 (d, *J* = 1.2 Hz, 1H), 4.57 (s, 2H), 4.53 - 4.44 (m, 3H), 4.01 (dd, *J* = 3.6, 8.4 Hz, 2H), 3.94 (s, 2H), 3.53 (t, *J* = 5.6 Hz, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 1.77 - 1.66 (m, 4H) ppm **LCMS** (AM3): rt = 0.754 min, (493.3 $[M+H]^+$), 99.32% purity **Purification method 1)** PM327 **then 2)** PM328
Example 112	(3-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)methanol	 3-(Hydroxymethyl)-5-(trifluoromethyl)benzaldehyde, (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.54 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.18 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 8.01 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.56 (d, *J* = 3.6 Hz, 3H), 7.27 (s, 1H), 6.27 (d, *J* = 1.2 Hz, 1H), 4.65 (s, 2H), 4.53 - 4.49 (m, 1H), 4.49 - 4.44 (m, 2H), 4.03 (dd, *J* = 4.0, 8.4 Hz, 2H), 3.83 (s, 2H), 3.55 - 3.48 (m, 2H), 2.63 (t, *J* = 6.8 Hz, 2H), 1.69 - 1.61 (m, 4H) ppm **LCMS** (AM11): rt = 0.770 min, (527.3 $[M+H]^+$), 100.00% purity **Purification method 1)** PM329 **then 2)** PM330

Example 113	2-(3-fluoro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile	 2-(3-Fluoro-5-formylphenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.18 (br s, 1H), 9.65 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.24 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.09 (s, 1H), 8.01 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.28 (s, 1H), 7.20 - 7.09 (m, 2H), 7.02 (d, *J* = 9.2Hz, 1H), 6.30 (d, *J* = 1.2 Hz, 1H), 4.50 - 4.39 (m, 3H), 4.04 (s, 2H), 3.97 (dd, *J* = 3.6, 8.4 Hz, 2H), 3.70 (s, 2H), 3.43 - 3.40 (m, 2H),2.49 - 2.47 (m, 2H), 1.61 - 1.46 (m, 4H) ppm **LCMS** (AM3): rt = 0.744 min, (486.2 $[M+H]^+$), 99.16% purity **Purification method 1)** PM329 then **2)** PM319
Example 114	2-(3-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)acetonitrile	 2-(3-Formyl-5-(trifluoromethyl)phenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.18 (br s, 1H), 9.65 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.24 (dd, *J* = 0.8, 5.6 Hz, 1H), 8.09 (s, 1H), 8.01 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.65 (d, *J* = 12.4 Hz, 2H), 7.56 (s, 1H), 7.28 (s, 1H), 6.30 (s, 1H), 4.50 - 4.39 (m, 3H), 4.15 (s, 2H), 3.97 (dd, *J* = 3.6, 8.4 Hz, 2H), 3.78 (s, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 2.49 - 2.48 (m, 2H), 1.61 - 1.47 (m, 4H) ppm **LCMS** (AM3): rt = 0.776 min, (536.2 $[M+H]^+$), 100.00% purity **Purification method 1)** PM327 **then 2)** PM331
Example 115	2-(3-methyl-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile	 2-(3-Formyl-5-methylphenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.65 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.24 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.09 (d, *J* = 0.8 Hz, 1H), 8.01 (dd, *J* = 2.8, 5.6 Hz, 1H), 7.28 (s, 1H), 7.08 (d, *J* = 4.8 Hz, 2H), 6.97 (s, 1H), 6.30 (d, *J* = 1.2 Hz, 1H), 4.49 - 4.38 (m, 3H), 3.97 (dd, *J* = 3.6, 8.4 Hz, 2H), 3.94 (s, 2H), 3.63 (s, 2H), 3.43 - 3.41 (m, 2H), 2.49 - 2.45 (m, 2H), 2.26 (s, 3H), 1.61 - 1.44 (m, 4H) ppm **LCMS** (AM3): rt = 0.764 min, (482.2 $[M+H]^+$), 100.00% purity **Purification method 1)** PM327 **then 2)** PM331

Example 133	2-(3-chloro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile	 2-(3-chloro-5-formylphenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.64 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.24 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.09 (s, 1H), 8.01 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.40 (s, 1H), 7.33 - 7.24 (m, 3H), 6.30 (d, *J* = 1.2 Hz, 1H), 4.49 - 4.40 (m, 3H), 4.05 (s, 2H), 3.97 (dd, *J* = 3.6, 8.4 Hz, 2H), 3.77 (s, 2H), 3.44 -3.41 (m, 2H), 2.56 (t, *J* = 6.4 Hz, 2H), 1.63 - 1.50 (m, 4H). ppm **LCMS** (AM3): rt = 0.570 min, (502.1 $[M+H]^+$), 97.10% purity **Purification Method** PM277
Example 134	2-(3-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile	 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.63 (br s, 1H), 9.24 (d, *J* = 5.2 Hz, 1H), 8.14 - 7.93 (m, 2H), 7.38 - 7.16 (m, 4H), 6.29 (s, 1H), 4.43 (d, *J* = 7.6 Hz, 3H), 4.08 (s, 2H), 3.97 (d, *J* = 4.8 Hz, 2H), 3.72 (s, 2H), 3.44 - 3.43 (m, 2H), 2.49 - 2.45 (m, 2H), 1.62 - 1.43 (m, 4H) ppm **LCMS** (AM3): rt = 0.600 min, (552.2 $[M+H]^+$), 100.00% purity **Purification Method** PM281

EXAMPLE 120

(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)methanol

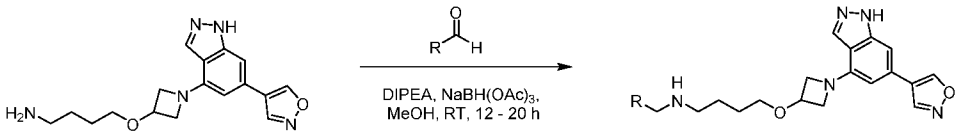


To a solution of **compound 2.115** (300 mg, 803.42 μmol) and 3-(Hydroxymethyl)-5-(trifluoromethyl)benzaldehyde (Ref: WO2022185041, 164.01 mg, 803.42 μmol) in MeOH (2 mL) was added DIPEA (311.50mg, 2.41 mmol). The mixture was stirred at 20 °C for 12 h, then $NaBH(OAc)_3$ (681.10 mg, 3.21 mmol) was added and the mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM205) to afford **EXAMPLE 120** (29.53 mg, 52.59 μmol, 6.55% yield, FA salt) as a brown solid.

LCMS (AM3): rt = 0.791 min, (516.3 $[M+H]^+$), 100% purity

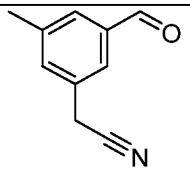
^{1}H NMR (400 MHz, MeOH-d_4) δ 9.07 (s, 1H), 8.85 (s, 1H), 8.48 (s, 1H), 7.98 (s, 1H), 7.72 (s, 3H), 7.08 (s, 1H), 6.19 - 6.14 (m, 1H), 4.69 (s, 2H), 4.53 - 4.48 (m, 1H), 4.46 - 4.41 (m, 2H), 4.26 (s, 2H), 3.98 (dd, *J* = 4.0, 8.0 Hz, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 3.10 (t, *J* = 8.0 Hz, 2H), 1.89 - 1.82 (m, 2H), 1.75 - 1.70 (m, 2H) ppm

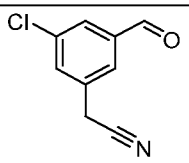
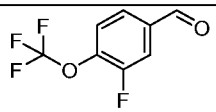
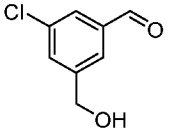
[00765] The following examples in Table 24 were made with non-critical changes or substitutions to the exemplified procedure for Example 120, that would be understood by one skilled in the art, using Intermediate 2.115

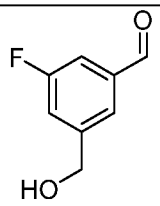
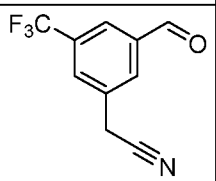
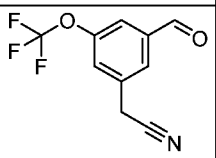


Intermediate 2.115

Table 24

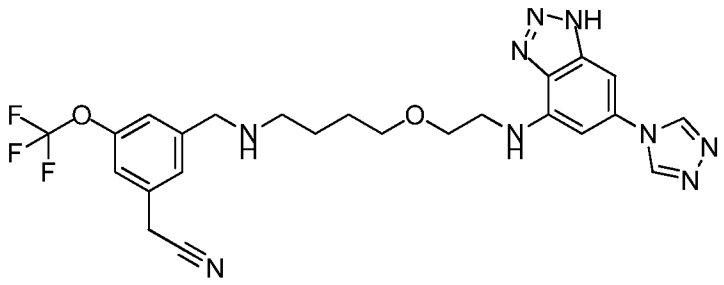
Example No.	Chemical IUPAC name	Aldehyde (Intermediate No./ CAS)	Analytical
Example 121	2-(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-methylphenyl) acetonitrile	 2-(3-Formyl-5-methylphenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.08 (s, 1H), 8.86 (s, 1H), 8.51 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.25 (d, *J* = 4.4 Hz, 2H), 7.18 (s, 1H), 7.11 - 7.08 (m, 1H), 6.18 (d, *J* = 1.2 Hz, 1H), 4.53 - 4.48 (m, 1H), 4.46 - 4.41 (m, 2H), 4.14 (s, 2H), 3.95 (dd, *J* = 4.0, 8.0 Hz, 2H), 3.84 (s, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 3.09 - 3.05 (m, 2H), 2.34 (s, 3H), 1.87 - 1.81 (m, 2H), 1.75 - 1.71 (m, 2H) ppm **LCMS** (AM3): rt = 0.788 min, (471.3 $[M+H]^+$), 100% purity **Purification Method** PM205

Example 122	2-(3-chloro-5-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile	 2-(3-chloro-5-formylphenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.08 (s, 1H), 8.85 (s, 1H), 8.48 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.50 (s, 1H), 7.42 (s, 2H), 7.10 (s, 1H), 6.18 (d, *J* = 1.2 Hz, 1H), 4.53 - 4.49 (m, 1H), 4.46 - 4.42 (m, 2H), 4.18 (s, 2H), 3.97 (dd, *J* = 8.4, 4.0 Hz, 2H), 3.91 (s, 2H), 3.56 (t, *J* = 6.0 Hz, 2H), 3.08 (t, *J* = 7.6 Hz, 2H), 1.87 - 1.83 (m, 2H), 1.75 - 1.72 (m, 2H) ppm **LCMS** (AM3): rt = 0.799 min, (491.2 $[M+H]^+$), 100% purity **Purification Method** PM205
Example 135	N-(3-fluoro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine	 CAS 473917-15-6	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.07 (s, 1H), 8.85 (s, 1H), 8.46 (s, 1H), 7.99 (d, *J* = 1.2 Hz, 1H), 7.51 - 7.46 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.09 (s, 1H), 6.18 (d, *J* = 1.2 Hz, 1H), 4.54 - 4.50 (m, 1H), 4.46 - 4.43 (m, 2H), 4.20 (s, 2H), 4.00 (dd, *J* = 8.4, 4.0 Hz, 2H), 3.56 (t, *J* = 6.0 Hz, 2H), 3.11 - 3.07 (m, 2H), 1.87 - 1.83 (m, 2H), 1.76 - 1.71 (m, 2H) ppm **LCMS** (AM3): rt = 0.820 min, (520.4 $[M+H]^+$), 100% purity **Purification Method** PM79
Example 136	(3-chloro-5-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol	 3-chloro-5-(hydroxymethyl)benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.44 (s, 1H), 9.17 (s, 1H), 8.21 (s, 1H), 8.00 (s, 1H), 7.31 (s, 1H), 7.26 (d, *J* = 4.4 Hz, 2H), 7.21 (s, 1H), 7.09 (s, 1H), 6.19 (s, 1H), 4.48 (s, 2H), 4.45 - 4.44 (m, 1H), 4.41 - 4.37 (m, 2H), 3.91 (dd, *J* = 8.4, 4.0 Hz, 2H), 3.82 (s, 2H), 3.44 - 3.41 (m, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 1.58 - 1.56 (m, 4H) ppm **LCMS** (AM3): rt = 0.771 min, (482.3 $[M+H]^+$), 100% purity **Purification Method** PM332

Example 138	(3-fluoro-5-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol	 3-Fluoro-5-(hydroxymethyl)benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.44 (s, 1H), 9.17 (s, 1H), 8.21 (s, 1H), 8.00 (s, 1H), 7.14 (s, 1H), 7.09-6.99 (m, 4H), 6.19 (s, 1H), 4.49 (s, 2H), 4.47-4.44 (m, 1H), 4.38 (t, *J* = 7.2 Hz, 2H), 3.91 (dd, *J* = 4.4, 8.4 Hz, 2H), 3.81 (s, 2H), 3.42 (s, 2H), 2.61 (t, *J* = 6.8 Hz, 2H), 1.57-1.53 (m, 4H) ppm **LCMS** (AM3): rt = 0.751 min, (466.3 $[M+H]^+$), 100% purity **Purification Method** PM227
Example 145	2-(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)acetonitrile	 2-(3-Formyl-5-(trifluoromethyl)phenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.08 (s, 1H), 8.85 (s, 1H), 8.47 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 7.09 (s, 1H), 6.18 (d, *J* = 0.8Hz, 1H), 4.53 - 4.50 (m, 1H), 4.46 - 4.43 (m, 2H), 4.27 (s, 2H), 4.03 (s, 2H), 3.98 (dd, *J* = 8.4, 4.0 Hz, 2H), 3.56 (t, *J* = 6.0 Hz, 2H), 3.11 - 3.07 (m, 2H), 1.87 - 1.81 (m, 2H), 1.75 - 1.72 (m, 2H) ppm **LCMS** (AM3): rt = 0.807 min, (525.3 $[M+H]^+$), 100% purity **Purification Method** PM205
Example 146	2-(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile	 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.07 (s, 1H), 8.85 (s, 1H), 8.45 (s, 1H), 7.98 (s, 1H), 7.51 (s, 1H), 7.43 (s, 1H), 7.34 (s, 1H), 7.09 (s, 1H), 6.17 (d, *J* = 0.8Hz, 1H), 4.51- 4.49 (m, 1H), 4.45 - 4.41 (m, 2H), 4.24 (s, 2H), 3.99 - 3.96 (m, 4H), 3.56 (t, *J* = 6.0 Hz, 2H), 3.10 (t, *J* = 8.0 Hz, 2H), 1.87 - 1.83 (m, 2H), 1.75 - 1.71 (m, 2H) ppm **LCMS** (AM3): rt = 0.816 min, (541.3 $[M+H]^+$), 100% purity **Purification Method** PM79

EXAMPLE 141

2-(3-(((4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile



To a solution of **compound 2.045** (300 mg, 704.65 μmol, HCl salt) and 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile (Ref: WO2022185041, 137.25 mg, 598.95 μmol) in DCE (3 mL) and MeOH (0.5 mL) was added DIPEA (273.21 mg, 2.11 mmol, 368.21 μL). The mixture was stirred at 25 °C for 15 h, then $NaBH_3CN$ (88.56 mg, 1.41 mmol) was added and the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM333) to afford a crude product. The product was further purified (PM334) to afford **EXAMPLE 141** (51.04 mg, 95.81 μmol, 13.60% yield) as a brown gum

LCMS (AM3): rt = 0.734 min, (530.1 $[M+H]^+$), 99.4% purity

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 2H), 7.35 (s, 1H), 7.29 (s, 1H), 7.20 (s, 1H), 7.14 (d, *J* = 1.6 Hz, 1H), 6.64 (t, *J* = 5.2 Hz, 1H), 6.58 (d, *J* = 1.6 Hz, 1H), 4.10 (s, 2H), 3.72 (s, 2H), 3.67 - 3.64 (m, 2H), 3.57 (d, *J* = 4.8 Hz, 4H), 2.49 - 2.45 (m, 2H), 1.59 - 1.51 (m, 2H), 1.50 - 1.43 (m, 2H)

[00766] The following examples in Table 25 were made with non-critical changes or substitutions to the exemplified procedure for Example 141, that would be understood by one skilled in the art, using 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile (WO2022185041)

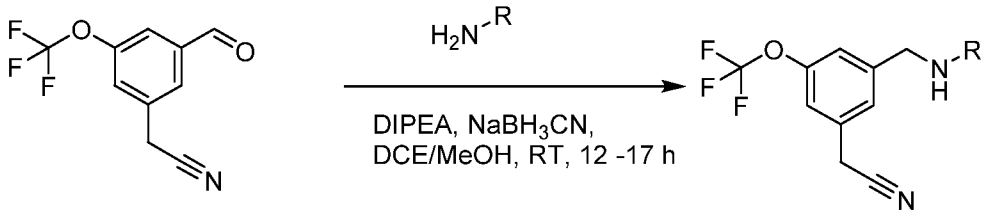
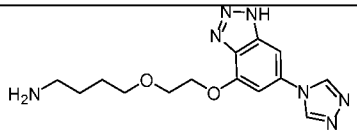
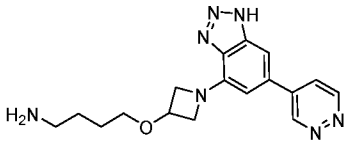


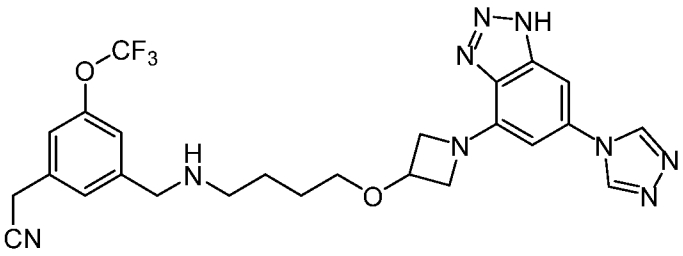
Table 25

Example No.	Chemical IUPAC name	H_2NR	Analytical

Example 148	2-(3-(((4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile	 **(Intermediate 2.347)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.17 (s, 2H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.39 (s, 1H), 7.35 (s, 1H), 7.23 (s, 1H), 7.05 (s, 1H), 4.47 (t, *J* = 4.0 Hz, 2H), 4.10 (s, 2H), 3.83 (s, 4H), 2.59 (t, *J* = 6.4 Hz, 2H), 2.53 - 2.51 (m, 2H), 1.60 - 1.49 (m, 4H) ppm **LCMS** (AM3): rt = 0.756 min, (531.3 $[M+H]^+$), 100.00% purity **Purification Method** PM335
Example 151	2-(3-(((4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile	 **(Intermediate 2.285)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.68 (dd, *J* = 1.2, 2.4 Hz, 1H), 9.27 (dd, *J* = 1.2, 5.6 Hz, 1H), 8.06 (dd, *J* = 2.4, 5.6 Hz, 1H), 7.48 (d, *J* = 1.2 Hz, 1H), 7.38 (s, 1H), 7.32 (s, 1H), 7.20 (s, 1H), 6.52 (d, *J* = 1.2 Hz, 1H), 4.58 - 4.52 (m, 2H), 4.52 - 4.47 (m, 1H), 4.11 (s, 2H), 4.10 - 4.06 (m, 2H), 3.77 (s, 2H), 3.44 (t, *J* = 6.0 Hz, 2H), 2.55 - 2.52 (m, 2H), 1.67 - 1.44 (m, 4H) ppm **LCMS** (AM3): rt = 0.747 min, (553.4 $[M+H]^+$), 99.19% purity **Purification Method** PM225

EXAMPLE 154

2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile



A mixture of 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile (Ref: WO2022185041, 108 mg, 471.30 μmol), **compound 2.304** (160 mg, 427.35 μmol, FA salt) and DIPEA (0.15 mL,

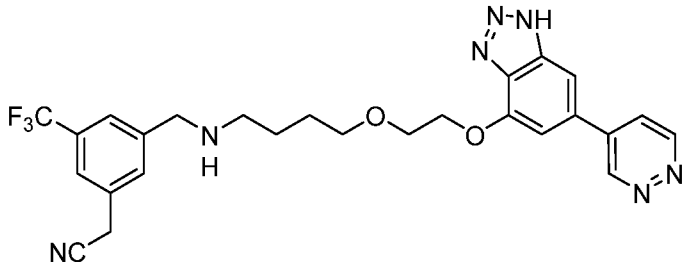
861.18 μmol) in MeOH (10 mL) was stirred at 25 °C for 16 h before $NaBH(OAc)_3$ (362 mg, 1.71 mmol) was added. The reaction mixture was stirred for 1 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM336) to afford **EXAMPLE 154** (33.18 mg, 14.07% yield) as a brown solid.

LCMS (AM3): rt = 0.789min, (542.2 $[M+H]^+$), 98.11% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 2H), 7.37 (s, 1H), 7.31 (s, 1H), 7.23 (s, 1H), 7.20 (s, 1H), 6.35 (s, 1H), 4.59 - 4.48 (m, 3H), 4.12 - 4.05 (m, 4H), 3.75 (s, 2H), 3.43 (t, *J* = 5.6 Hz, 2H), 2.52 - 2.50 (m, 2H), 1.66 - 1.55 (m, 2 H), 1.55 - 1.45 (m, 2H) ppm

EXAMPLE 155

2-(3-(((4-(2-((6-(pyridazin-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)acetonitrile



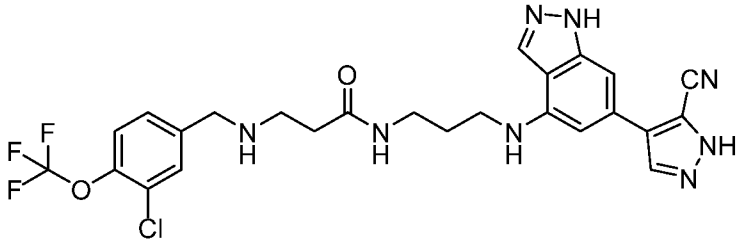
To a solution of **compound 2.367** (71.61 mg, 312.47 μmol) in MeOH (2 mL) was added DIPEA (85.02 mg, 657.84 μmol, 114.58 μL) and 2-(3-Formyl-5-(trifluoromethyl)phenyl)acetonitrile (Ref: WO2022185041, 120 mg, 328.92 μmol). The reaction was stirred at 20 °C for 12 h before $NaBH(OAc)_3$ (348.56 mg, 1.64 mmol) was added. The reaction was stirred at 25°C for 2 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM337) to afford **EXAMPLE 155** (63.63 mg, 116.33 μmol, 35.37% yield, 99% purity) as a yellow solid.

LCMS (AM3): rt = 0.761min, (542.5 $[M+H]^+$), 99.30% purity

^{1}H NMR (400 MHz,MeOH-d_4) δ 9.73 - 9.72 (m, 1H), 9.24 - 9.23 (m, 1H), 8.09 - 8.07 (m, 1H), 7.97 (s, 1H), 7.37 (s, 1H), 7.32 (s, 1H), 7.20 - 7.18 (m, 2H), 4.51 (t, *J* = 4.8 Hz, 2H), 4.09 (s, 2H), 3.82 (t, *J* = 4.4 Hz, 2H), 3.62 (s, 2H), 3.50 (t, *J* = 6.0 Hz, 2H), 2.55 - 2.50 (m, 2H), 1.59 - 1.52 (m, 4H) ppm

EXAMPLE 156

3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(5-cyano-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



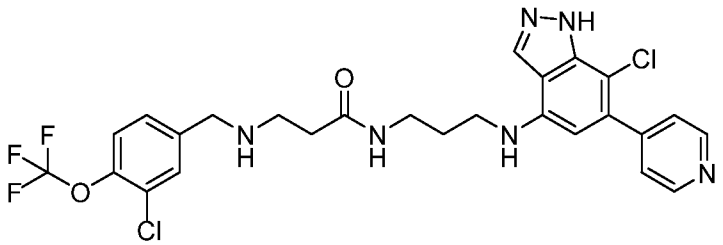
To a solution of **compound 2.226** (100 mg, 120.58 μmol) in DCM (5 mL) was added TFA (1 mL, 13.51 mmol) at 20 °C and the mixture was stirred for 2 h. Sat. $NaHCO_3$ (aq.) (40 mL) was added and the mixture was extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 15 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM235) to afford **EXAMPLE 156** (4.55 mg, 8.07 μmol, 6.37% yield) as a yellow solid.

LCMS (AM16): rt = 0.603 min, (561.2 $[M+H]^+$), 99.53% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.14 (d, *J* = 6.4 Hz, 2H), 7.53 (s, 1H), 7.31 (s, 2H), 7.07 (s, 1H), 6.45 (s, 1H), 3.73 (s, 2H), 3.37 (t, *J* = 6.4 Hz, 4H), 2.83 (t, *J* = 6.4 Hz, 2H), 2.42 (t, *J* = 6.8 Hz, 2H), 2.03 - 1.84 (m, 2H).

EXAMPLE 158

3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-chloro-6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



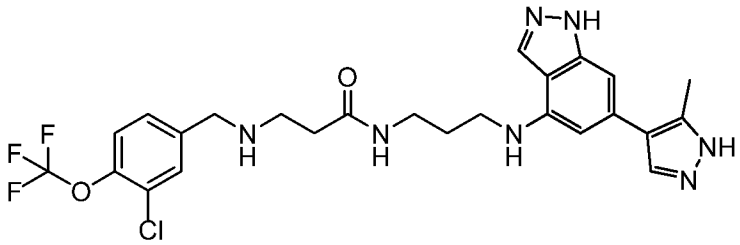
To a solution of **compound 2.249** (60 mg, 78.37 μmol) in DCM (3 mL) was added TFA (0.3 mL, 4.05 mmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was added to saturated sodium bicarbonate aqueous solution (10 mL) until pH = 9 and extracted with EA (10 mL × 3). The combined organic layers were washed (brine, 15 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM338) to afford **EXAMPLE 158** (16.62 mg, 28.19 μmol, 35.97% yield) as a white solid.

LCMS (AM11): rt = 0.314 min, (581.1 $[M+H]^+$), 98.61% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.62 - 8.57 (m, 2H), 8.24 (s, 1H), 7.60 - 7.50 (m, 3H), 7.31 (s, 2H), 6.12 (s, 1H), 3.72 (s, 2H), 3.36 - 3.31 (m, 4H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.38 (t, *J* = 6.4 Hz, 2H), 1.95 - 1.86 (m, 2H) ppm.

EXAMPLE 159

3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(5-methyl-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



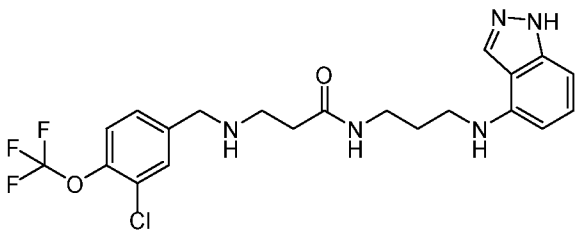
To a solution of **compound 2.252** (30 mg, 36.66 μmol) in DCM (3 mL) was added TFA (0.3 mL, 4.05 mmol) and the mixture was stirred at 25 °C for 1 hour. The reaction mixture was added to sat. $NaHCO_3$ (aq.) (10 mL) until pH = 9 and extracted with EA (10 mL × 3). The combined organic layers were washed (brine, 15 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM237) to afford **EXAMPLE 159** (8.22 mg, 14.30 μmol, 39.00% yield) as a yellow gum.

LCMS (AM11): rt = 0.330 min, (550.2 $[M+H]^+$), 95.66% purity.

^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (s, 1H), 7.70 (s, 1H), 7.52 (s, 1H), 7.30 (s, 2H), 6.78 (s, 1H), 6.23 (s, 1H), 3.71 (s, 2H), 3.40 - 3.33 (m, 4H), 2.81 (t, *J* = 6.8 Hz, 2H), 2.44 (s, 3H), 2.41 - 2.38 (m , 2H), 1.99 - 1.86 (m, 2H) ppm.

EXAMPLE 163

N-(3-((1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide



To a solution of **compound 2.390** (28 mg, 49.12 μmol) in DCM (10 mL) was added TFA (1 mL, 13.51 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into saturated $NaHCO_3$ (20mL) solution and extracted with EA (20 mL × 3). The combined organic phase was washed (brine, 20 mL × 3), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM339) to afford **EXAMPLE 163** (4.63 mg, 9.34 μmol, 19.02% yield, 94.8% purity) as a yellow gum.

LCMS (AM12): rt = 0.508 min, (470.2, $[M+H]^+$), 94.81% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.11 (s, 1H), 7.55 (s, 1H), 7.33 (s, 2H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.15 (d, *J* = 8.0 Hz, 1H), 3.75 (s, 2H), 3.37 - 3.32 (m, 4H), 2.83 (t, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 6.4 Hz, 2H), 1.95 -1.86 (m, 2H) ppm

[00767] The following examples in Table 26 were made with non-critical changes or substitutions to the exemplified procedure for Example 163, that would be understood by one skilled in the art.

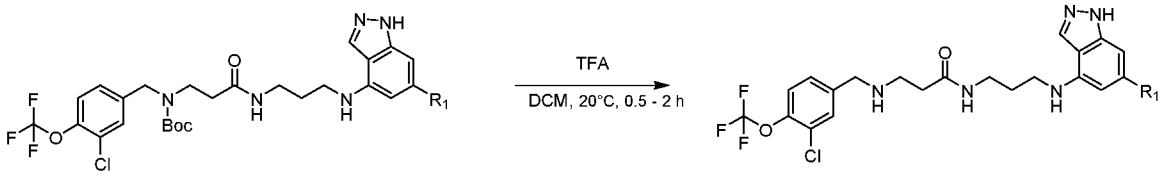
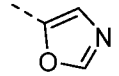
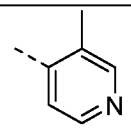


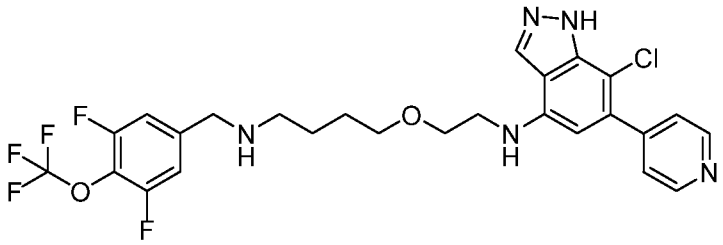
Table 26

Example No.	Chemical IUPAC name	R_1 (Intermediate)	Analytical
Example 164	3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(oxazol-5-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.389)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.87 (br s, 1H), 8.88 (br. s, 2H), 8.40 (s, 1H), 8.22 (t, *J* = 5.6 Hz, 1H), 8.18 (s, 1H), 7.86 (d, *J* = 1.6 Hz, 1H), 7.70 - 7.62 (m, 2H), 7.60 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.01 (s, 1H), 6.46 - 6.26 (m, 2H), 4.21 (s, 2H), 3.33 - 3.20 (m, 4H), 3.16 - 3.06 (m, 2H), 2.56 - 2.53 (m, 2H), 1.86 - 1.76 (m, 2H) ppm **LCMS** (AM12): rt = 0.438 min, (537.3 $[M+H]^+$), 99.58% purity **Purification Method** PM340

Example 165	3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-methylpyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.393)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.42 (s, 1H), 8.36 (d, J = 4.8 Hz, 1H), 8.18 (s, 1H), 7.54 (s, 1H), 7.35 - 7.26 (m, 3H), 6.68 (s, 1H), 6.06 (s, 1H), 3.73 (s, 2H), 3.38 - 3.33 (m, 4H), 2.81 (t, J = 6.8 Hz, 2H), 2.38 (t, J = 6.8 Hz, 2H), 2.31 (s, 3H), 1.95 - 1.86 (m, 2H) ppm **LCMS** (AM16): rt = 0.665 min, (561.2 $[M+H]^+$), 97.20% purity. **Purification Method** PM341

EXAMPLE 166

7-chloro-N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(pyridin-4-yl)-1H-indazol-4-amine



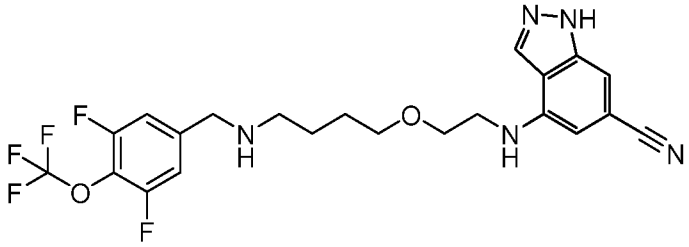
To a solution of **compound 2.255** (48 mg, 63.64 μmol) in DCM (3 mL) was added TFA (0.6 mL, 8.10 mmol). The mixture was stirred at 20°C for 1 h. The reaction mixture was poured into saturated $NaHCO_3$ aqueous solution (30 mL) and extracted with EA (30 mL × 3). The combined organic phases were washed by brine (30 mL × 2), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give a residue, which was purified (PM342) to afford **EXAMPLE 166** (20.71 mg, 35.12 μmol, 55.19% yield) as a white solid.

LCMS (AM11): rt = 0.319 min, (570.1 $[M+H]^+$),96.66% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.63 (d, J = 6.0 Hz, 2H), 8.25 (s, 1H), 7.60 - 7.58 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.20 (s, 1H), 3.79 (s, 2H), 3.72 (t, J = 5.6 Hz, 2H), 3.55 (t, J = 5.6 Hz, 2H), 3.48 (t, J = 5.6 Hz, 2H), 2.67 (t, J = 5.6 Hz, 2H), 1.78 - 1.59 (m, 4H) ppm.

EXAMPLE 167

4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carbonitrile



To a mixture of **compound 2.248** (30 mg, 44.93 μmol) in DCM (1 mL) was added TFA (0.3 mL, 4.05 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM343) to afford **EXAMPLE 167** (17.59 mg, 35.81 μmol, 79.70% yield) as an off-white solid.

LCMS (AM12): rt = 0.458 min, (484.3 $[M+H]^+$), 98.42% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.22 (s, 1H), 7.17 (s, 1H), 7.14 (d, *J* = 3.6 Hz, 2H), 6.37 (s, 1H), 3.72 - 3.69 (m, 4H), 3.53 (t, *J* = 6.4 Hz, 2H), 3.48 (t, *J* = 5.4 Hz, 2H), 2.58 (t, *J* = 6.4 Hz, 2H), 1.65 - 1.60 (m, 4H) ppm.

[00768] The following examples in Table 27 were made with non-critical changes or substitutions to the exemplified procedure for Example 167, that would be understood by one skilled in the art

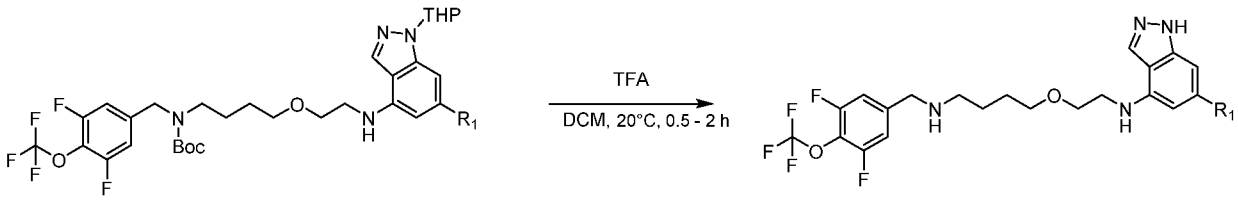
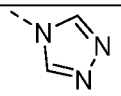
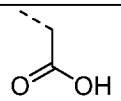


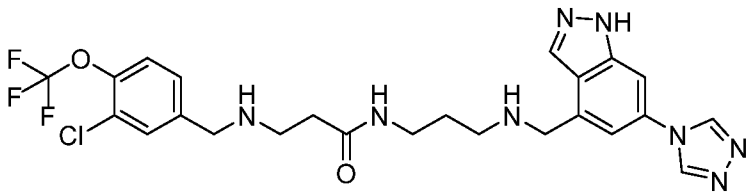
Table 27

Example No.	Chemical IUPAC name	R_1 (Intermediate)	Analytical

Example 171	4-(2-(((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)methyl)amino)ethoxy)-N-(3,5-difluoro-4-(trifluoromethoxy)benzyl)butan-1-amine	 **(Intermediate 2.490)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.05 (s, 2H), 8.33 (s, 1H), 7.73 (s, 1H), 7.40 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 4.22 (s, 2H), 3.75 (s, 2H), 3.57 (t, *J* = 4.0 Hz, 2H), 3.46 (t, *J* = 4.0 Hz, 2H), 2.85 (t, *J* = 5.2 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.62 - 1.56 (m, 4H) ppm **LCMS** (AM11): rt = 0.311 min, (540.2 $[M+H]^+$), 99.51% purity **Purification Method** PM344
Example 198	2-(4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)acetic acid	 **(Intermediate 1.3)**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.68 - 12.56 (m, 1 H), 12.37 - 12.00 (m, 1H), 8.81 - 8.73 (m, 2 H), 8.09 (s, 1 H), 7.54 (br d, *J* = 8.8 Hz, 2 H), 6.57 (s, 1 H), 6.22 - 6.06 (m, 1 H), 5.96 (s, 1 H), 4.16 (br s, 2 H), 3.62 (br t, *J* = 6.0 Hz, 2 H), 3.51 (s, 2 H), 3.46 (t, *J* = 6.0 Hz, 2 H), 2.99 - 2.93 (m, 2 H), 2.62 - 2.58 (m, 2H), 1.70 - 1.64 (m, 2 H), 1.62 - 1.57 (m, 2 H) ppm **LCMS** (AM11): rt = 0.374 min, (517.1 $[M+H]^+$), 96.05% purity **Purification method 1)** PM246 **then 2)** PM244

EXAMPLE 172

N-(3-(((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)methyl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide



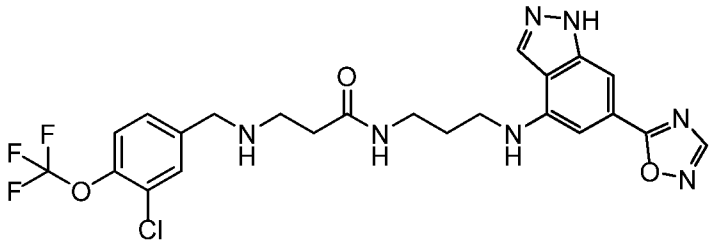
To a solution of **compound 2.489** (70 mg, 95.21 μmol) in DCM (5 mL) was added TFA (1 mL, 13.51 mmol). The mixture was stirred at 20 °C for 1 hour. The mixture was basified to pH = 8 by saturated $NaHCO_3$ aqueous solution and then concentrated in *vacuo* to give a residue, which was purified (PM248) to afford **EXAMPLE 172** (20.15 mg, 36.08 μmol, 37.90% yield) as a yellow gum.

LCMS (AM16): rt = 0.556 min, (551.2, $[M+H]^+$), 98.66% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.06 (s, 2H), 8.35 (d, *J* = 0.4 Hz, 1H), 7.73 (s, 1H), 7.56 (s, 1H), 7.40 (d, *J* = 1.2 Hz, 1H), 7.35 (s, 2H), 4.18 (s, 2H), 3.75 (s, 2H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 6.8 Hz, 2H), 2.72 (t, *J* = 6.8 Hz, 2H), 2.37 (t, *J* = 6.8 Hz, 2H), 1.76 (m, 2H) ppm

EXAMPLE 173

N-(3-((6-(1,2,4-oxadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide



To a solution of **compound -0** (35 mg, 44.98 μmol, 82% purity) in DCM (2 mL) was added TFA (0.4 mL, 5.40 mmol). The mixture was stirred at 20 °C for 0.5 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM345) to afford **EXAMPLE 173** (6.19 mg, 11.08 μmol, 24.63% yield) as a white solid.

LCMS (AM12): rt = 0.468 min, (538.2 $[M+H]^+$), 96.28% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.72 (s, 1H), 8.23 (s, 1H), 7.59 (s, 1H), 7.54 (s, 1H), 7.31 (d, *J* = 2.8 Hz, 2H), 6.84 (s, 1H), 3.77 (s, 2H), 3.41 - 3.37 (m, 4H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.45 (t, *J* = 6.8 Hz, 2H), 1.96 (t, *J* = 6.8 Hz, 2H) ppm.

[00769] The following examples in Table 28 were made with non-critical changes or substitutions to the exemplified procedure for Example 173, that would be understood by one skilled in the art

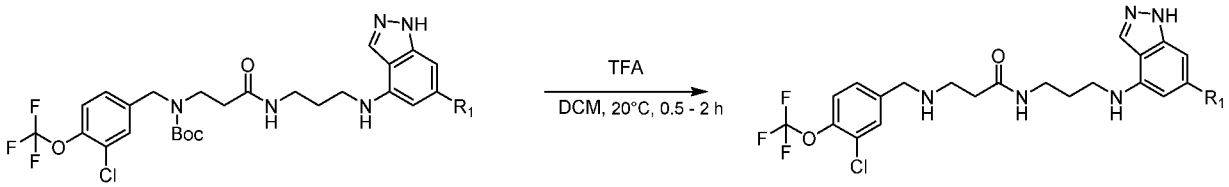
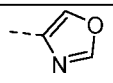
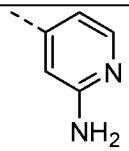
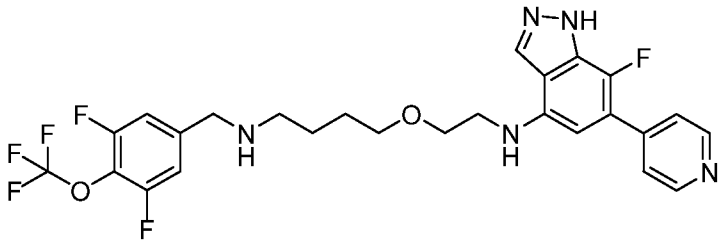


Table 28

Example No.	Chemical IUPAC name	R_1 (Intermediate)	Analytical
Example 175	3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(oxazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide	 **(Intermediate 2.341)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.31 (s, 1H), 8.26 (s, 1H), 8.11 (s, 1H), 7.75 (s, 1H), 7.53 (s, 2H), 7.20 (s, 1H), 6.55 (s, 1H), 4.25 (s, 2H), 3.40 (q, *J* = 6.8 Hz, 6H), 2.67 (t, *J* = 6.4 Hz, 2H), 1.96 (quin, *J* = 6.8 Hz, 2H) ppm **LCMS** (AM14): rt = 0.562 min, (537.3, $[M+H]^+$), 96.4% purity **Purification Method** PM346
Example 184	N-(3-((6-(2-aminopyridin-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide	 **(Intermediate 2.323)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.17 (s, 1H), 7.93 (d, *J* = 5.2 Hz, 1H), 7.54 (s, 1H), 7.32 (s, 2H), 7.00 (s, 1H), 6.92 (dd, *J* = 6.4, 1.6 Hz, 1H), 6.88 (s, 1H), 6.38 (s, 1H), 3.73 (s, 2H), 3.42 - 3.37 (m, 4H), 2.83 (t, *J* = 6.8, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 1.97 (t, *J* = 6.8 Hz, 2H) ppm **LCMS** (AM11): rt = 0.340 min, (562.2 $[M+H]^+$), 100% purity **Purification Method** PM347

EXAMPLE 176

N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-7-fluoro-6-(pyridin-4-yl)-1H-indazol-4-amine



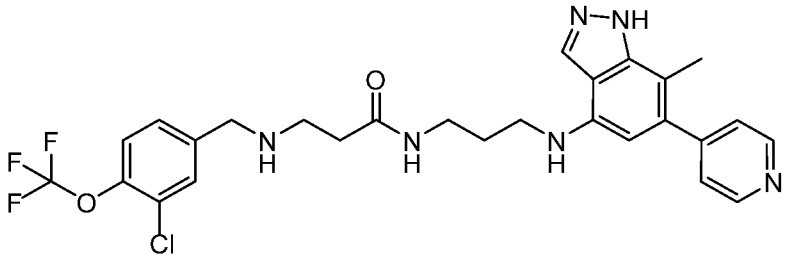
To a solution of **compound 2.264** (105 mg, 142.33 μmol) in DCM (6 mL) was added TFA (1 mL, 13.51 mmol) at 20 °C. The mixture was stirred at 20°C for 1 h. The reaction mixture was concentrated in *vacuo* below 30°C. The residue was diluted with MeOH (3 mL) and basified to pH=10 by NH_3•H_2O, then the resulting mixture was purified (PM348) to afford **EXAMPLE 176** (24.02 mg, 41.86 μmol, 29.41% yield) as a grey solid.

LCMS (AM12): rt = 0.397 min, (554.3 $[M+H]^+$), 96.47% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.62 - 8.57 (m, 2H), 8.22 (d, J = 3.2 Hz, 1H), 7.69 (d, J = 4.8 Hz, 2H), 7.16 - 7.13 (m, 2H), 6.18 (d, J = 4.4 Hz, 1H), 3.73 (t, J = 5.6 Hz, 2H), 3.70 (s, 2H), 3.53 (t, J = 6.0 Hz, 2H), 3.48 (t, J = 5.6 Hz, 2H), 2.56 (t, J = 6.8 Hz, 2H), 1.66 - 1.56 (m, 4H) ppm.

EXAMPLE 178

3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-methyl-6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



To a solution of **compound 2.026** (50 mg, 58.21 μmol, 86.753% purity) in DCM (1 mL) was added TFA (308.00 mg, 2.70 mmol, 0.2 mL) dropwise. The mixture was stirred at 20°C for 1 h. The mixture was concentrated in *vacuo* and adjusted to pH = 8 with DIPEA. The residue was purified (PM349) and (PM350) to afford **EXAMPLE 178** (4.76 mg, 8.38 μmol, 14.40% yield) as a yellow solid.

LCMS (AM3): rt = 0.750 min, (561.2 $[M+H]^+$), 98.752% purity.

^{1}H NMR (400 MHz, MeOH-d_4): δ 8.57 (d, J = 6.0 Hz, 2H), 8.43 (s, 1H), 8.17 (s, 1H), 7.67 (s, 1H), 7.46 - 7.45 (m, 1H), 7.44 (s, 2H), 6.04 (s, 1H), 4.04 (s, 2H), 3.77 - 3.33 (m, 2H), 3.29 - 3.27 (m, 2H), 3.09 (t, J = 6.4 Hz, 2H), 2.54 (t, J = 6.4 Hz, 2H), 2.31 (s, 3H), 1.90 (t, J = 6.4 Hz, 2H) ppm.

^{19}F NMR (400 MHz, MeOH-d_4): δ -59.571 ppm

[00770] The following examples in Table 29 were made with non-critical changes or substitutions to the exemplified procedure for Example 178, that would be understood by one skilled in the art

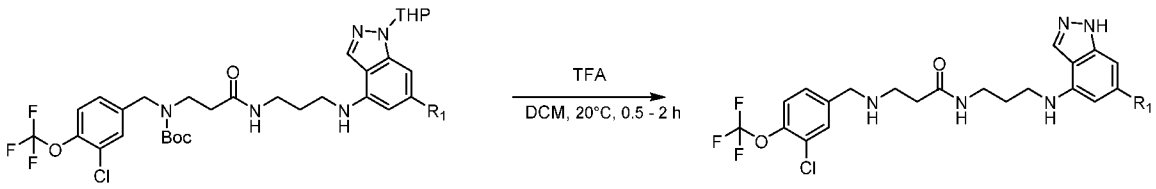
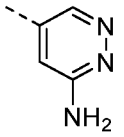
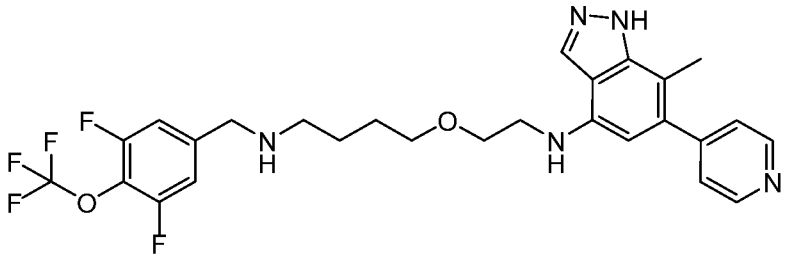


Table 29

Example No.	Chemical IUPAC name	R1 (Intermediate)	Analytical
Example 188	N-(3-((6-(6-aminopyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide	 **(Intermediate 2.027)**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.73 (d, J = 1.6 Hz, 1H), 8.18 (s, 1H), 7.53 (s, 1H), 7.30 (s, 2H), 7.17 (s, 1H), 7.05 (s, 1H), 6.35 (s, 1H), 3.74 (s, 2H), 3.41 - 3.33 (m, 4H), 2.83 (t, J = 6.8 Hz, 2H), 2.42 (t, J = 6.8 Hz, 2H), 1.95 (t, J = 6.8 Hz, 2H) ppm **LCMS** (AM3): rt = 0.733 min, (563.1 [M+H]$^+$), 99.725% purity. **Purification Method** PM351

EXAMPLE 179

N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-7-methyl-6-(pyridin-4-yl)-1H-indazol-4-amine



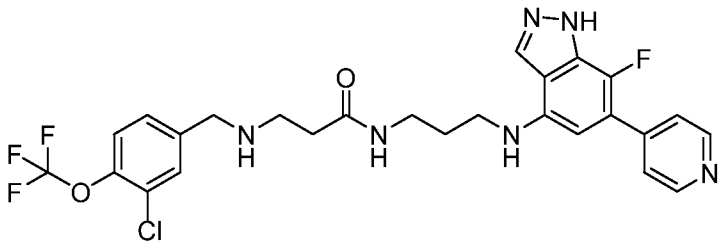
To a solution of **compound 2.382** (70 mg, 95.40 μmol) in DCM (1 mL) was added TFA (308.00 mg, 2.70 mmol, 0.2 mL). The reaction was stirred at 20°C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM352) to afford **EXAMPLE 179** (21.84 mg, 38.16 μmol, 40.00% yield) as a yellow solid.

LCMS (AM3): rt = 0.547 min, (550.1 [M+H]$^+$), 96.02% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.58 (dd, J = 4.8, 1.6 Hz, 2H), 8.16 (s, 1H), 7.46 (dd, J = 4.8, 1.6 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.10 (s, 1H), 3.88 (s, 2H), 3.72 (t, J = 5.2 Hz, 2H), 3.55 (t, J = 5.6 Hz, 2H), 3.44 (t, J = 5.2 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H), 2.32 (s, 3H), 1.69 - 1.67 (m, 4H) ppm.

EXAMPLE 180

3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-fluoro-6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



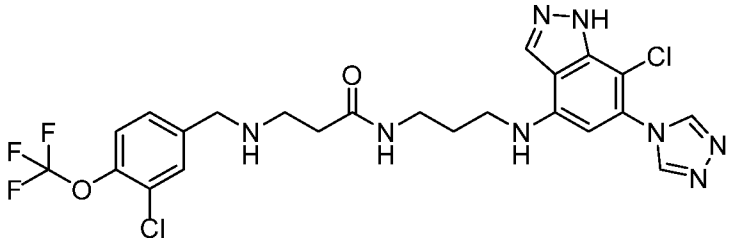
To a solution of **compound 2.320** (60 mg, 80.09 μmol) in DCM (5 mL) was added TFA (1 mL, 13.51 mmol). The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated in *vacuo* to give a residue, which was purified (PM353) to afford **EXAMPLE 180** (19.01 mg, 33.65 μmol, 42.02% yield) as a white solid.

LCMS (AM11): rt = 0.345 min, (565.0 $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.62 - 8.57 (m, 2H), 8.22 (d, *J* = 2.8 Hz, 1H), 7.71 - 7.66 (m, 2H), 7.54 (d, *J* = 0.8 Hz, 1H), 7.32 (d, *J* = 1.6 Hz, 2H), 6.11 (d, *J* = 4.8 Hz, 1H), 3.75 (s, 2H), 3.40 - 3.32 (m, 4H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.41 (t, *J* = 6.4 Hz, 2H), 1.97 - 1.86 (m, 2H) ppm.

EXAMPLE 181

3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-chloro-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



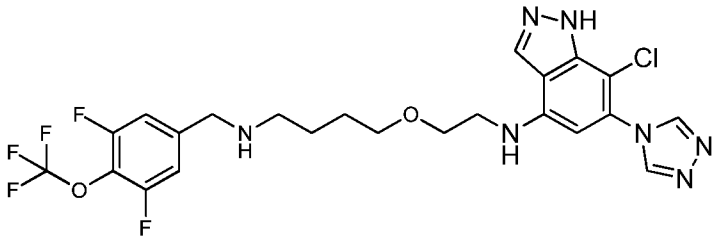
To a solution of **compound 2.322** (55 mg, 72.79 μmol) in DCM (6.8 mL) was added TFA (2.16 g, 18.91 mmol). The mixture was stirred at 20 °C for 2 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM354) to afford **EXAMPLE 181** (32.08 mg, 53.79 μmol, 73.89% yield) as a colourless gum.

LCMS (AM14): rt = 0.511 min, (571.2 $[M+H]^+$), 95.86% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.82 (s, 2H), 8.29 (s, 1H), 7.58 (s, 1H), 7.36 (s, 2H), 6.21 (s, 1H), 3.80 (s, 2H), 3.36 - 3.32 (m, 2H), 3.29 (s, 2H), 2.87 (t, *J* = 6.4 Hz, 2H), 2.42 (t, *J* = 6.8 Hz, 2H), 1.94 -1.87 (m, 2H) ppm.

EXAMPLE 182

7-chloro-N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine



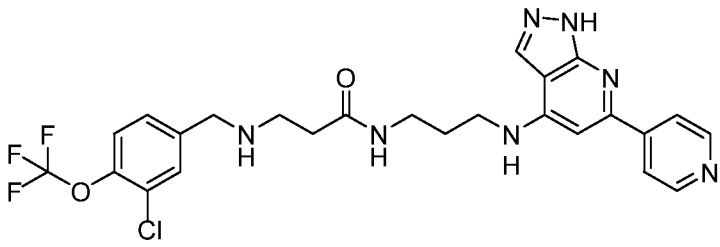
To a solution of **compound 2.376** (35 mg, 47.03 μmol) in DCM (6 mL) was added TFA (1.05 mL, 14.18 mmol). The mixture was stirred at 20 °C for 2 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM257) to afford **EXAMPLE 182** (16.42 mg, 29.33 μmol, 62.35% yield) as a white solid.

LCMS (AM12): rt = 0.436 min, (560.1 $[M+H]^+$), 100% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.83 (s, 2H), 8.30 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.30 (s, 2H), 3.73 - 3.68 (m, 4H), 3.52 (t, *J* = 5.6 Hz, 2H), 3.47 (t, *J* = 5.2 Hz, 2H), 2.56 (t, *J* = 6.8 Hz, 2H), 1.63 - 1.55 (m, 4H) ppm

EXAMPLE 185

3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)amino)propyl)propanamide



To a mixture of **compound 2.324** (180 mg, 277.75 μmol) in DCM (6 mL) was added TFA (0.6 mL, 8.1 mmol) at 20°C. The mixture was stirred at 20°C for 1 h. The mixture was concentrated

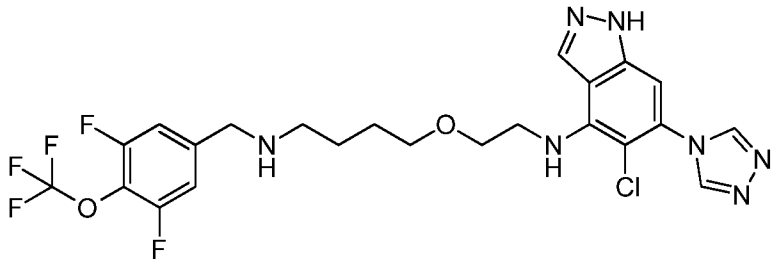
in *vacuo* to give a residue, which was purified (PM355) to afford **EXAMPLE 185** (14.47 mg, 25.87 μmol, 9.31% yield) as a white solid.

LCMS (AM11): rt = 0.314 min, (547.9 $[M+H]^+$), 97.95% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.64 (dd, *J* = 6.4 Hz, 1.6 Hz, 2H), 8.17 (s, 1H), 8.04 (dd, *J* = 4.8 Hz, 1.6 Hz, 2H), 7.55 (s, 1H), 7.33 (s, 2H), 6.77 (s, 1H), 3.75 (s, 2H), 3.53 (t, *J* = 6.8 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.03 - 1.92 (m, 2H) ppm.

EXAMPLE 186

5-chloro-N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine



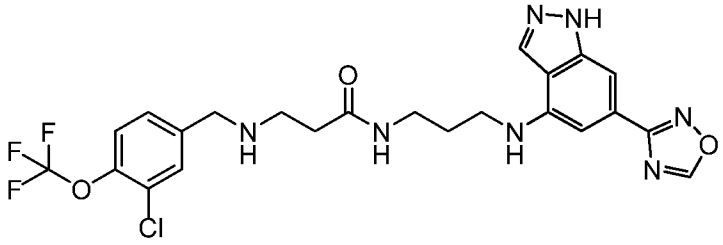
To a solution of **compound 2.396** (74 mg, 99.44 μmol) in DCM (5 mL) was added TFA (1 mL, 13.51 mmol). The mixture was stirred at 20 °C for 2 hours. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM193) to afford **EXAMPLE 186** (38.63 mg, 68.03 μmol, 68.41% yield) as a colourless gum.

LCMS (AM14): rt = 0.586 min, (560.2, $[M+H]^+$), 98.65% purity

^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (s, 2H), 8.37 (d, *J* = 0.8 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 0.8 Hz, 1H), 3.91 (t, *J* = 5.2 Hz, 2H), 3.75 (t, *J* = 6.8 Hz, 4H), 3.54 (t, *J* = 5.6 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 1.65 - 1.60 (m, 4H) ppm

EXAMPLE 189

N-(3-((6-(1,2,4-oxadiazol-3-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide



To a solution of **compound 2.038** (50 mg, 68.37 μmol, 87.25% purity) in DCM (2 mL) was added TFA (537.47 mg, 4.71 mmol, 349.00 μL). The mixture was stirred at 20°C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was adjusted to pH = 8 with DIPEA and then purified (PM356) to afford **EXAMPLE 189** (11.65 mg, 21.58 μmol, 31.56% yield) as a yellow oil.

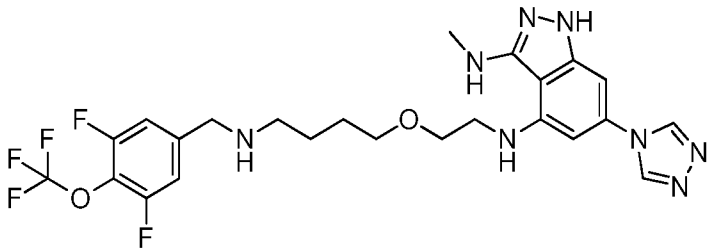
LCMS (AM3): rt = 0.792 min, (538.1 $[M+H]^+$), 99.62% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.24 (s, 1H), 8.19 (s, 1H), 7.53 (d, *J* = 2.0 Hz, 2H), 7.31 (d, *J* = 2.0 Hz, 2H), 6.83 (s, 1H), 3.76 (s, 2H), 3.39 - 3.36 (m, 4H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.44 (t, *J* = 6.8 Hz, 2H), 1.95 (t, *J* = 6.8 Hz, 2H) ppm.

^{19}F NMR (400 MHz, MeOH-d_4) δ -59.624 ppm.

EXAMPLE 190

N4-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-N3-methyl-6-(4H-1,2,4-triazol-4-yl)-1H-indazole-3,4-diamine



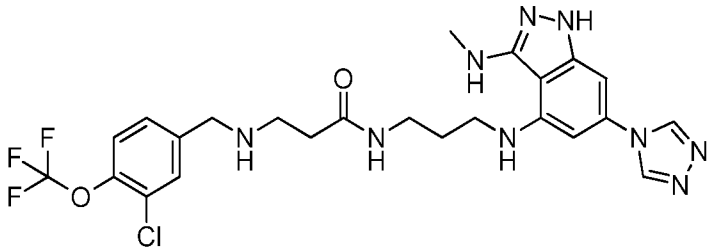
To a solution of **compound 2.499** (70 mg, 83.45 μmol) in DCM (5 mL) was added TFA (1 mL, 13.51 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was basified to pH = 8 by saturated $NaHCO_3$ aqueous solution and then concentrated in *vacuo* at to give a residue, which was purified (PM357) to afford **EXAMPLE 190** (75 mg, 75.50 μmol, 39.02% yield) as a brown gum.

LCMS (AM11): rt = 0.368 min, (555.3, $[M+H]^+$), 99.70% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.94 (s, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 1.6 Hz, 1H), 6.21 (d, *J* = 1.6 Hz, 1H), 3.74 (t, *J* = 4.2 Hz, 2H), 3.70 (s, 2H), 3.55 (t, *J* = 5.6 Hz, 2H), 3.42 (t, *J* = 4.2 Hz, 2H), 2.91 (s, 3H), 2.57 (t, *J* = 9.8 Hz, 2H), 1.65 - 1.60 (m, 4H) ppm.

EXAMPLE 191

3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((3-(methylamino)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide



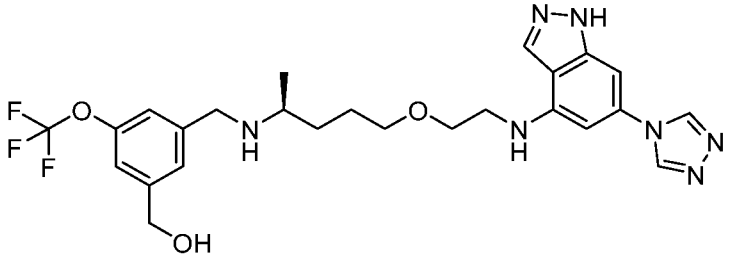
To a solution of **compound 2.500** (70 mg, 82.32 µmol) in DCM (5 mL) was added TFA (1 mL, 82.32 µmol). The mixture was stirred at 20 °C for 1 h. The mixture was basified to pH = 8 by $NaHCO_3$ (1 mL) aqueous solution. The resulting mixture was concentrated in *vacuo* to give a residue, which was purified (PM177) to afford **EXAMPLE 191** (13.38 mg, 22.90 µmol, 27.82% yield) as a brown gum.

LCMS (AM11): rt = 0.340 min, (566.1[M+H]+), 96.87% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.95 (s, 2H), 7.55 (s, 1H), 7.33 (s, 2H), 6.69 (d, *J* = 1.6 Hz, 1H), 6.15 (d, *J* = 1.2 Hz, 1H), 3.75 (s, 2H), 3.37 – 3.30 (m, 4H), 2.93 (s, 3H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 2H), 1.90 (t, *J* = 6.8 Hz, 2H) ppm.

EXAMPLE 192

(S)-(3-(((5-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol



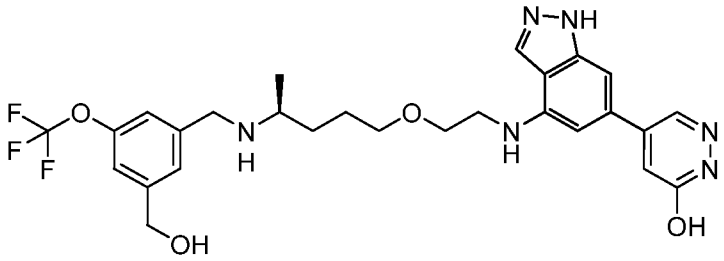
To a solution of **compound 2.432** (200 mg, 455.81 μmol, HCl salt) in MeOH (4 mL) was added 3-(Hydroxymethyl)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041, 200.69 mg, 911.61 μmol) and DABCO (255.64 mg, 2.28 mmol). The mixture was stirred at 20 °C for 1 h, then $NaBH_3CN$ (57.29 mg, 911.61 μmol) was added. The mixture was stirred at 20 °C for 12 h. The mixture was filtered and the filtrate was purified (PM250) to afford **EXAMPLE 192** (84.37 mg, 157.06 μmol, 34.46% yield) as a yellow solid.

LCMS (AM11): rt = 0.304 min, (534.3, $[M+H]^+$), 99.32% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.98 (s, 2H), 8.20 (s, 1H), 7.26 (s, 1H), 7.15 (br d, *J* = 5.2 Hz, 2H), 6.92 (s, 1H), 6.35 (d, *J* = 1.2 Hz, 1H), 4.61 (s, 2H), 3.78 - 3.68 (m, 4H), 3.52 (q, *J* = 5.6 Hz, 4H), 2.69 - 2.59 (m, 1H), 1.65 - 1.53 (m, 3H), 1.45 - 1.31 (m, 1H), 1.05 (d, *J* = 6.4 Hz, 3H) ppm

EXAMPLE 193

(S)-5-(4-((2-((4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)pentyl)oxy)ethyl)amino)-1H-indazol-6-yl)pyridazin-3-ol

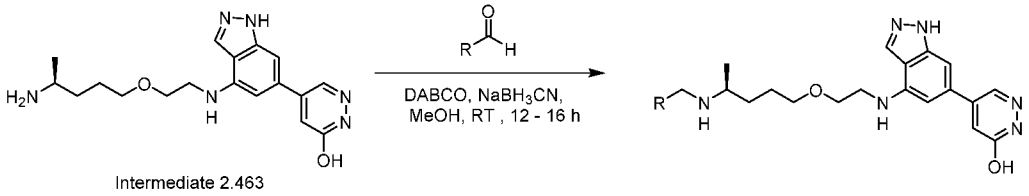


To a solution of **compound 2.463** (100 mg, 214.68 μmol, HCl salt) in MeOH (4 mL) was added 3-(Hydroxymethyl)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041, 94.52 mg, 429.36 μmol) and DABCO (168.57 mg, 1.50 mmol). The mixture was stirred at 20 °C for 1 h, then $NaBH_3CN$ (26.98 mg, 429.36 μmol) was added. The mixture was stirred at 20 °C for 12 h. The mixture was filtered and the filtrate was directly purified (PM370) and further purified (PM358) to afford **EXAMPLE 193** (31.11 mg, 38.81 μmol, 18.08% yield, TFA salt) as a yellow solid.

LCMS (AM12): rt = 0.406 min, (561.1, $[M+H]^+$), 98.38% purity.

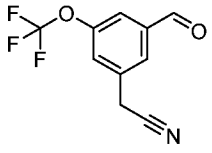
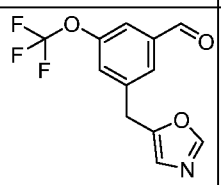
^{1}H NMR (400 MHz, MeOH-d_4) δ 8.33 (d, *J* = 2.0 Hz, 1H), 8.16 (s, 1H), 7.37 (s, 1H), 7.35 (s, 1H), 7.25 (s, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 7.10 (s, 1H), 6.46 (d, *J* = 0.8 Hz, 1H), 4.65 (s, 2H), 4.16 - 4.07 (m, 2H), 3.81 - 3.75 (m, 2H), 3.62 - 3.55 (m, 4H), 3.37 - 3.34 (m, 1H), 2.01 - 1.90 (m, 1H), 1.83 - 1.72 (m, 1H), 1.69 - 1.62 (m, 2H), 1.34 (d, *J* = 6.4 Hz, 3H) ppm

[00771] The following examples in Table 30 were made with non-critical changes or substitutions to the exemplified procedure for Example 193, that would be understood by one skilled in the art, using Intermediate 2.463



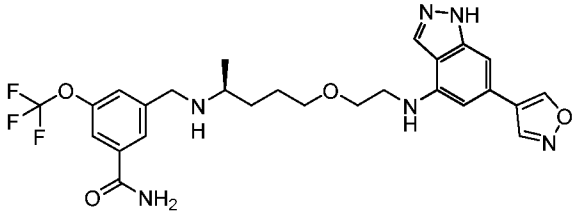
Intermediate 2.463

Table 30

Example No.	Chemical IUPAC name	Aldehyde (Intermediate No./ CAS)	Analytical
Example 194	(S)-2-(3-(((5-(2-((6-(6-hydroxypyridazin-4-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile	 2-(3-Formyl-5-(trifluoromethoxy)phenyl)acetonitrile (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.13 - 12.90 (m, 2H), 8.81 - 8.56 (m, 2H), 8.29 (d, J = 1.6 Hz, 1H), 8.23 (s, 1H), 7.52 (br d, J = 6.4 Hz, 2H), 7.43 (s, 1H), 7.09 (s, 1H), 7.05 (s, 1H), 6.59 - 6.40 (m,1H), 6.36 (s, 1H), 4.23 - 4.16 (m, 4H), 3.66 (t, J = 5.6 Hz, 2H), 3.48 (br t, J = 5.2 Hz, 4H), 3.27 - 3.22 (m,1H), 1.91 - 1.79 (m, 1H) 1.67 - 1.51 (m, 3H), 1.25 (d, J = 6.4 Hz, 3H) ppm **LCMS** (AM11): rt = 0.327 min, (570.1 $[M+H]^+$), 97.26% purity **Purification method** PM359
Example 195	(S)-5-(4-((2-((4-((3-(oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)pentyl)oxy)ethyl)amino)-1H-indazol-6-yl)pyridazin-3-ol	 3-(Oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 8.31 (d, J = 2.0 Hz, 1H), 8.18 (s, 1H), 8.09 (s, 1H), 7.18 (s, 1H), 7.13 (br d, J = 2.0 Hz, 2H), 7.08 (s, 1H), 7.04 (s, 1H), 6.88 (s, 1H), 6.43 (s, 1H), 4.05 (s, 2H), 3.75 - 3.63 (m, 4H), 3.52 (dt, J = 14.4, 5.6 Hz, 4H), 2.64 - 2.54 (m, 1H), 1.65 - 1.52 (m, 3H), 1.41 - 1.30 (m, 1H), 1.03 (d, J = 6.0 Hz, 3H) ppm **LCMS** (AM11): rt = 0.337 min, (612.4 $[M+H]^+$), 99.76% purity **Purification method** PM360

EXAMPLE 196

(S)-3-(((5-(2-((6-(isoxazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)benzamide



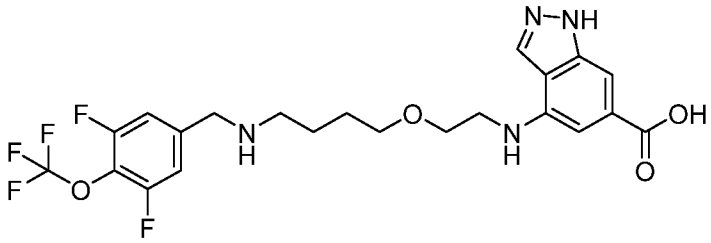
To a solution of **compound 2.468** (60 mg, 89.36 μmol, TFA salt) and 3-Formyl-5-(trifluoromethoxy)benzamide (Ref: WO2022185041, 27.08 mg, 116.16 μmol) in MeOH (4 mL) was added DABCO (50.12 mg, 446.78 μmol). The mixture was stirred at 20 °C for 1 h, then $NaBH_3CN$ (11.23 mg, 178.71 μmol) was added. The mixture was stirred at 20 °C for 1 h. The mixture was acidified to pH = 6 by 10% TFA aqueous solution and then directly purified (PM361) to afford **EXAMPLE 196** (21.63 mg, 27.41 μmol, 30.67% yield, 2 x TFA salt) as a brown gum.

LCMS (AM15): rt = 0.549 min, (547.2, $[M+H]^+$), 98.15% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (br s, 1H), 9.42 (s, 1H), 9.15 (s, 1H), 8.81 - 8.72 (m, 1H), 8.70 - 8.61 (m, 1H), 8.23 - 8.12 (m, 2H), 8.09 (s, 1H), 7.91 (s, 1H), 7.72 - 7.63 (m, 2H), 6.97 (s, 1H), 6.36 (s, 1H), 4.31 - 4.16 (m, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.30 - 3.19 (m, 2H), 2.59 - 2.52 (m, 2H), 2.48 - 2.42 (m, 1H), 1.88 - 1.77 (m, 1H), 1.70 - 1.60 (m, 1H), 1.59 - 1.47 (m, 2H), 1.25 (d, *J* = 6.8 Hz, 3H) ppm

EXAMPLE 197

4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxylic acid



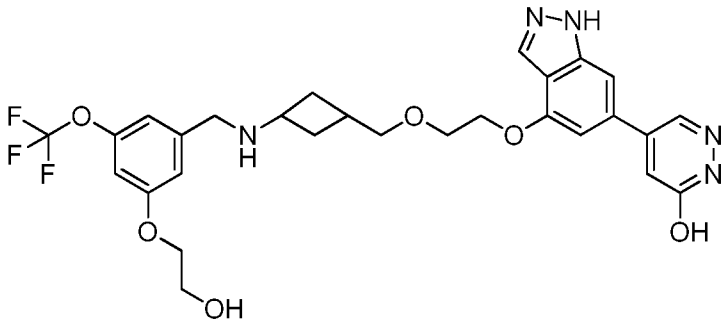
To a solution of **compound 2.512** (80 mg, 132.77 μmol) in DCM (4 mL) was added TFA (1.23 g, 10.80 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated in *vacuo* to give a residue, which was purified (PM362) to afford **EXAMPLE 197** (28.89 mg, 46.86 μmol, 35.30% yield, TFA salt) as a yellow solid.

LCMS (AM11): rt = 0.373 min, (503.5 $[M+H]^+$), 100.00% purity.

^{1}H NMR (400 MHz, MeOH-d_4) δ 8.17 (s, 1H), 7.52 (s, 1H), 7.29 (s, 1H), 7.27 (s, 1H), 6.85 (s, 1H), 4.10 (s, 2H), 3.75 (t, *J* = 5.6 Hz, 2H), 3.59 (t, *J* = 5.6 Hz, 2H), 3.53 (t, *J* = 5.2 Hz, 2H), 3.10 (t, *J* = 8.8 Hz, 2H), 1.83 (t, *J* = 7.60 Hz, 2H), 1.75 - 1.68 (m, 2H) ppm .

EXAMPLE 199

5-(4-(2-((3-((3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzyl)amino)cyclobutyl)methoxy)ethoxy)-1H-indazol-6-yl)pyridazin-3-ol

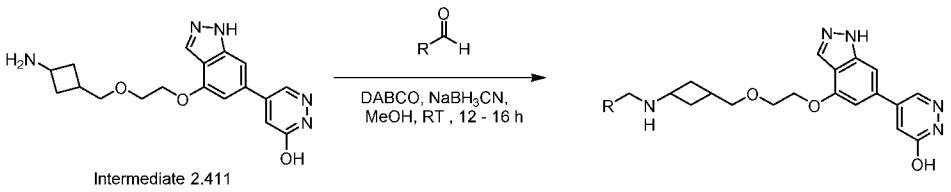


To a solution of **compound 2.411** (80 mg, 186.78 μmol, HCl salt) in MeOH (1 mL) was added DABCO (104.76 mg, 933.90 μmol) and 3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041, 46.73 mg, 186.78 μmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (23.48 mg, 373.56 μmol) was added and the mixture was stirred at 20 °C for 0.5 h. The reaction was acidified to pH = 5 by 20% TFA aqueous solution and filtered. The filtrate was purified (PM358) to afford compound **EXAMPLE 199** (45.09 mg, 64.09 μmol, 34.31% yield, TFA salt) as a yellow solid.

LCMS (AM11): rt = 0.349 min, (590.5, $[M+H]^+$), 100.00% purity.

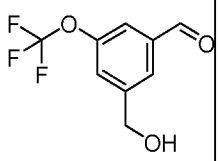
^{1}H NMR (400 MHz, MeOH-d_4) δ 8.41 - 8.35 (m, 1H), 8.11 (s, 1H), 8.51 (d, *J* = 4.0 Hz, 1H), 7.22 - 7.17 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 3.6 Hz, 1H), 6.92 (s, 1H), 6.86 (d, *J* = 13.2 Hz, 1H), 4.44 (d, *J* = 2.0 Hz, 2H), 4.11 - 4.02 (m, 4H), 3.97 (d, *J* = 2.4 Hz, 2H), 3.92 - 3.85 (m, 2.5 H), 3.75 - 3.70 (m, 0.5 H), 3.66 (dd, *J* = 25.8 Hz, 5.6 Hz, 2H), 3.72 - 3.61 (m, 0.5 H), 2.57 - 2.49 (m, 0.5 H), 2.48 - 2.41 (m, 1H), 2.40 - 2.71 (m, 2H), 2.15 - 2.02 (m, 1H) ppm.

[00772] The following examples in Table 31 were made with non-critical changes or substitutions to the exemplified procedure for Example 199, that would be understood by one skilled in the art, using Intermediate 2.411



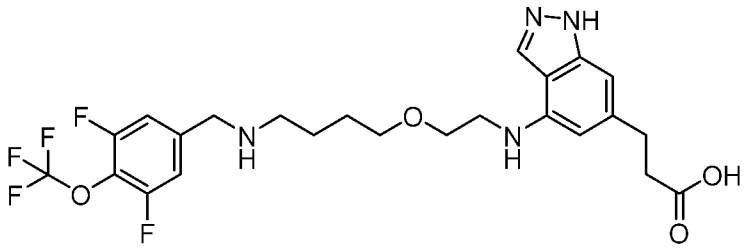
Intermediate 2.411

Table 31

Example No.	Chemical IUPAC name	Aldehyde (Intermediate No./ CAS)	Analytical
Example 200	5-(4-(2-((3-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)cyclobutyl)methoxy)ethoxy)-1H-indazol-6-yl)pyridazin-3-ol	 3-(Hydroxymethyl)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (MeOH-d_4, 400 MHz) δ 8.37 (d, *J* = 2.0 Hz, 1H), 8.11 (s, 1H), 7.50 (s, 1H), 7.40 (s, 1H), 7.34 (s, 1H), 7.30 (s, 1H), 7.22 - 7.15 (m, 1H), 6.85 (s, 1H), 4.65 (s, 2H), 4.43 (s, 2H), 4.12 (s, 2H), 3.97 (s, 2H), 3.76 - 3.59 (m, 3H), 2.72 - 2.49 (m, 1H), 2.48 - 2.30 (m, 2.5 H), 2.13 - 2.02 (m, 1.5H) ppm **LCMS** (AM11): rt = 0.343 min, (560.4 $[M+H]^+$), 99.10% purity **Purification method** PM264

EXAMPLE 201

3-(4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)propanoic acid



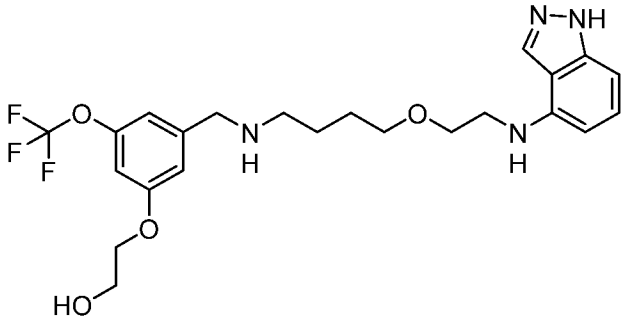
To a solution of **compound 2.515** (90 mg, 116.76 μmol) in DCM (9 mL) was added TFA (3 mL, 40.52 mmol), then the mixture was stirred at 20°C for 1 h. The reaction was concentrated in *vacuo* to give a residue, which was purified (PM362) to afford **EXAMPLE 201** (46.23 mg, 71.73 μmol, 61.43% yield, TFA salt) as a brown gum.

LCMS (AM11): rt = 0.369 min, (531.6, $[M+H]^+$), 100% purity

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (br s, 1H), 8.86 (s, 2H), 8.06 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 6.50 (s, 1H), 5.94 (s, 1H), 4.17 (t, *J* = 5.2 Hz, 2H), 3.62 (s, 2H), 3.46 (s, 2H), 3.36 - 3.33 (m, 2H), 2.96 (br s, 2H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.56 - 2.53 (m, 2H), 1.70 - 1.57 (m, 4H) ppm

EXAMPLE 202

2-(3-(((4-(2-((1H-indazol-4-yl)amino)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenoxy)ethan-1-ol



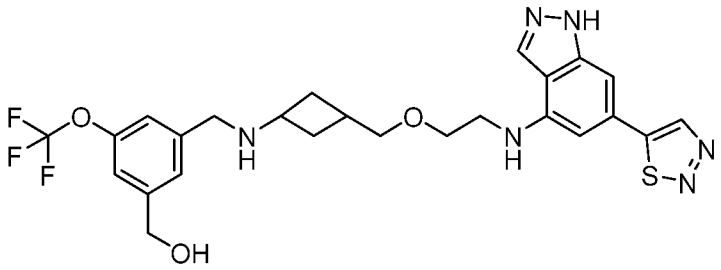
To a solution of 3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041, 48.96 mg, 195.69 μmol) in MeOH (1.5 mL) was added **compound 2.576** (70 mg, 195.69 μmol) and DABCO (109.75 mg, 978.46 μmol). The mixture was stirred at 20°C for 3 h, then $NaBH_3CN$ (43.04 mg, 684.92 μmol) was added. The resulting mixture was at for 20°C for 1 h. The reaction mixture was acidified to pH = 6 by 20% TFA aqueous solution and filtered. The filtrate was directly purified (PM363), then further purified (PM364) to afford **EXAMPLE 202** (1.8 mg, 3.72 μmol, 1.90% yield, 99.60% purity) as a yellow gum

LCMS (AM11): rt = 0.348 min, (483.3, $[M+H]^+$), 100% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (s, 1H), 8.14 (s, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.94 (s, 1H), 6.88 (s, 1H), 6.75 (s, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.14 (t, *J* = 5.2 Hz, 1H), 6.03 (d, *J* = 7.2 Hz, 1H), 4.86 (t, *J* = 5.2 Hz, 1H), 4.00 (t, *J* = 4.8 Hz, 2H), 3.72 - 3.68 (m, 2H), 3.67 (s, 2H), 3.59 (t, *J* = 5.6 Hz, 2H), 3.42 (t, *J* = 6.4 Hz, 4H), 2.48 - 2.46 (m, 2H), 1.58 - 1.52 (m, 2H), 1.48 - 1.43 (m, 2H).

EXAMPLE 203

(3-(((3-((2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)methyl)cyclobutyl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol

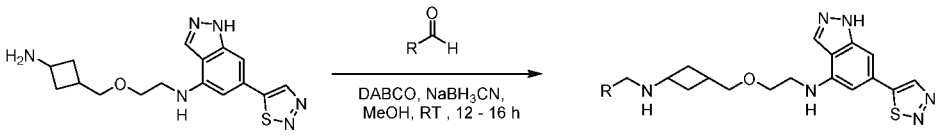


To a solution of **compound 2.529** (60 mg, 135.93 μmol) and 3-(hydroxymethyl)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041, 32.92 mg, 149.52 μmol) in MeOH (2 mL) was added DABCO (45.74 mg, 407.79 μmol) in one portion. The mixture was stirred at 25 °C for 12 h, then $NaBH_3CN$ (12.81 mg, 203.90 μmol) was added and the mixture was stirred at 25 °C for 1 h. The mixture was acidified to pH = 4 by 20% TFA aqueous solution and filtered. The filtrate was directly purified (PM359) to afford **EXAMPLE 203** (13.36 mg, 20.06 μmol, 14.75% yield, TFA salt) as a yellow solid.

LCMS (AM11): rt = 0.368 min, (549.3 $[M+H]^+$), 99.47% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.16 - 9.08 (m, 1H), 8.17 (s, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.28 (s, 1H), 7.16 (s, 1H), 6.52 - 6.40 (m, 1H), 4.67 - 4.63 (m, 2H), 4.13 - 3.99 (m, 2H), 3.83 - 3.76 (m, 2H), 3.68 (t, J = 7.6 Hz, 1H), 3.60 - 3.51 (m, 4H), 2.65 - 2.28 (m, 3.5H), 2.06 - 1.98 (m, 1.5H) ppm.

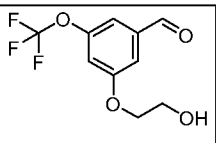
[00773] The following examples in Table 32 were made with non-critical changes or substitutions to the exemplified procedure for Example 203, that would be understood by one skilled in the art, using Intermediate 2.529



Intermediate 2.529

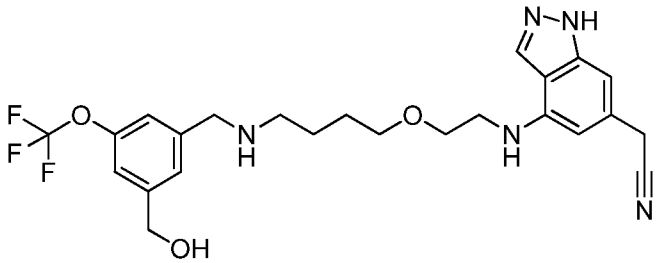
Table 32

Example No.	Chemical IUPAC name	Aldehyde (Intermediate No./ CAS)	Analytical

Example 205	2-(3-(((3-((2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)methyl)cyclobutyl)amino)methyl)-5-(trifluoromethoxy)phenoxy)ethan-1-ol	 3-(2-Hydroxyethoxy)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041)	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.19 - 12.86 (m, 1H), 9.41 (s, 1H), 8.25 (s, 1H), 7.11 (s, 1H), 6.92 (s, 1H), 6.85 (s, 1H), 6.74 (s, 1H), 6.62 - 6.55 (m, 1H), 6.39 (s, 1H), 4.99 - 4.77 (m, 1H), 3.99 (t, *J* = 4.8 Hz, 2H), 3.70 (t, *J* = 4.8 Hz, 2H), 3.66 - 3.60 (m, 2H), 3.59 - 3.52 (m, 2H), 3.47 - 3.43 (m, 2H), 3.39 (d, *J* = 6.0 Hz, 1H), 3.25 (s, 1H), 3.05 - 2.90 (m, 1H), 2.30 - 2.05 (m, 0.5H), 2.18 - 2.07 (m, 2H), 1.88 - 1.76 (m, 1H), 1.45 - 1.35 (m, 1.5H) ppm. **LCMS** (AM11): rt = 0.365 min, (579.2, $[M+H]^+$), 99.58% purity. **Purification method** PM365

EXAMPLE 204

2-(4-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)acetonitrile



To a solution of **compound 2.454** (100 mg, 194.02 μmol, TFA salt) in MeOH (2 mL) was added 3-(hydroxymethyl)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041, 46.98 mg, 213.42 μmol) and DABCO (76.17 mg, 679.08 μmol). The mixture was stirred at 20 °C for 1 h, then $NaBH_3CN$ (24.39 mg, 388.04 μmol) was added and the mixture was stirred at 20 °C for 0.5 h. The reaction mixture was acidified to pH = 5 by 20% TFA aqueous solution and filtered. The filtrate was directly purified (PM358) to afford **EXAMPLE 204** (13.02 mg, 20.79 μmol, 10.72% yield, TFA salt) as a brown gum.

LCMS (AM11): rt = 0.321 min, (492.1 $[M+H]^+$), 96.69% purity.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (br. s, 1H), 8.92 (s, 2H), 8.15 (s, 1H), 7.45 (s, 1H), 7.37 (s, 1H), 7.33 (s, 1H), 6.67 (s, 1H), 6.00 (s, 1H), 4.57 (s, 2H), 4.16 (t, *J* = 6.0 Hz, 2H), 3.97 (s, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 3.46 (t, *J* = 6.4 Hz, 2H), 3.36 (t, *J* = 5.6 Hz, 2H), 3.00 - 2.90 (m, 2H), 1.73 - 1.64 (m, 2H), 1.62 - 1.53 (m, 2H) ppm.

[00774] The following examples in Table 33 were made with non-critical changes or substitutions to the exemplified procedure for Example 204, that would be understood by one skilled in the art, using 3-(hydroxymethyl)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041)

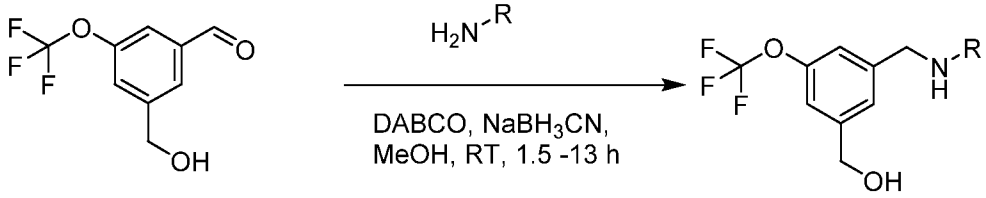
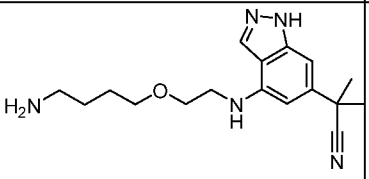
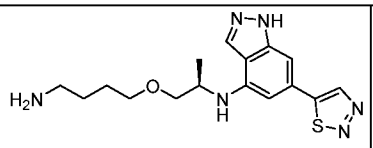


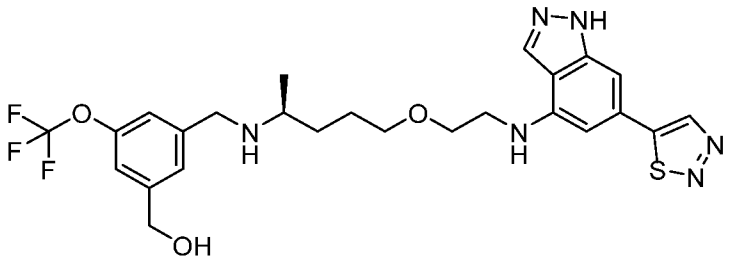
Table 33

Example No.	Chemical IUPAC name	H_2NR	Analytical
Example 206	2-(4-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)-2-methylpropanenitrile	 **Compound 2.537**	**^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.00 - 12.64 (m, 1H), 8.87 - 8.71 (m, 2H), 8.15 (s, 1H), 7.46 (s, 1H), 7.37 (s, 1H), 7.34 (s, 1H), 6.77 (s, 1H), 6.16 (d, *J* = 1.2 Hz, 1H), 4.57 (s, 2H), 4.21 - 4.11 (m, 2H), 3.64 (t, *J* = 5.6 Hz, 2H), 3.47 (t, *J* = 6.0 Hz, 2H), 3.41 (t, *J* = 6.0 Hz, 2H), 3.00 - 2.90 (m, 2H), 1.70 (s, 6H), 1.69 - 1.63 (m, 2H), 1.62 - 1.54 (m, 2 H) ppm. **LCMS** (AM22): rt = 0.795 min, (520.4, $[M+H]^+$), 99.54% purity. **Purification method 1)** PM366 **then 2)** PM367

Example 208	(R)-(3-(((4-(2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol	 **Compound 2.548**	**^{1}H NMR** (400 MHz, MeOH-d_4) δ 9.11 (s, 1H), 8.22 (s, 1H), 7.24 (s, 1H), 7.17 (s, 1H), 7.12 (s, 2H), 6.49 (s, 1H), 4.62 (s, 2H), 4.01 - 3.94 (m, 1H), 3.69 (s, 2H), 3.62 - 3.58 (m, 1H), 3.57 - 3.50 (m, 3H), 2.56 (t, J = 7.2 Hz, 2H), 1.61 - 1.58 (m, 4H), 1.33 (d, J = 6.4 Hz, 3H) ppm. **LCMS** (AM12): rt = 0.437 min, (551.4, $[M+H]^+$), 98.27% purity. **Purification method 1)** PM209 **then 2)** PM368

EXAMPLE 207

(S)-(3-(((5-(2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol



To a solution of **compound 2.531** (60 mg, 143.07 μmol, HCl salt) in MeOH (3 mL) was added 3-(hydroxymethyl)-5-(trifluoromethoxy)benzaldehyde (Ref: WO2022185041, 37.80 mg, 171.69 μmol) and DABCO (80.24 mg, 715.36 μmol). The mixture was stirred at 20 °C for 12 h, then $NaBH_3CN$ (26.97 mg, 429.21 μmol) was added. The mixture was stirred at 20 °C for 1 h. The mixture was filtered and the filtrate was purified (PM369) to afford **EXAMPLE 207** (30.79 mg, 55.44 μmol, 38.75% yield) as a yellow solid.

LCMS (AM22): rt = 0.438 min, (551.4, $[M+H]^+$), 99.14% purity

^{1}H NMR (400 MHz, MeOH-d_4) δ 9.12 (s, 1H), 8.17 (s, 1H), 7.24 (s, 1H), 7.16 (s, 1H), 7.13 (s, 2H), 6.47 (s, 1H), 4.60 (s, 2H), 3.77 - 3.65 (m, 4H), 3.53 (q, J = 5.6 Hz, 4H), 2.68 - 2.59 (m, 1H), 1.67 - 1.54 (m, 3H), 1.43 - 1.33 (m, 1H), 1.05 (d, J = 6.4 Hz, 3H) ppm

Biological assays

Assay 1: Biochemical assay for inhibitors of CK2α kinase activity

[00775] 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.

[00776] 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.

[00777] 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 RT 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 RT 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).

[00778] 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

[00779] 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

[00780] 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.

[00781] 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 h 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 $(MEAN_{0\%inhibition\ control\ wells}$ – test well reading) / $(MEAN_{0\%inhibition\ control\ wells} - MEAN_{100\%inhibition\ control\ wells})$ X 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™ assay for binding to intracellular CK2α (nM)
1	1.38	226.3	124.0
2	12.50	1234.0	5879.0
3	0.77	33.4	134.7
4	3.63	1009.0	241.8
5	2.15	306.5	239.9
6	0.19	235.1	50.8
7	0.25	69.8	146.4
8	0.62	1097.0	303.7
9	7.69	568.1	8550.0
10	6.96	132.5	449.0
11	0.29	31.7	249.3
12	0.60	612.4	6828.0
13	1.43	51.7	3894.0
14	1.60	322.4	2116.0
15	27.12	1833.0	>50000
16	14.12	371.0	3399.0
17	8.26	2781.0	3845.0
18	2.81	1623.0	4420.0
19	3.13	574.1	5069.0
20	23.51	157.7	3295.0
21	2.93	446.1	346.5
22	1.35	1122.0	363.0

23	19.91	86.1	17500.0
24	0.78	344.4	591.0
25	0.44	18.2	93.6
26	20.43	4462.0	875.2
27	0.95	56.4	321.6
28	0.54	107.0	70.6
29	22.14	648.9	2088.0
30	0.99	2562.0	816.5
31	0.32	526.4	753.4
32	0.47	75.9	17.7
33	0.48	77.8	452.2
34	3.32	70.8	9891.0
35	17.54	112.4	>50000
36	1.39	48.9	1396.0
37	0.78	30.7	959.8
38	0.53	121.2	791.7
39	0.28	63.3	2078.0
40	9.06	87.5	>50000
41	0.58	78.1	7622.0
42	6.94	83.8	>50000
43	0.62	38.4	20250.0
44	1.46	39.6	16760.0
45	0.95	123.4	6377.0
46	2.65	237.1	13360.0
47	2.65	133.3	11950.0
48	20.25	992.9	2746.0
49	0.44	90.5	106.2

50	2.20	94.0	152.8
51	0.71	224.8	72.1
52	1.43	38.4	294.1
53	0.33	118.5	158.7
54	1.44	217.2	128.4
55	1.25	4736.0	148.9
56	6.59	3150.0	387.0
57	0.60	781.0	69.8
58	0.28	40.9	9294.0
59	132.00	21840.0	>50000
60	215.20	30170.0	
61	103.60	3472.0	176.0
62	181.60	14270.0	29590.0
63	68.31	2370.0	4982.0
64	7.88	349.5	1845.0
65	163.10	4162.0	>50000
66	176.40	1004.0	15570.0
67	277.80	4160.0	13780.0
68	136.50	566.2	18660.0
69	46.63	688.0	2846.0
70	255.50	1520.0	>50000
71	1.37	415.9	2163.0
72	0.70	431.0	294.4
73	44.28	1957.0	742.7
74	19.66	10030.0	2128.0
75	0.89	403.5	76.5
76	2.64	18.6	735.2

77	5.71	95.7	>50000
78	471.90	>50000	>50000
79	0.33	406.6	5086.0
80	46.72	1918.0	8050.0
81	7.49	684.4	807.6
82	23.28	1868.0	2121.0
83	2.56	1091.0	2260.0
84	395.40	10490.0	36470.0
85	743.00	37060.0	>50000
86	6.36	1675.0	1351.0
87	12.33	1763.0	1296.0
88	>1000	41320.0	>50000
89	>1000	18380.0	>50000
90	212.10	8776.0	10550.0
91	4.17	979.3	4588.0
92	19.09	24.1	1777.0
93	0.77	568.8	179.8
94	202.60	5791.0	29250.0
95	6.56	203.2	335.8
96	26.99	226.8	1999.0
97	1.42	104.4	321.3
98	0.82	122.1	105.2
99	20.14	27990.0	1011.0
100	22.32	22920.0	1409.0
101	223.30	48610.0	>50000
102	392.60	42980.0	>50000
103	26.51	128.6	10660.0

104	64.16	264.0	14880.0
105	21.55	167.5	5335.0
106	41.69	368.1	26630.0
107	28.15	2638.0	3741.0
108	20.86	2734.0	2377.0
109	42.45	2918.0	2807.0
110	384.40	2721.0	20630.0
111	227.80	2304.0	14230.0
112	204.70	632.9	13980.0
113	67.51	2707.0	8088.0
114	50.53	2146.0	2524.0
115	115.20	6462.0	9907.0
116	246.70	>50000	>50000
117	3.00	1265.0	214.3
118	0.86	1105.0	204.4
119	22.65	616.7	1618.0
120	84.56	140.7	3248.0
121	44.91	209.1	3671.0
122	29.78	106.5	840.3
123	305.90	44740.0	>50000
124	7.44	133.7	1993.0
125	161.50	151.9	49220.0
126	11.05	18080.0	3631.0
127	5.06	1382.0	306.1
128	3.96	187.4	>50000
129	23.53	494.1	>50000
130	105.90	325.8	15370.0

131	28.08	146.2	3003.0
132	10.90	441.6	868.8
133	31.55	2041.0	3067.0
134	5.25	2676.0	808.9
135	13.33	230.1	1830.0
136	33.08	123.8	3351.0
137	13.04	332.7	2873.0
138	33.68	114.8	5923.0
139	10.88	498.3	2361.0
140	10.22	2025.0	2801.0
141	2.77	17830.0	2055.0
142	5.43	4791.0	3861.0
143	7.01	624.7	563.9
144	4.72	270.7	346.8
145	25.42	185.9	1726.0
146	8.18	152.2	299.1
147	8.80	299.8	528.0
148	138.50	>50000	>50000
149	255.10	15300.0	>50000
150	338.40	17680.0	39270.0
151	186.60	39800.0	19300.0
152	49.68	5821.0	>50000
153	136.40	11650.0	34250.0
154	170.40	24720.0	>50000
155	59.81	>50000	2957.0
156	0.64	71.0	107.6
157	9.06	1649.0	827.8

158	10.96	613.6	737.7
159	1.93	64.3	703.3
160	19.06	221.1	1106.0
161	2.02	667.1	193.5
162	6.53	806.7	402.2
163	216.90	6571.0	26780.0
164	2.98	242.1	134.5
165	72.87	7325.0	3736.0
166	21.30	783.3	2674.0
167	21.04	774.4	830.6
168	0.64	81.2	208.1
169	79.15	5682.0	6511.0
170	6.64	6390.0	>50000
171	45.28	23340.0	4898.0
172	125.70	44610.0	>50000
173	1.17	3175.0	361.2
174	7.41	5976.0	4638.0
175	10.67	1914.0	1239.0
176	5.99	331.8	216.9
177	56.18	1251.0	11730.0
178	23.89	1496.0	2540.0
179	42.73	1930.0	1453.0
180	3.68	190.3	100.0
181	17.03	447.9	11390.0
182	29.62	1824.0	5411.0
183	2.39	906.7	144.7
184	0.94	17.0	177.2

185	0.76	787.1	106.3
186	717.00	4751.0	>48880
187	8.62	4680.0	948.8
188	0.50	52.9	515.6
189	19.24	3496.0	1634.0
190	1.45	1102.0	74.0
191	0.57	132.6	842.0
192	10.63	664.8	377.1
193	1.21	354.9	87.1
194	0.76	194.8	14.9
195	0.41	226.8	21.4
196	12.40	300.5	54.7
197	>1000	>50000	>3000
198	72.63	>50000	>3000
199	21.51	1213.0	1941.0
200	38.16	594.1	2960.0
201	0.87	7831.0	141.7
202	216.00	23340.00	>3000
203	36.13	307.40	546.40
204	46.20	3442.00	405.20
205	12.72	213.90	467.50
206	63.85	2264.00	595.10
207	1.71	240.00	8.66
208	8.92	69.73	69.93

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CLAIMS

1. A compound of formula I, or a pharmaceutically acceptable salt, hydrate or solvate thereof:

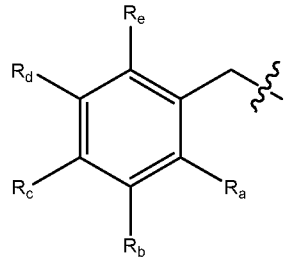
R_L-L-R_R

I

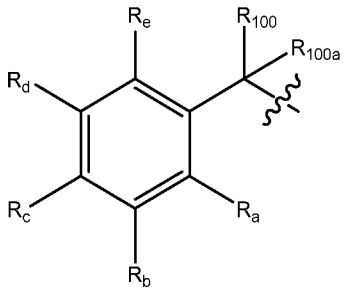
wherein:

L is linker that separates R_L from R_R by 7 to 13 bond lengths;

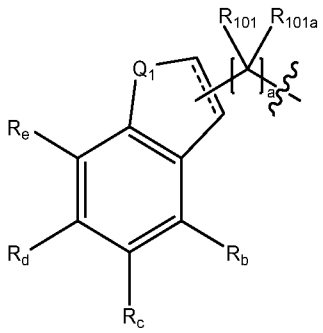
R_L is selected from one of formulae Ic, Id, Ie, If, Ig, Ih, Ii, Ij or Ik shown below:



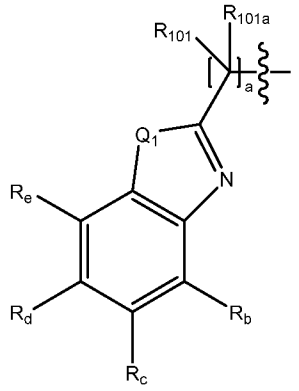
Ic



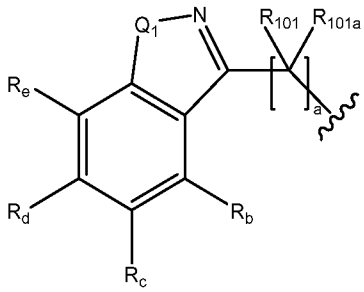
Id



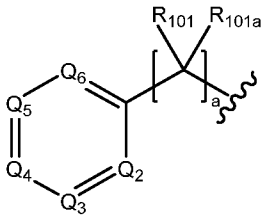
Ie


R101
R101a
a
Q1
N
Re
Rd
Rb
Rc

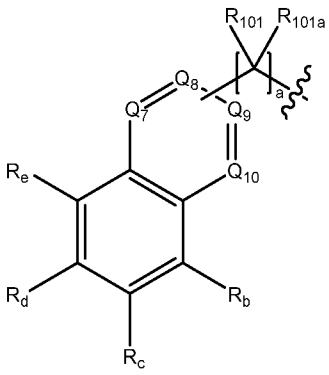
If


Q1
N
R101
R101a
a
Re
Rd
Rb
Rc

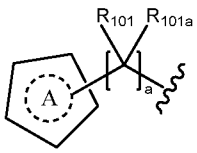
Ig


R101
R101a
a
Q6
Q5
Q4
Q3
Q2

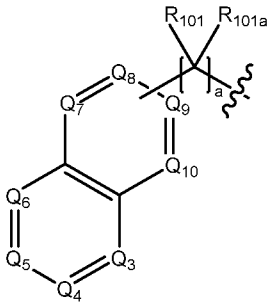
Ih


R101
R101a
a
Q8
Q7
Q9
Q10
Re
Rd
Rb
Rc

Ii


R101
R101a
a
A

Ij



(Ik)

wherein:

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

R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, (3-6C)cycloalkyl,

$-[CH_2]_{0-3}$-(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]$_2$,

$-[CH_2]_{0-3}-NH_2$,

$-[CH_2]_{0-3}$-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)OH,

$-[CH_2]_{0-3}$-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),

$-[CH_2]_{0-3}-S(O)_2NH$(1-4C)alkyl,

$-[CH_2]_{0-3}-S(O)_2N$[(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, cycloalkyl or -[CH_2]- 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, (3-6C)cycloalkyl

-[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_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)OH,

-[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),

$-[CH_2]_{0-3}-S(O)_2NH(1\text{-}4C)alkyl$,

$-[CH_2]_{0-3}-S(O)_2N[(1\text{-}4C)alkyl]_2$,

$-[CH_2]_{0-3}-N(R_i)SO_2-(1\text{-}4C)alkyl$ (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, cycloalkyl or $-[CH_2]-$ 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, $-C(O)NH(1\text{-}2C)alkyl$, $-C(O)N[(1\text{-}2C)alkyl]_2$, $-NH(1\text{-}2C)alkyl$, $-N[(1\text{-}2C)alkyl]_2$, $-S(O)_q-(1\text{-}2C)alkyl$ (wherein q is 0, 1 or 2), $-C(O)(1\text{-}2C)alkyl$, $-C(O)O-(1\text{-}2C)alkyl$, $-N(R_f)C(O)-(1\text{-}2C)alkyl$, $-S(O)_2NH(1\text{-}2C)alkyl$, $-S(O)_2N[(1\text{-}2C)alkyl]_2$, or $-NHSO_2-(1\text{-}2C)alkyl$, 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_{100} is (1-2C)alkyl optionally substituted by hydroxy or halo;

R_{100a} is selected from hydrogen or methyl;

or R_{100} and R_{100a} are linked to form a cyclopropyl or cyclobutyl ring;

R_{101} is hydrogen or (1-2C)alkyl optionally substituted by hydroxy or halo;

R_{101a} is selected from hydrogen or methyl;

or R_{101} and R_{101a} are linked to form a cyclopropyl or cyclobutyl ring;

integer a is 0, 1 or 2;

Q_1 is selected from $-NR_{102}-$, -O-, -S- or -CH-;

R_{102} is hydrogen or (1-2C)alkyl;

------ represents a single or double bond;

Q_2 is N or CR_a;

Q_3 is N or CR_b;

Q_4 is N or CR_c;

Q_5 is N or CR_d;

Q_6 is N or CR_e;

R_a, R_b, R_c, R_d and R_e are each as defined above;

with the proviso that one to three of Q_2, Q_3, Q_4, Q_5 or Q_6 is/are N;

Q_7 is N or CR_f;

Q_8 is N or CR_f;

Q_9 is N or CR_f;

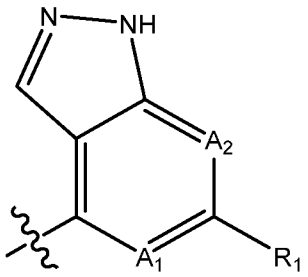
Q_{10} is N or CR_f;

with the proviso that one or two of Q_7, Q_8, Q_9 or Q_{10} is/are N;

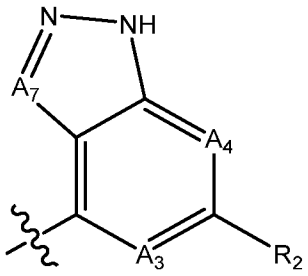
each R_f present is independently selected from hydrogen, methyl or halo;

Ring A is a five-membered heteroaryl ring optionally substituted by one R_b and/or one or two R_c substituents;

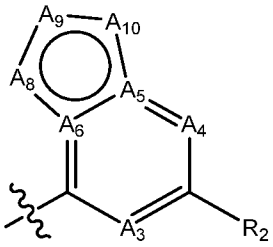
R_R is selected from one of formulae Im, In or Io shown below:



Im



In



Io

wherein:

~~~ denotes the point of attachment;

A_1 and A_2 are both CH; or one of A_1 and A_2 is N and the other is CH;

R_1 is a 5- or 6-membered heteroaryl ring which is optionally substituted on any available carbon atom by one or more R_{1A} substituent groups and on any available nitrogen atom by one or more R_{1B} substituent groups; and wherein:

each R_{1A} group present is selected from hydroxy, cyano, amino, halo, -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 (wherein R_f is hydrogen or methyl), -$S(O)_2$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];

and R_{1B} is (1-2C)alkyl or (3-4C)cycloalkyl;

A_3 is selected from CH, CR_3 or N;

A_4 is selected from CH, CR_4 or N;

A_5 and A_6 are both C, or one of A_5 and A_6 is N and the other is C;

A_7 is selected from CH, CR_7 or N;

R_2 is selected from:

(iii) a group R_1 defined above;

(iv) hydrogen, halo, cyano, (1-4C)alkyl, (1-4C)cyanoalkyl, (1-4C)hydroxyalkyl, (1-4C)haloalkyl, (1-4C)aminoalkyl,
-$[CH_2]_{0-3}$-(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)OH,
-$[CH_2]_{0-3}$-C(O)O-(1-4C)alkyl,
-$[CH_2]_{0-3}$-N(R_{2a})C(O)-(1-4C)alkyl (wherein R_{2a} 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_{2b})SO$_2$-(1-4C)alkyl (wherein R_{2b} is hydrogen or methyl),
a 4- to 7-membered heterocyclyl,
(3-6C)cycloalkyl,
(3-6C)cycloalkyl(1-2C)alkyl,
phenyl, or
phenyl(1-2C)alkyl;
and wherein any cycloalkyl, heterocyclyl or phenyl group present is optionally substituted by one or more hydroxy, cyano, amino, halo, -C(O)OH, -C(O)NH$_2$, (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, -C(O)O-(1-2C)alkyl, -N(R_f)C(O)-(1-2C)alkyl (wherein R_f is hydrogen or methyl), -S(O)$_2$NH(1-2C)alkyl, -S(O)$_2$N[(1-2C)alkyl]$_2$, or -NHSO$_2$-(1-2C)alkyl;

R_3 is selected from fluoro, chloro, methyl, methoxy or cyano;

R_4 is selected from fluoro, chloro, methyl, methoxy or cyano;

R_7 is selected from methyl, -NH(1-2C)alkyl or -NH(3-4C)cycloalkyl;

and wherein R_2 is not a group R_1 when A_3, A_4 and A_7 are all CH and A_5 and A_6 are C;

A_8 is selected from CH, CR_8, O, S, NH or N;

A_9 is selected from CH, CR_9, O, S, NH or N;

A_{10} is selected from CH, CR_{10}, O, S, NH or N;

R_8, R_9 and R_{10} are selected from methyl, amino, -NH(1-2C)alkyl or -NH(3-4C)cycloalkyl;

and wherein:

(i) only one of A_8, A_9 and A_{10} can be NH;

(ii) one to four of A_5, A_8, A_9 and A_{10} or A_6, A_8, A_9 and A_{10} can be N

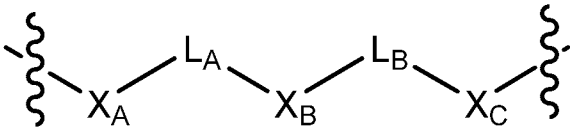
(iii) only one of A_8, A_9 or A_{10} can be O or S;

(iv) when one of A_8, A_9 or A_{10} are O or S, A_5 and/or A_6 cannot be N.

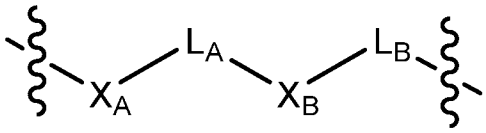
2. A compound according to claim 1, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein L is linker that separates R_L from R_R by 8 to 12 bond lengths, 9 to 11 bond lengths, or 10 bond lengths.

3. A compound according to any one of claims 1 or 2, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein L is a linker selected from:

(ii) a group of the formula:



(II)



(III)

wherein:

X_A is selected from: -O-, -S-, -SO-, -SO_2-, -N(R_{xa})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{xa})-, -N(R_{xa})C(O)-, -N(R_{xa1})C(O)N(R_{xa})-, -$S(O)_2$N(R_{xa})- or -N(R_{xa})SO_2-, wherein R_{xa} and R_{xa1} are selected from hydrogen or methyl;

L_A is a (1-6C)alkylene optionally substituted by one or more R_{LA} substituent groups, or a –[(0-3C)alkylene-(3-6C)cycloalkylene-(0-3C)alkylene]- group optionally substituted by one or more R_{LA} substituent groups;

each R_{LA} group present is selected from hydroxy, halo, (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

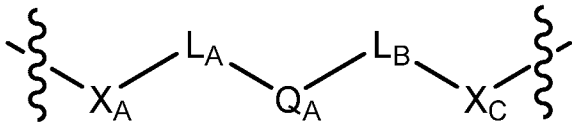
X_B is selected from: -O-, -S-, -SO-, -SO_2-, -N(R_{xb})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{xb})-, -N(R_{xb1})C(O)-, -N(R_{xb1})C(O)N(R_{xb})-, -$S(O)_2$N(R_{xb})- or -N(R_{xb})SO_2-, wherein R_{xb} and R_{xb1} are selected from hydrogen or methyl;

L_B is a (1-6C)alkylene optionally substituted by one or more R_{LB} substituent groups, or a –[(0-3C)alkylene-(3-6C)cycloalkylene-(0-3C)alkylene]- group optionally substituted by one or more R_{LB} substituent groups;

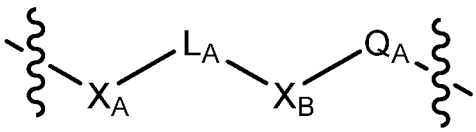
each R_{LB} group present is selected from hydroxy, halo, (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

X_c is selected from: -O-, -S-, -SO-, -SO_2-, -N(R_{xc})-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R_{xc})-, -N(R_{xc1})C(O)-, -N(R_{xc1})C(O)N(R_{xc})-, -$S(O)_2$N(R_{xc})- or -N(R_{xc})SO_2-, wherein R_{xc} and R_{xc1} are selected from hydrogen or methyl;

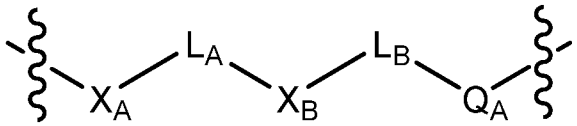
(ii) a group of the formula:



(IV)



(V)



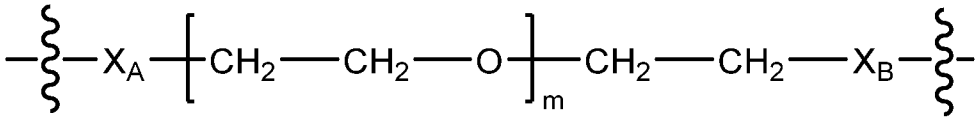
(VI)

wherein:

X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from a 5 or 6-membered heteroaryl ring, a 9 or 10-membered bicyclic heteroaryl ring, (3-6C)cycloalkyl, a phenyl, or a 4 to 6 membered heterocyclic ring;

(iii) a group of the formula:



(VII)

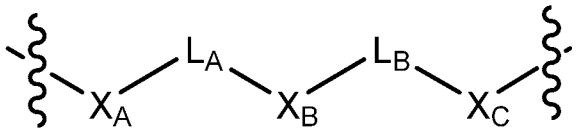
wherein:

X_A and X_B are each as defined above;

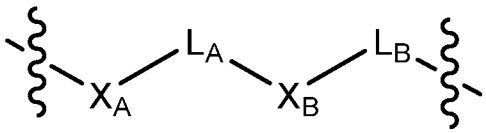
integer m is 1 or 2.

4. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein L is a linker selected from:

(i) a group of the formula:



(II)



(III)

wherein:

X_A is selected from: -O-, -SO_2-, -N(R_{xa})-, -C(O)-, -C(O)N(R_{xa})-, -N(R_{xa})C(O)-, -$S(O)_2$N(R_{xa})- or -N(R_{xa})SO_2-, wherein R_{xa} is selected from hydrogen or methyl;

L_A is a (1-5C)alkylene optionally substituted by one or more R_{LA} substituent groups, or a –[(0-2C)alkylene-(3-6C)cycloalkylene-(0-2C)alkylene]- group optionally substituted by one or more R_{LA} substituent groups;

each R_{LA} group present is selected from (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

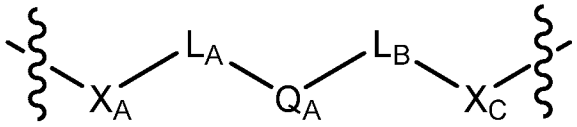
X_B is selected from: -O-, -SO_2-, -N(R_{xb})-, -C(O)-, -C(O)N(R_{xb})-, -N(R_{xb1})C(O)-, -$S(O)_2$N(R_{xb})- or -N(R_{xb})SO_2-, wherein R_{xb} and R_{xb1} are selected from hydrogen or methyl;

L_B is a (1-4C)alkylene optionally substituted by one or more R_{LB} substituent groups, or a –[(0-2C)alkylene-(3-6C)cycloalkylene-(0-2C)alkylene]- group optionally substituted by one or more R_{LB} substituent groups;

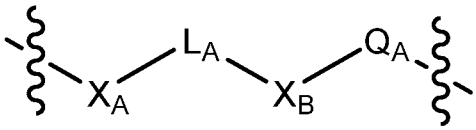
each R_{LB} group present is selected from (1-2C)alkyl, (1-2C)hydroxyalkyl or (1-2C)haloalkyl;

X_c is selected from: -O-, -SO_2-, -N(R_{xc})-, -C(O)-, -C(O)N(R_{xc})-, -N(R_{xc1})C(O)-, -$S(O)_2$N(R_{xc})- or -N(R_{xc})SO_2-, wherein R_{xc} and R_{xc1} are selected from hydrogen or methyl;

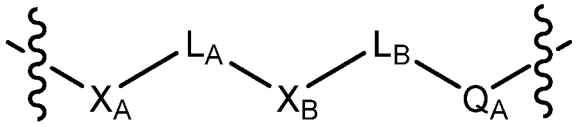
(ii) a group of the formula:



(IV)



(V)



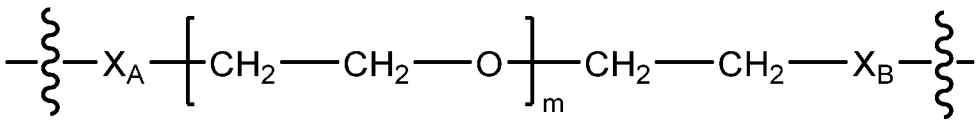
(VI)

wherein:

X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from a 5 or 6-membered heteroaryl ring, or a 4 to 6 membered heterocyclic ring;

(iii) a group of the formula:



(VII)

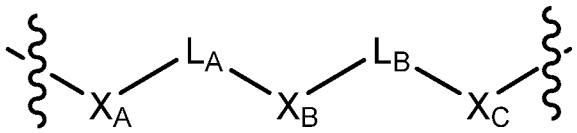
wherein:

X_A and X_B are each as defined above;

integer m is 1.

5. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein L is a linker selected from:

(i) a group of the formula:



(II)

wherein:

X_A is selected from: -O-, -N(R_{xa})-, -C(O)N(R_{xa})-, or -N(R_{xa})C(O)-, wherein R_{xa} is selected from hydrogen or methyl;

L_A is a (2-5C)alkylene optionally substituted by one or more R_{LA} substituent groups, or a –[(4-6C)cycloalkylene-(0-1C)alkylene]- group,,

each R_{LA} group present is (1-2C)alkyl;

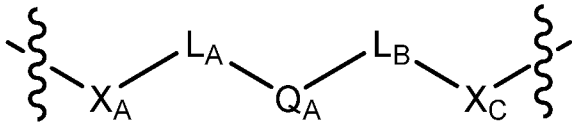
X_B is selected from: -O-, -N(R_{xb})-, -C(O)N(R_{xb})-, or -N(R_{xb1})C(O)-, wherein R_{xb} and R_{xb1} are selected from hydrogen or methyl;

L_B is a (1-4C)alkylene optionally substituted by one or more R_{LB} substituent groups,

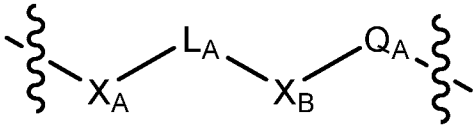
each R_{LB} group present is (1-2C)alkyl;

X_c is selected from: -O-, -N(R_{xc})-, -C(O)N(R_{xc})- or -N(R_{xc1})C(O)-, wherein R_{xc} and R_{xc1} are selected from hydrogen or methyl;

(ii) a group of the formula:



(IV)



(V)

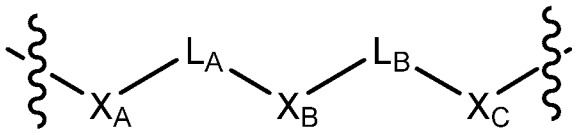
wherein:

X_A, L_A, X_B, L_B and X_C are as defined above;

Q_A is selected from a 5 or 6-membered heteroaryl ring, or a 4 to 6 membered heterocyclic ring.

6. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein L is a linker selected from:

(i) a group of the formula:



(II)

wherein:

X_A is selected from: -N(H)-, or -N(Me)-;

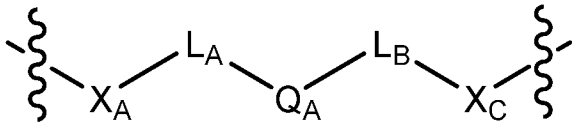
L_A is a (2-4C)alkylene optionally substituted by a methyl group, or L_A is a –[cyclobutylene-(0-1C)alkylene]- group;

X_B is selected from: -O-, -N(H)-, -N(Me)-, -C(O)N(H)-, or -C(O)N(Me)-;

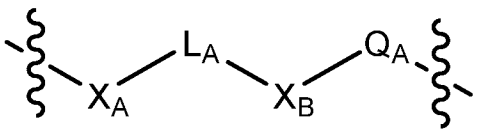
L_B is a (1-4C)alkylene;

X_c is selected from: -O-, -N(H)-, -N(Me)-, -C(O)N(H)- or -C(O)N(Me)- ;

(ii) a group of the formula:



(IV)



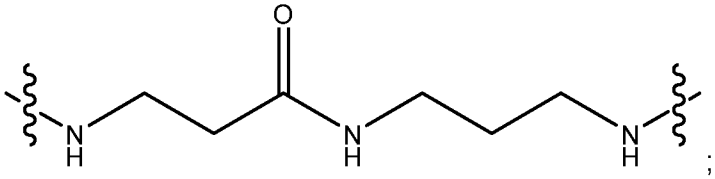
(V)

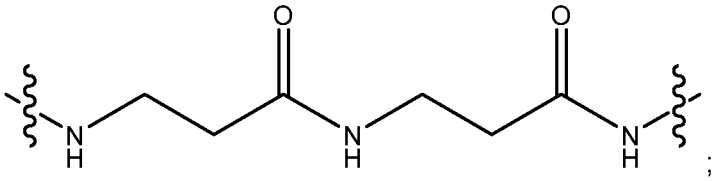
wherein:

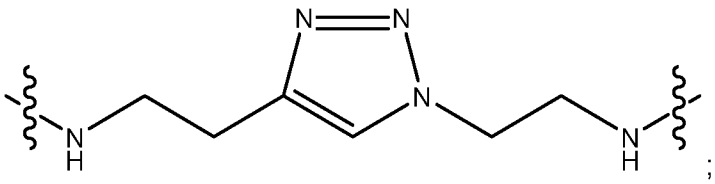
X_A, L_A, X_B, L_B and X_C are as defined above;

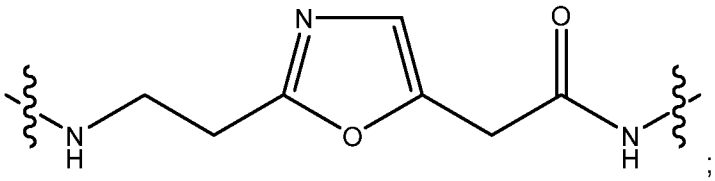
Q_A is selected from an oxazole group, triazole group or a azetidine group.

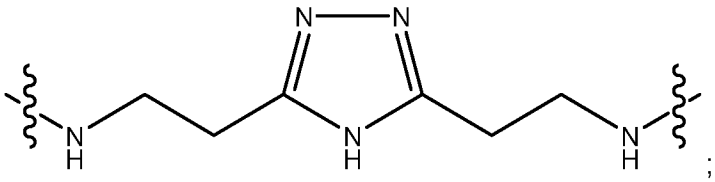
7. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein L is a linker selected from:

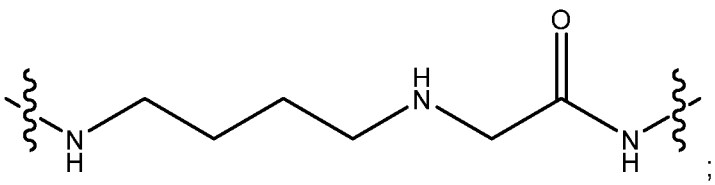

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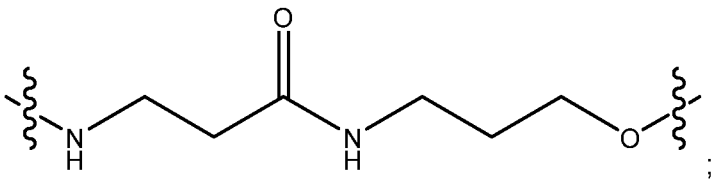

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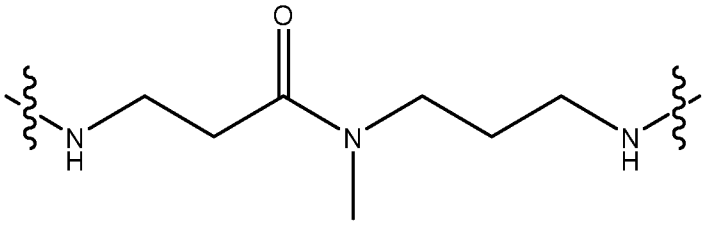

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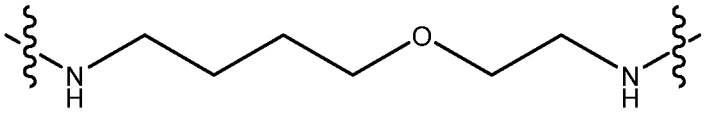

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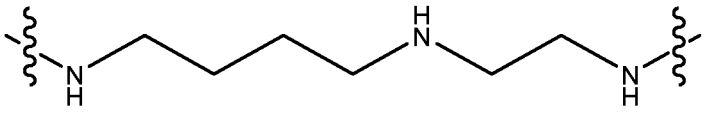

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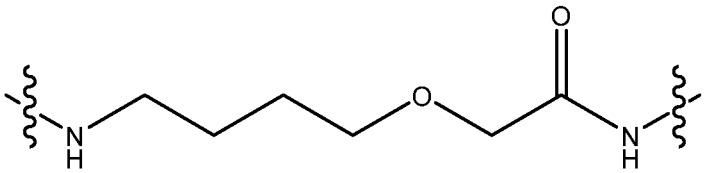

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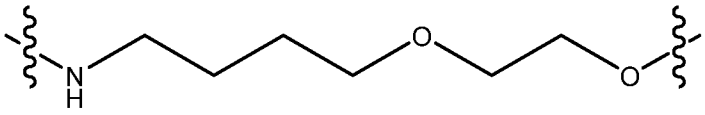

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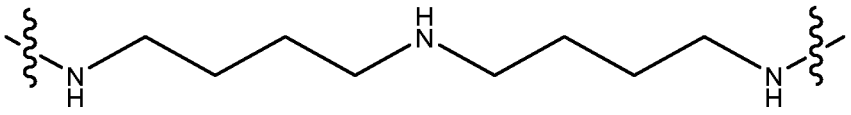

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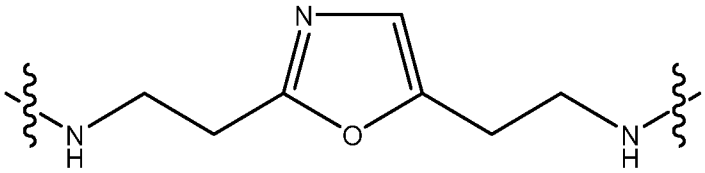

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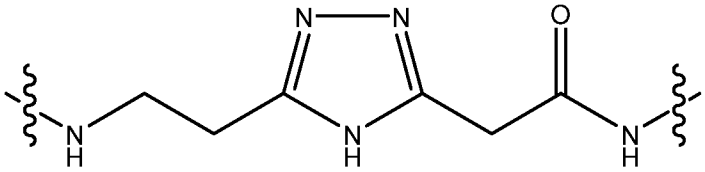

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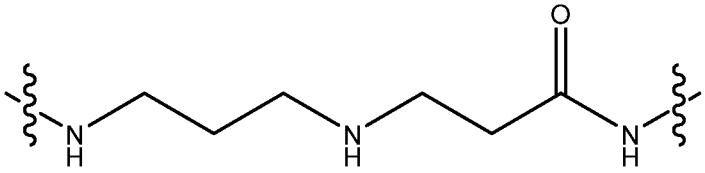

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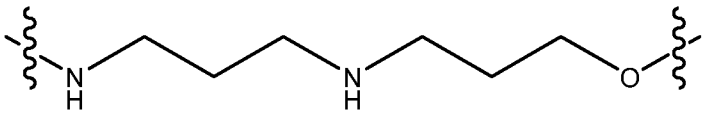

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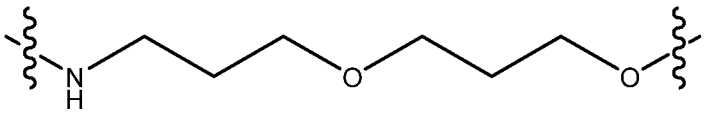

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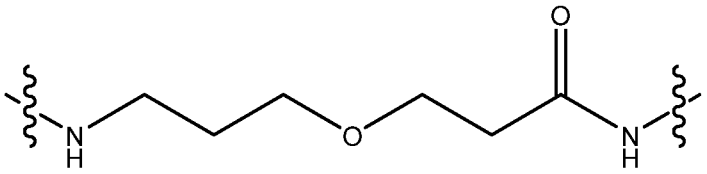

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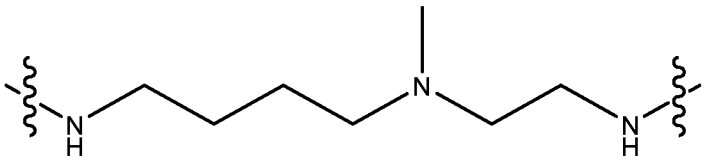

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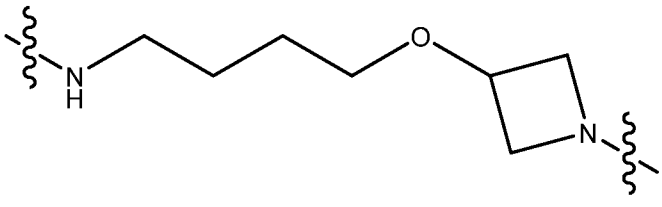

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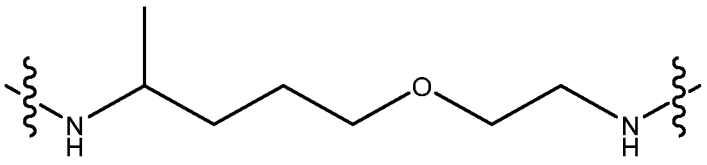

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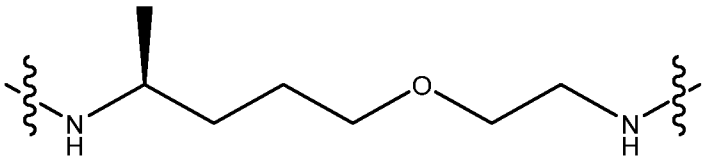

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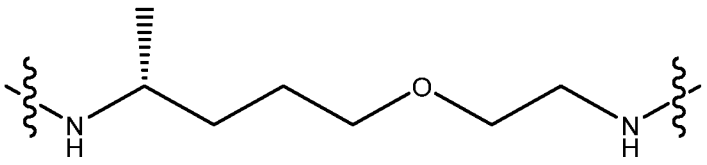

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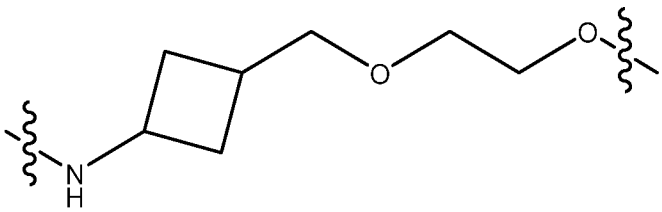

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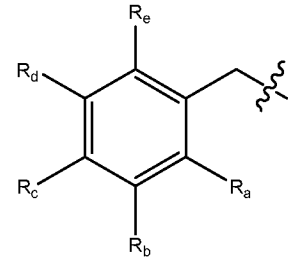

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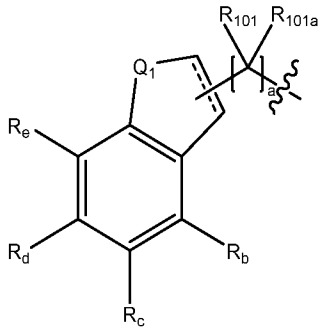

; or


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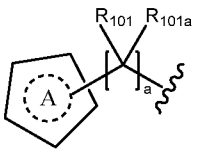
8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_L is selected from one of formulae Ic, Ie or If shown below:



Ic



Ie

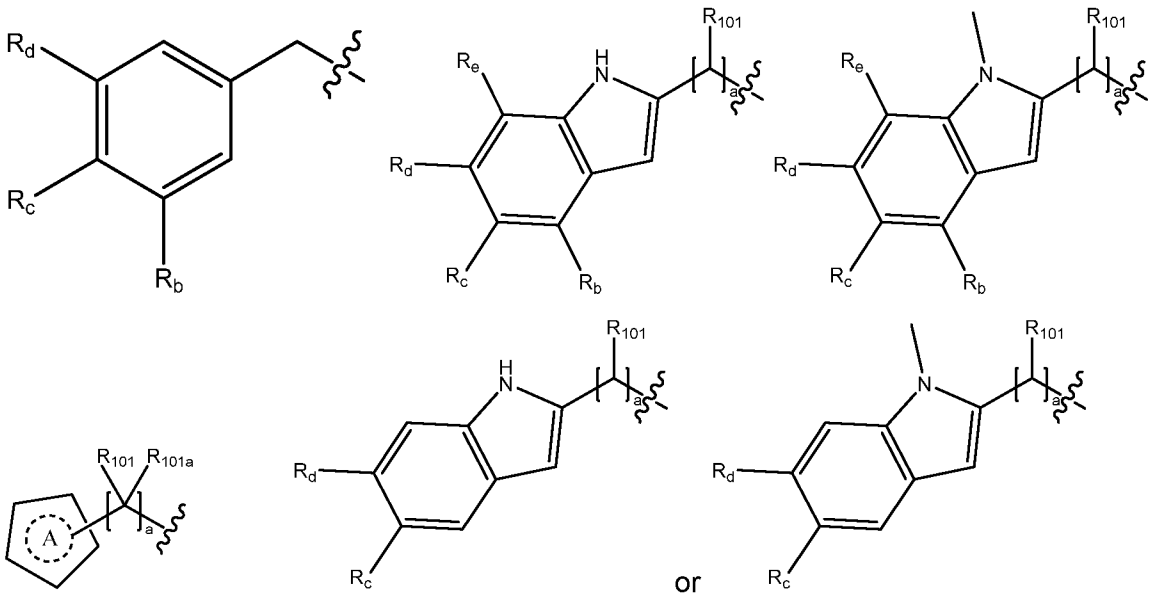


Ij

wherein:

denotes the point of attachment;

9. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_L is selected from one of formulae shown below:



wherein:

~~~ denotes the point of attachment.

10. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_a and R_e are both hydrogen.

11. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_b and R_d are each independently selected from hydrogen, halo, cyano, (1-4C)alkyl, (3-6C)cycloalkyl,

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

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

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

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

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

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, cycloalkyl or -[CH_2]- 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]$_2$, -C(O)(1-2C)alkyl, -C(O)O-(1-2C)alkyl or -N(R_f)C(O)-(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.

12. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein one of R_b and R_d is hydrogen or halogen and the other is selected from hydrogen, fluoro, chloro cyano, methyl, ethyl, methoxy, ethoxy, -C(O)NH_2, -CH_2-oxazole, -CH_2OH, -CH_2CN, -CH_2CH_2OH, -CF3, -OCF_3, -O-CH_2CH_2OH or -CH_2-C(O)NH_2.

13. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_c is selected from hydrogen, halo, cyano, -C(O)NH_2, (1-4C)alkyl, (3-6C)cycloalkyl, -(1-4C)alkoxy,

a group of the formula:

$$-Y_2-Z_2$$

wherein Y_2 is absent, -O-, -NH- or -NMe-; and

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

and wherein:

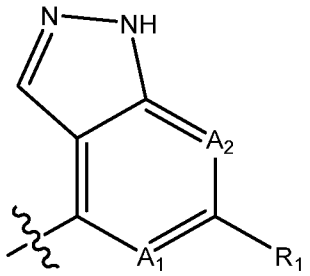
any alkyl, alkoxy, cycloalkyl or -[CH_2]- moiety within a R_c substituent group is optionally substituted by one or more substituents selected from halo, hydroxy, cyano, amino, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, or (3-4C)cycloalkoxy; and

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]$_2$, -C(O)(1-2C)alkyl or -C(O)O-(1-2C)alkyl, and wherein any (1-2C)alkoxy, (1-

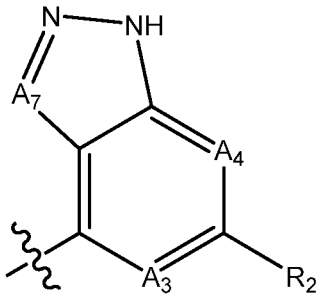
2C)alkyl, (3-4C)cycloalkyl or (3-4C)cycloalkoxy group is optionally substituted by one or more substituents selected from halo, cyano, hydroxy, (1-2C)alkyl, (1-2C)alkoxy or (1-2C)alkoxy-(1-2C)alkyl.

14. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_c is selected from hydrogen, $-CF_3$, $-OCF_3$, cyclopropyl, phenyl, -O-cyclobutyl or -phenyl-CH_2-OH;

15. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_R is selected from one of formulae Im or In shown below:



Im



In

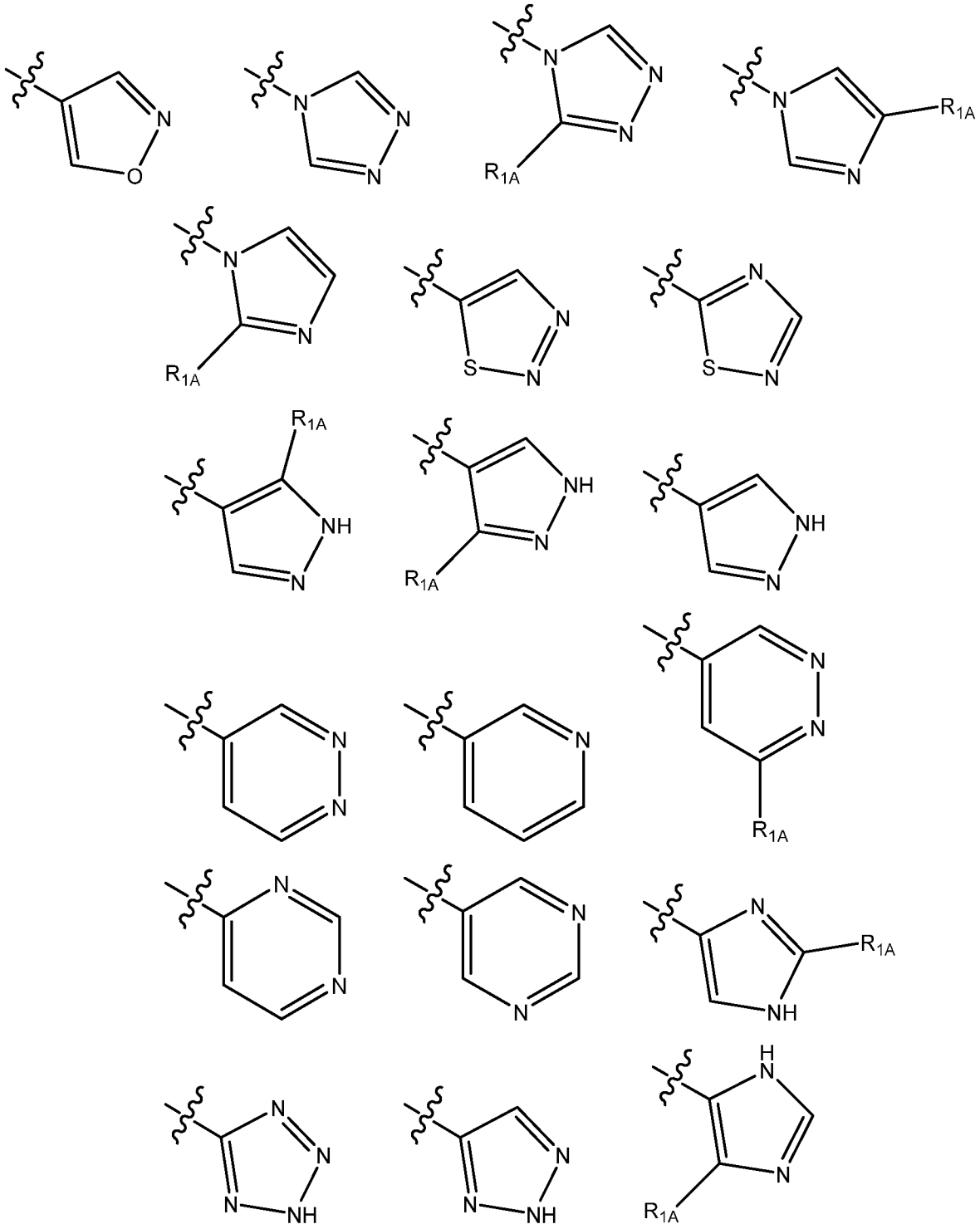
wherein:

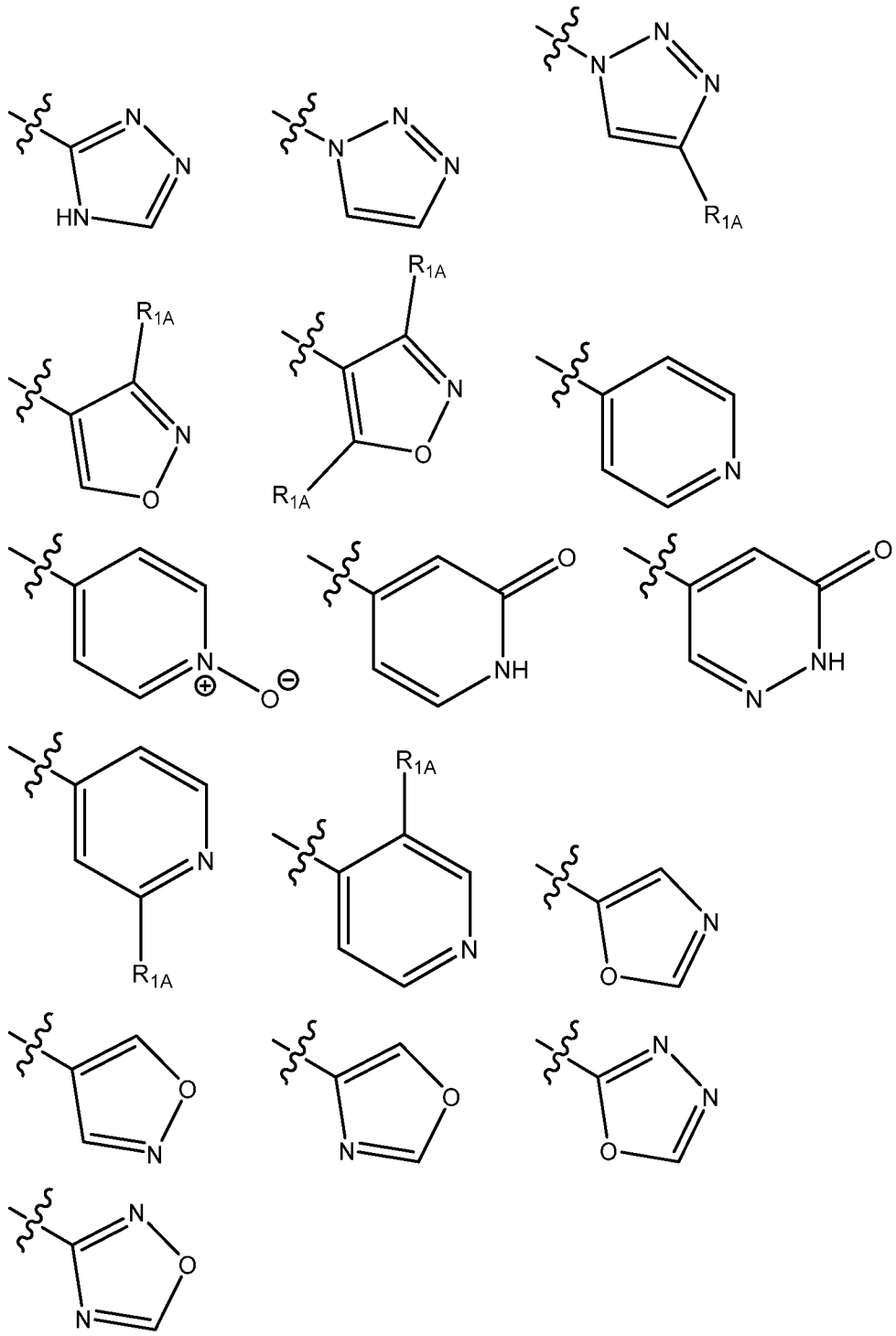
~~~~ denotes the point of attachment;

16. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_1 is a 5- or 6-membered heteroaryl ring comprising one, two, three or four heteroatoms selected from N, O or S which is optionally
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substituted on any available carbon atom by one or more R_{1A} substituent groups and on any available nitrogen atom by one or more R_{1B} substituent groups;

17. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_1 is selected from:





wherein R_{1A} is as defined herein;

18. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein each R_{1A} group present is selected from hydroxy, cyano, amino, chloro, fluoro, -C(O)OH, -C(O)NH_2, (1-2C)alkoxy, (1-2C)alkyl; and wherein any (1-2C)alkoxy, (1-2C)alkyl 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.

19. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein each R_{1B} group is methyl.

20. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, halo, cyano, (1-2C)alkyl, (1-2C)cyanoalkyl, (1-2C)hydroxyalkyl, (1-2C)haloalkyl, (1-2C)aminoalkyl,

$-[CH_2]_{0-1}$-(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]$_2$,

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

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

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

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

a 4- to 6-membered heterocyclyl,

(4-6C)cycloalkyl,

(4-6C)cycloalkyl(1-2C)alkyl,

phenyl, or

phenyl(1-2C)alkyl;

and wherein any cycloalkyl, heterocyclyl or phenyl group present is optionally substituted by one or more hydroxy, cyano, amino, halo, $-C(O)OH$, $-C(O)NH_2$, methoxy, methyl, -C(O)NH(Me), $-C(O)N(Me)_2$, -NH(Me), $-N(Me)_2$, $-S(O)_q$-(Me) (wherein q is 0, 1 or 2), -C(O)(Me), -C(O)O-(Me), -N(H)C(O)-(Me), $-S(O)_2NH(Me)$, $-S(O)_2N(Me)_2$, or $-NHSO_2$-(Me).

21. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein R_2 is selected from:

(i) a group R_1 defined above;

(ii) hydrogen, cyano, -C(O)NH_2, -C(O)N(Me)$_2$, CH_2CH_2-C(O)OH, -C(O)OH, -morpholino, -oxetane, -tetrahydrofuran or -tetrahydropyran.

22. 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:

3-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;

4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1H-indazole-6-carboxamide;

N-(3-((6-(1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;

N-(3-((6-(1H-1,2,4-triazol-1-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;

3-((3-Chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-cyano-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)propyl)propanamide;

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methyl-1H-imidazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;

3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-cyano-1H-indazol-4-yl)amino)propyl)propanamide;

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propanamide;

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chlorobenzyl)amino)propanamide;

N-(2-(4-(2-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)ethyl)-1H-1,2,3-triazol-1-yl)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-(2-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)oxazol-5-yl)acetamide;

N-(2-(5-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)-4H-1,2,4-triazol-3-yl)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-((4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butyl)amino)acetamide;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-(3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamido)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-methylpropanamide;
3-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methylpyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-Chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methoxypyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(2-(4-(((6-chloro-1H-benzo[d]imidazol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N1-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)-N4-(3-chloro-4-(trifluoromethoxy)benzyl)butane-1,4-diamine;
N-(3-((6-(2H-1,2,3-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyridin-3-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-methyl-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(isoxazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(4-methyl-1H-imidazol-1-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
4-(4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1H-indazol-6-yl)pyridine 1-oxide ;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(2-oxo-1,2-dihydropyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;

N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((4-chloro-5-phenyl-1H-pyrazol-3-yl)methyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(hydroxymethyl)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((6-chloro-1-methyl-1H-indol-2-yl)methyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((6-chloro-1H-indol-2-yl)methyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((1-methyl-5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-cyano-4-cyclobutoxybenzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(2-hydroxyethyl)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((4-cyclobutoxy-3-(hydroxymethyl)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(2-hydroxyethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-5-(hydroxymethyl)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(hydroxymethyl)-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-cyano-4-cyclopropylbenzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-cyano-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-(cyanomethyl)benzyl)amino)propanamide;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)acetamide;
6-(4H-1,2,4-triazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
N-(2-(4-(((6-chloro-1-methyl-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(2-(4-(((1-methyl-5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;

N-(2-(4-(((6-chloro-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(2-(4-(((5-cyclobutoxy-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-(2-((6-(isoxazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butan-1-amine;
N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-(2-((6-(pyridazin-4-yl)-1H-indazol-4-yl)oxy)ethoxy)butan-1-amine;
4-(2-((6-(pyridazin-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
N-(2-(4-(((5-cyclobutoxy-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(pyridazin-4-yl)-1H-indazol-4-amine;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-1H-indazole-6-carboxylic acid;
4-((4-((4-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)butyl)amino)butyl)amino)-1H-indazole-6-carboxylic acid;
N-(3-((1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
4-((3-(3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamido)propyl)amino)-N,N-dimethyl-1H-indazole-6-carboxamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(hydroxymethyl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(2-(2-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)oxazol-5-yl)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-2-(5-(2-((3-chloro-4-(trifluoromethoxy)benzyl)amino)ethyl)-4H-1,2,4-triazol-3-yl)acetamide;
N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-((3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propyl)amino)propanamide;
N1-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propyl)-N3-(3-chloro-4-(trifluoromethoxy)benzyl)propane-1,3-diamine;
N-(2-(4-(((6-chloro-1-methyl-1H-benzo[d]imidazol-2-yl)methyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
3-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)propoxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)propan-1-amine;

N-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)-3-(3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propoxy)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-methyl-4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N1-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethyl)-N4-(3-chloro-4-(trifluoromethoxy)benzyl)-N1-methylbutane-1,4-diamine;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyrimidin-5-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-cyanopyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(pyrimidin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(3-methoxy-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((4-cyclopropyl-3-(hydroxymethyl)benzyl)amino)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-morpholino-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((6-(2H-tetrazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(2-methyl-1H-imidazol-1-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(oxetan-3-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(tetrahydrofuran-3-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((5-(4H-1,2,4-triazol-4-yl)-1H-indazol-7-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
methyl 4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxylate;
4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxylic acid;
6-(3-methyl-4H-1,2,4-triazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine ;
6-(2-methoxypyridin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;

methyl 3-(4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)propanoate;
3-(4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)propanoic acid;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(tetrahydro-2H-pyran-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-(((2-chloro-[1,1'-biphenyl]-4-yl)methyl)amino)-N-(3-((6-(4-methyl-1H-imidazol-5-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
6-(3-methoxy-1H-pyrazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
6-(pyridazin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
6-(pyrimidin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
4-((2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carbonitrile;
6-(isoxazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-indazol-4-amine;
N-(2-(4-(((5-cyclobutoxy-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-6-(isoxazol-4-yl)-1H-indazol-4-amine;
N-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine;
6-(pyridazin-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-benzo[d][1,2,3]triazol-4-amine;
4-(2-((6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-(2-((6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butan-1-amine;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-fluorophenyl)acetonitrile;
(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)methanol;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)acetonitrile;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-methylphenyl)acetonitrile;

N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
N-(3-fluoro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
(3-fluoro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol;
(3-chloro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol;
(3-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)methanol;
2-(3-fluoro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile;
2-(3-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)acetonitrile;
2-(3-methyl-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile;
4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-cyclobutoxy-1H-indol-2-yl)methyl)butan-1-amine;
N-((5-cyclobutoxy-1H-indol-2-yl)methyl)-4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)methanol;
2-(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-methylphenyl)acetonitrile;
2-(3-chloro-5-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile;
4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)butan-1-amine;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-cyclobutoxy-1H-indol-2-yl)methyl)butan-1-amine;

(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-fluorophenyl)methanol;
N-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine;
N-(2-(4-((3-chloro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(isoxazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-amine;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-(3-fluoro-4-(trifluoromethoxy)benzyl)butan-1-amine;
(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-chlorophenyl)methanol;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-chlorophenyl)acetonitrile;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)butan-1-amine;
2-(3-chloro-5-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)acetonitrile;
2-(3-(((4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
N-(3-fluoro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
(3-chloro-5-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol;
N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
(3-fluoro-5-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)phenyl)methanol;
4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
4-((1-(6-(pyridazin-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
2-(3-(((4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)amino)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
6-(4H-1,2,4-triazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-benzo[d][1,2,3]triazol-4-amine;

6-(isoxazol-4-yl)-N-(2-(4-(((5-(trifluoromethyl)-1H-indol-2-yl)methyl)amino)butoxy)ethyl)-1H-benzo[d][1,2,3]triazol-4-amine;
4-(2-((6-(isoxazol-4-yl)-1H-indazol-4-yl)oxy)ethoxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
2-(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethyl)phenyl)acetonitrile;
2-(3-(((4-((1-(6-(isoxazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
2-(3-(((4-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
N-(3-chloro-4-(trifluoromethoxy)benzyl)-4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butan-1-amine;
2-(3-(((4-((1-(6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)-N-((5-(trifluoromethyl)-1H-indol-2-yl)methyl)butan-1-amine;
4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)-N-(3-chloro-4-(trifluoromethoxy)benzyl)butan-1-amine;
2-(3-(((4-((1-(6-(4H-1,2,4-triazol-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)azetidin-3-yl)oxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
2-(3-(((4-(2-((6-(pyridazin-4-yl)-1H-benzo[d][1,2,3]triazol-4-yl)oxy)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(5-cyano-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((6-(1,3,4-oxadiazol-2-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-chloro-6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(5-methyl-1H-pyrazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-cyano-1H-indazol-4-yl)amino)propyl)propanamide;

N-(3-((6-(1H-1,2,3-triazol-1-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-fluoropyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(3-((1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(oxazol-5-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-methylpyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
7-chloro-N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(pyridin-4-yl)-1H-indazol-4-amine;
4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carbonitrile;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(6-oxo-1,6-dihydropyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-chloropyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(2-oxo-1,2-dihydropyrimidin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
4-(2-(((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)methyl)amino)ethoxy)-N-(3,5-difluoro-4-(trifluoromethoxy)benzyl)butan-1-amine;
N-(3-(((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)methyl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(1,2,4-oxadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(4H-1,2,4-triazol-3-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(oxazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-7-fluoro-6-(pyridin-4-yl)-1H-indazol-4-amine;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(3-cyano-4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-methyl-6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;

N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-7-methyl-6-(pyridin-4-yl)-1H-indazol-4-amine;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-fluoro-6-(pyridin-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((7-chloro-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
7-chloro-N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(3-((6-(1,2,4-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(2-aminopyridin-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((6-(pyridin-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)amino)propyl)propanamide;
5-chloro-N-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-amine;
N-(3-((6-(6-aminopyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(6-aminopyridazin-4-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N-(3-((6-(1,2,4-oxadiazol-3-yl)-1H-indazol-4-yl)amino)propyl)-3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)propanamide;
N4-(2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)-N3-methyl-6-(4H-1,2,4-triazol-4-yl)-1H-indazole-3,4-diamine;
3-((3-chloro-4-(trifluoromethoxy)benzyl)amino)-N-(3-((3-(methylamino)-6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)propyl)propanamide;
(S)-(3-(((5-(2-((6-(4H-1,2,4-triazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol;
(S)-5-(4-((2-((4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)pentyl)oxy)ethyl)amino)-1H-indazol-6-yl)pyridazin-3-ol;
(S)-2-(3-(((5-(2-((6-(6-hydroxypyridazin-4-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)phenyl)acetonitrile;
(S)-5-(4-((2-((4-((3-(oxazol-5-ylmethyl)-5-(trifluoromethoxy)benzyl)amino)pentyl)oxy)ethyl)amino)-1H-indazol-6-yl)pyridazin-3-ol;
(S)-3-(((5-(2-((6-(isoxazol-4-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)benzamide;

4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazole-6-carboxylic acid;
2-(4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)acetic acid;
5-(4-(2-((3-((3-(2-hydroxyethoxy)-5-(trifluoromethoxy)benzyl)amino)cyclobutyl)methoxy)ethoxy)-1H-indazol-6-yl)pyridazin-3-ol;
5-(4-(2-((3-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)cyclobutyl)methoxy)ethoxy)-1H-indazol-6-yl)pyridazin-3-ol;
3-(4-((2-(4-((3,5-difluoro-4-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)propanoic acid;
2-(3-(((4-(2-((1H-indazol-4-yl)amino)ethoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenoxy)ethanol;
(3-(((3-((2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)methyl)cyclobutyl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol;
2-(4-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)acetonitrile;
2-(3-(((3-((2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)methyl)cyclobutyl)amino)methyl)-5-(trifluoromethoxy)phenoxy)ethan-1-ol;
2-(4-((2-(4-((3-(hydroxymethyl)-5-(trifluoromethoxy)benzyl)amino)butoxy)ethyl)amino)-1H-indazol-6-yl)-2-methylpropanenitrile;
(S)-(3-(((5-(2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)ethoxy)pentan-2-yl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol; and
(R)-(3-(((4-(2-((6-(1,2,3-thiadiazol-5-yl)-1H-indazol-4-yl)amino)propoxy)butyl)amino)methyl)-5-(trifluoromethoxy)phenyl)methanol.

23. A pharmaceutical composition comprising a compound according to any one of claims 1 to 22, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and a pharmaceutically acceptable excipient.

24. A compound according to any one of claims 1 to 22, or a pharmaceutically acceptable salt of solvate thereof, or a pharmaceutical composition according to claim 23 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;

(i) 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;

(ii) the treatment of a cancer; and/or

(iii) the treatment of a viral infection.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2023/052339

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/56 C07D403/04 C07D403/14 C07D413/14 C07D417/04
A61P35/00 A61K31/416
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)
A61P C07D

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/143759 A1 (EXELIXIS INC [US]; KOLTUN ELENA S [US] ET AL.) 27 November 2008 (2008-11-27) page 1; examples	1-24
A	WO 2011/025859 A1 (CYLENE PHARMACEUTICALS INC [US]; PIERRE FABRICE [US] ET AL.) 3 March 2011 (2011-03-03) pages 1-9; examples	1-24

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[x] Further documents are listed in the continuation of Box C.
[x] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2023	08/11/2023

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	Lauro, Paola

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2023/052339

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2017/197324 A1 (UNIV LELAND STANFORD JUNIOR [US]) 16 November 2017 (2017-11-16) pages 88-89	1,23,24
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X	US 4 346 093 A (FRIEBE WALTER-GUNAR ET AL) 24 August 1982 (1982-08-24) see RN 76651-15-5	1,23,24
X	US 5 478 830 A (HIGLEY C ANNE [US] ET AL) 26 December 1995 (1995-12-26) table 1	1,23,24
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