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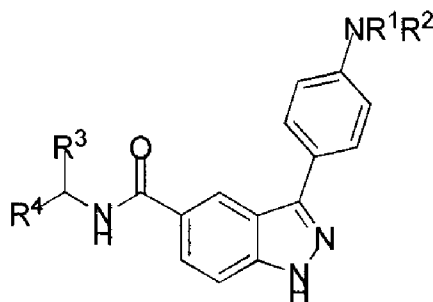
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(I)

(57) Abstract: The invention is a compound represented by Structural Formula (I) or a pharmaceutically acceptable salt thereof. Values for the variables are provided herein. Also included is a pharmaceutical composition comprising the compound represented by Structural Formula (I) and a pharmaceutically acceptable carrier or diluent and methods of treating a subject with cancer with the compound of Structural Formula (I).

KINASE INHIBITORS AND METHOD OF TREATING CANCER WITH SAME

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/813,011, filed April 17, 2013. This application also claims the benefit of International Application No. PCT/CA2012/000955, filed October 12, 2012. The entire teachings of these two applications are incorporated herein by reference.

BACKGROUND

Protein kinases have been the subject of extensive study in the search for new therapeutic agents in various diseases, for example, cancer. Protein kinases are known to mediate intracellular signal transduction by effecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor that is involved in a signaling pathway. There are a number of kinases and pathways through which extracellular and other stimuli cause a variety of cellular responses to occur inside the cell.

Human TTK protein kinase (TTK), also known as tyrosine threonine kinase, dual specificity protein kinase TTK, Monopolar Spindle 1 (Mps1) and Phosphotyrosine-Picked Threonine Kinase (PYT), is a conserved multispecific kinase that is capable of phosphorylating serine, threonine and tyrosine residues when expressed in *E. coli* (Mills *et al.*, *J. Biol. Chem.* 22(5): 16000-16006 (1992)). TTK mRNA is not expressed in the majority of physiologically normal tissues in human (*Id.*). TTK mRNA is expressed in some rapidly proliferating tissues, such as testis and thymus, as well as in some tumors (for example, TTK mRNA was not expressed in renal cell carcinoma, was expressed in 50% of breast cancer samples, was expressed in testicular tumors and ovarian cancer samples) (*Id.*). TTK is expressed in some cancer cell lines and tumors relative to normal counterparts (*Id.*; see also WO 02/068444 A1).

Therefore, agents which inhibit a protein kinase, in particular TTK, have the potential to treat cancer. There is a need for additional agents which can act as protein kinase inhibitors, in particular TTK inhibitors.

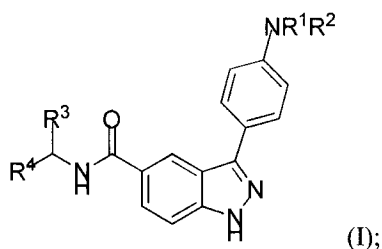
In addition, cancer recurrence, drug resistance or metastasis is one of the major challenges in cancer therapies. Cancer patients who responded favorably to the initial anti-cancer therapy often develop drug resistance and secondary tumors that lead to the relapse of the disease. Recent research evidences suggest that the capability of a tumor to grow and propagate is dependent on a small subset of cells within the tumor. These cells are termed tumor-initiating cells (TICs) or cancer stem cells. It is thought that the TICs are responsible for drug resistance, cancer relapse and metastasis. Compounds that can inhibit the growth and survival of these tumor-initiating cells can be used to treat

cancer, metastasis or prevent recurrence of cancer. Therefore, a need exists for new compounds that can inhibit the growth and survival of tumor-initiating cells.

SUMMARY OF THE INVENTION

Applicants have now discovered that certain indazole compounds are potent kinase inhibitors, such as TTK protein kinase, polo-like kinase 4 (PLK4) and Aurora kinases (*see* Example B, E, and F). Applicants have also now discovered that these indazole compounds have potent anticancer activity against breast cancer cells, colon cancer cells, and ovarian cancer cells in cell culture study (*see* Examples C-D). Based on these discoveries, indazole compounds, pharmaceutical compositions thereof, and methods of treating cancer with the indazole compounds are disclosed herein.

One embodiment of the invention is a compound represented by Structural Formula (I):



or a pharmaceutically acceptable salt thereof.

-NR¹R² taken together forms a bridged bicyclic group optionally comprising one ring oxygen atom and optionally substituted with alkyl, haloalkyl, hydroxyl, alkoxy, halo, hydroxyalkyl or alkoxyalkyl; or -NR¹R² taken together forms a piperazinyl group *N*-substituted with oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, hydroxyethyl or alkoxyethyl and optionally *C*-substituted with alkyl; and

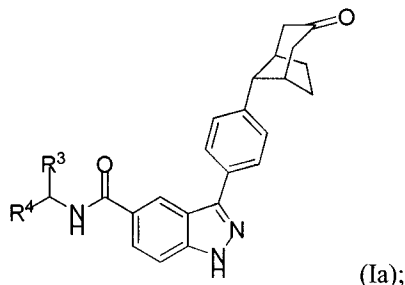
R³ is i) (C₂-C₆) alkyl optionally substituted with hydroxyl, alkoxy or halo; or ii) cycloalkyl optionally substituted with alkyl, haloalkyl, hydroxyl, alkoxy or halo; and

R⁴ is phenyl or monocyclic heteroaryl, each optionally substituted with one to three groups represented by R⁵;

each R⁵ is independently selected from halo, alkyl, haloalkyl, hydroxyl, alkoxy, -CN, -NO₂, -haloalkoxy and -NRᵃRᵃ; and

each Rᵃ is independently hydrogen or alkyl.

Another embodiment of the invention is a compound represented by Structural Formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein:

R^3 is i) (C_2 - C_6) alkyl optionally substituted with hydroxyl, alkoxy or halo; or ii) cycloalkyl optionally substituted with alkyl, haloalkyl, hydroxyl, alkoxy or halo; and

R^4 is phenyl or monocyclic heteroaryl, each optionally substituted with one to three groups represented by R^5 ;

each R^5 is independently selected from halo, alkyl, haloalkyl, hydroxyl, alkoxy, -CN, -NO₂, -haloalkoxy and -NR^aR^a; and

each R^a is independently hydrogen or alkyl.

Another embodiment of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by Structural Formula (I) or (Ia) described above or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method of treating a subject with cancer comprising administering to the subject an effective amount of a compound of Structural Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method of inhibiting TTK activity in a subject in need of inhibition of TTK activity, comprising administering to the subject an effective amount of a compound represented by Structural Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof.

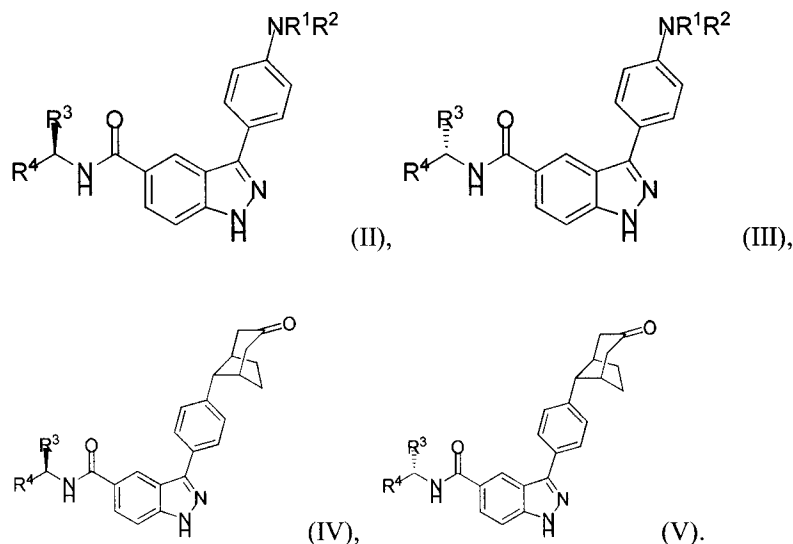
Another embodiment of the invention is a compound represented by Structural Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof for use in therapy. In some embodiments, the therapy is for treating a subject with cancer. Alternatively, the therapy is for inhibiting TTK activity in a subject in need of inhibition of TTK activity.

Another embodiment of the invention is the use of a compound represented by Structural Formula (I) or (Ia) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a subject with cancer.

Another embodiment of the invention the use of a compound represented by Structural Formulas (I) or (Ia) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting TTK activity in a subject in need of inhibition of TTK activity.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present teachings are directed to a compound represented by Structural Formula (I), (Ia), or a pharmaceutically acceptable salt thereof. Alternatively, the invention is directed to a compound represented by Structural Formula (II), (III), (IV), or (V):

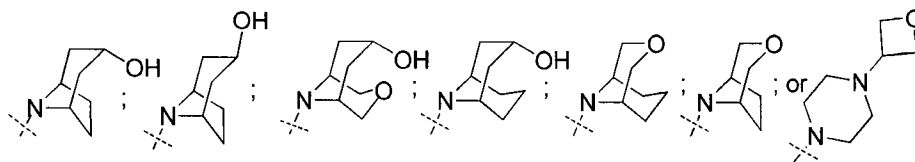


Pharmaceutically acceptable salts of the compounds represented by Structural Formulas (II), (III) (IV), and (V) are also included in the invention. Values for the variables in Structural Formulas (II) and (III) are as described for Structural Formula (I). Values for the variables in Structural Formulas (IV) and (V) are as described for Structural Formula (Ia).

In a first embodiment, the invention is directed to a compound represented by Structural Formula (I), (II) or (III), wherein the bridged bicyclic group formed by $-NR^1R^2$ is a [3.3.1] or a [3.2.1] bridged bicyclic group, and values for the remainder of the variables are as described above for Structural Formula (I). Typically, the bridged bicyclic group comprises one ring nitrogen atom, zero or one ring oxygen atom and the remainder of the ring atoms are carbon atoms for a total of eight or nine ring atoms. Alternatively, $-NR^1R^2$ taken together forms a piperazinyl group *N*-substituted with oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, hydroxyethyl or alkoxyethyl and optionally *C*-substituted with alkyl, and values for the remainder of the variables are as described above for Structural Formula (I).

In a second embodiment, the invention is directed to a compound represented by Structural Formula (I), (Ia), (II), (III), (IV), or (V), wherein R^4 is phenyl, pyridyl, pyrimidyl or thienyl, each optionally substituted with one to three groups represented by R^5 , and values for the remainder of the variables are as described above for Structural Formula (I) or (Ia), or in the first embodiment (for a compound represented by Structural Formula (I), (II), or (III)).

In a third embodiment, the invention is directed to a compound represented by Structural Formula (I), (II) or (III), wherein $-NR^1R^2$ is represented by



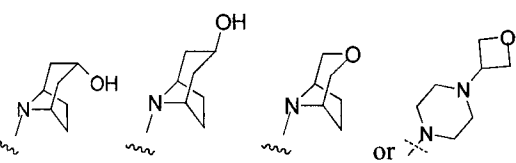
, and values for

the remainder of the variables are as described above for Structural Formula (I) or in the first embodiment or in the second embodiment.

In a fourth embodiment, the invention is directed to a compound represented by Structural Formula (I), (Ia), (II), (III), (IV), or (V), wherein R^3 is cyclopropyl, isopropyl, cyclopentyl, isobutyl, cyclopropylmethyl or 2,2-dimethylpropan-1-yl, and values for the remainder of the variables are as described above for Structural Formula (I) or in the first embodiment (for a compound represented by Structural Formula (I), (II), or (III)) or in the second embodiment or in the third embodiment (for a compound represented by Structural Formula (I), (II), or (III)). Alternatively, R^3 is cyclopropyl, cyclopentyl or isobutyl.

In a fifth embodiment, the invention is directed to a compound represented by Structural Formula (I), (Ia), (II), (III), (IV), or (V), wherein R^4 is pyrid-2-yl or 2-chlorophenyl, and values for the remainder of the variables are as described above for Structural Formula (I), in the first embodiment (for a compound represented by Structural Formula (I), (II), or (III)) or in the second preferred embodiment or in the third embodiment (for a compound represented by Structural Formula (I), (II), or (III)) or in the fourth embodiment.

In a sixth embodiment, the invention is directed to a compound represented by Structural

Formula (I), (II) or (III), wherein $-NR^1R^2$ is , and values for the remainder of the variables are as described above for Structural Formula (I) or in the first embodiment, or in the second embodiment or in the third embodiment or in the fourth embodiment or in the fifth embodiment.

In a seventh embodiment, the invention is directed to a compound represented by Structural Formula (I), (Ia), (II), (III), (IV), or (V), wherein R^5 is chloro or fluoro, and values for the remainder of the variables are as described above for Structural Formula (I) or in the first embodiment (for a compound represented by Structural Formula (I), (II), or (III)) or in the second embodiment or in the third embodiment (for a compound represented by Structural Formula (I), (II), or (III)) or in the fourth embodiment or in the fifth embodiment or in the sixth embodiment (for a compound represented by Structural Formula (I), (II), or (III)).

The invention also includes the compounds depicted by structure and/or described by name in the Exemplification. The invention includes both the neutral form of these compounds as well as

pharmaceutically acceptable salts thereof. Treatments with and/or uses of these compounds includes the neutral form of these compounds as well as pharmaceutically acceptable salts thereof.

The term “alkyl” used alone or as part of a larger moiety, such as “alkoxy” or “haloalkyl” and the like, means saturated aliphatic straight-chain or branched monovalent hydrocarbon radical. Unless otherwise specified, an alkyl group typically has 1-6 carbon atoms, i.e. (C₁-C₆)alkyl. As used herein, a “(C₁-C₆)alkyl” group means a radical having from 1 to 6 carbon atoms in a linear or branched arrangement.

“Alkoxy” means an alkyl radical attached through an oxygen linking atom, represented by –O-alkyl. For example, “(C₁-C₄)alkoxy” includes methoxy, ethoxy, propoxy, and butoxy.

The terms “haloalkyl” and “haloalkoxy” means alkyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term “halogen” means F, Cl, Br or I. Preferably the halogen in a haloalkyl or haloalkoxy is F.

“Hydroxyalkyl” is an alkyl group substituted with hydroxy.

“Alkoxyalkyl” is an alkyl group substituted with alkoxy.

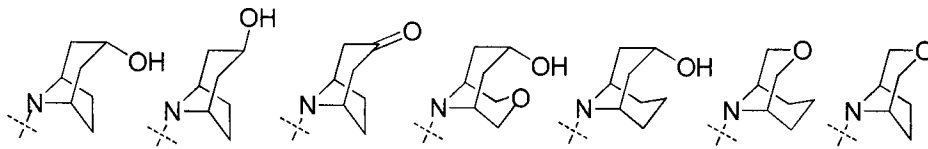
“Cycloalkyl” means a saturated aliphatic cyclic hydrocarbon radical, typically containing from 3-8 ring carbon atoms, i.e., a (C₃-C₈)cycloalkyl. A (C₃-C₈)cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term “heteroaryl”, “heteroaromatic”, “heteroaryl ring”, “heteroaryl group”, “heteroaromatic ring”, and “heteroaromatic group”, are used interchangeably herein. A “monocyclic heteroaryl” is a heteroaryl with one ring. “Monocyclic heteroaryl” refers to aromatic ring groups having five or six ring atoms selected from carbon and at least one (typically 1 to 4, more typically 1 or 2) heteroatoms (e.g., oxygen, nitrogen or sulfur).

Examples of monocyclic 5-6 membered heteroaryl groups include furanyl (e.g., 2-furanyl, 3-furanyl), imidazolyl (e.g., N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 2-oxadiazolyl, 5-oxadiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), pyrazolyl (e.g., 3-pyrazolyl, 4-pyrazolyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl, triazolyl (e.g., 2-triazolyl, 5-triazolyl), tetrazolyl (e.g., tetrazolyl), and thienyl (e.g., 2-thienyl, 3-thienyl).

As used herein, the term “bridged bicyclic group” refers to a ring system which includes two rings that share at least three adjacent ring atoms. Typically, a bridged bicyclic group is 7-10 membered having ring atoms (typically 8-9) selected from carbon, nitrogen and oxygen, typically one nitrogen atom, 0-1 oxygen atoms and the remainder carbon atoms. A bridged bicyclic group has bridgehead atoms and bridges. The bridgehead atoms are bonded to three other ring atoms and are typically carbon. Bridges are the ring atoms between the bridgeheads. The nomenclature of a bridged

bicyclic group provides brackets within which are numbers separated by periods. The numbers are, in descending order, the number of carbon atoms between each of the bridgeheads. For example in bicyclo[2.2.1]heptane the molecule has three bridges having 2, 2 and 1 carbon atoms, designated with the prefix bicyclo[2.2.1]. The bridged bicyclic groups of the present invention are preferably [3.3.1] or a [3.2.1]. Exemplary bridged bicyclic groups are



The term “C-substituted” means substituted on a carbon atom. In the context of a cyclic group such as a bridged bicyclic group, “C-substituted” means substituted on a ring carbon atom. The term “N-substituted” means substituted on a nitrogen atom. In the context of a cyclic group such as a bridged bicyclic group, “N-substituted” means substituted on a ring nitrogen atom.

The present teachings also include various isomers and mixtures thereof. “Isomer” refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light (stereoisomers).

Certain of the compounds described herein may exist in various stereoisomeric or tautomeric forms. Stereoisomers are compounds which differ only in their spatial arrangement. The present teachings encompass all such forms, including compounds in the form of essentially pure enantiomers, racemic mixtures and tautomers, which includes forms not depicted structurally. When a disclosed compound is named or depicted by structure without indicating stereochemistry, it is understood that the name or structure encompasses all possible stereoisomers, tautomers, geometric isomers or a combination thereof.

When a geometric isomer is depicted by name or structure, it is to be understood that the geometric isomeric purity of the named or depicted geometric isomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% pure by weight. Geometric isomeric purity is determined by dividing the weight of the named or depicted geometric isomer in the mixture by the total weight of all of the geometric isomers in the mixture.

Racemic mixture means 50% of one enantiomer and 50% of its corresponding enantiomer. The present teachings encompass all enantiomerically-pure, enantiomerically-enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures, and diastereomeric mixtures of the compounds described herein.

Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers can also be obtained

from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

When a compound is designated by a name or structure that indicates a single enantiomer, unless indicated otherwise, the compound is at least 60%, 70%, 80%, 90%, 99% or 99.9% optically pure (also referred to as “enantiomerically pure”). Optical purity is the weight in the mixture of the named or depicted enantiomer divided by the total weight in the mixture of both enantiomers.

When the stereochemistry of a disclosed compound is named or depicted by structure, and the named or depicted structure encompasses more than one stereoisomer (e.g., as in a diastereomeric pair), it is to be understood that one of the encompassed stereoisomers or any mixture of the encompassed stereoisomers are included. It is to be further understood that the stereoisomeric purity of the named or depicted stereoisomers at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight. The stereoisomeric purity in this case is determined by dividing the total weight in the mixture of the stereoisomers encompassed by the name or structure by the total weight in the mixture of all of the stereoisomers.

Included in the present teachings are pharmaceutically acceptable salts of the compounds disclosed herein. The disclosed compounds have basic amine groups and therefore can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p- toluenesulfonic, and tartaric acids). Compounds of the present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid.

Compounds described herein can inhibit various kinases, including the TTK, PLK (such as PLK4), Aurora A, Aurora B, CHK (such as CHK2), ALK, cKit(V560G), JNK3, MELK, and MUSK. Thus, generally, compounds described herein are useful in the treatment of diseases or conditions associated with such kinases. In some embodiments, compounds described herein can inhibit TTK, PLK (such as PLK4), and/or Aurora B kinases. In some embodiments, compounds described herein can inhibit ALK, Aurora B, cKit(V560G), JNK3, MELK, and/or MUSK kinases.

In one embodiment, the compounds described herein are TTK, PLK, Aurora A, Aurora B and/or CHK inhibitors, and are useful for treating diseases, such as cancer, associated with such kinase(s). Alternatively, the compounds described herein are TTK inhibitors and are useful for treating diseases associated with TTK, such as cancer. In another alternative embodiment, the compounds described herein are Aurora A and/or B inhibitors and are useful in inhibiting Aurora A and/or B activity for the treatment of various conditions such as cancers. In yet another specific embodiment, the compounds described herein are PLK inhibitors and are useful in inhibiting PLK activity for the treatment of various conditions such as cancers. Typically, the PLK is PLK4, PLK2 and/or PLK1. In one example, the PLK is PLK1 and/or PLK4. In another example, the PLK is PLK4. In another alternative embodiment, the compounds described herein are CHK inhibitors and are useful in inhibiting CHK activity for the treatment of various conditions such as cancers. In another alternative embodiment, the compounds described herein are ALK inhibitors and are useful in inhibiting ALK activity for the treatment of various conditions such as cancers. In another alternative embodiment, the compounds described herein are cKit(V560G)inhibitors and are useful in inhibiting cKit(V560G)activity for the treatment of various conditions such as cancers. In another alternative embodiment, the compounds described herein are JNK3inhibitors and are useful in inhibiting JNK3activity for the treatment of various conditions such as cancers. In another alternative embodiment, the compounds described herein are MELK inhibitors and are useful in inhibiting MELK activity for the treatment of various conditions such as cancers. In another alternative embodiment, the compounds described herein are MUSK inhibitors and are useful in inhibiting MUSK activity for the treatment of various conditions such as cancers.

Another aspect of the present teachings relates to a method of treating a subject with cancer comprising administering to the subject an effective amount of a compound described herein. In one embodiment, the compounds described herein inhibit the growth of a tumor. For example, the compounds described herein inhibit the growth of a tumor that overexpresses at least one of TTK, PLK, Aurora A, Aurora B, CHK, ALK, cKit(V560G), JNK3, MELK, and MUSK.

In one embodiment, the compounds described herein inhibit the growth of a tumor that overexpresses TTK.

Cancers that can be treated (including reduction in the likelihood of recurrence) by the methods of the present teachings include lung cancer, breast cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiform, ovarian cancer, lymphoma, leukemia, melanoma, sarcoma, paraneoplasia, osteosarcoma, germinoma, glioma and mesothelioma. In one embodiment, the cancer is selected from leukemia, acute myeloid leukemia, chronic myelogenous leukemia, breast cancer, brain cancer, colon cancer, colorectal cancer, head and neck cancer, hepatocellular carcinoma, lung adenocarcinoma, metastatic melanoma, pancreatic cancer, prostate cancer, ovarian cancer and renal cancer. In one embodiment, the cancer is lung cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiform or

ovarian cancer. In another embodiment, the cancer is lung cancer, breast cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiform or ovarian cancer. In yet another embodiment, the cancer is breast cancer, colon cancer and lung cancer. In yet another embodiment, the cancer is a breast cancer. In yet another embodiment, the cancer is a basal sub-type breast cancer or a luminal B sub-type breast cancer. In yet another embodiment, the cancer is a basal sub-type breast cancer that overexpresses TTK. In yet another embodiment, the basal sub-type breast cancer is ER (estrogen receptor), HER2 and PR (progesterone receptor) negative breast cancer. In yet another embodiment, the cancer is a soft tissue cancer. A “soft tissue cancer” is an art-recognized term that encompasses tumors derived from any soft tissue of the body. Such soft tissue connects, supports, or surrounds various structures and organs of the body, including, but not limited to, smooth muscle, skeletal muscle, tendons, fibrous tissues, fatty tissue, blood and lymph vessels, perivascular tissue, nerves, mesenchymal cells and synovial tissues. Thus, soft tissue cancers can be of fat tissue, muscle tissue, nerve tissue, joint tissue, blood vessels, lymph vessels, and fibrous tissues. Soft tissue cancers can be benign or malignant. Generally, malignant soft tissue cancers are referred to as sarcomas, or soft tissue sarcomas. There are many types of soft tissue tumors, including lipoma, lipoblastoma, hibernoma, liposarcoma, leiomyoma, leiomyosarcoma, rhabdomyoma, rhabdomyosarcoma, neurofibroma, schwannoma (neurilemoma), neuroma, malignant schwannoma, neurofibrosarcoma, neurogenic sarcoma, nodular tenosynovitis, synovial sarcoma, hemangioma, glomus tumor, hemangiopericytoma, hemangioendothelioma, angiosarcoma, Kaposi sarcoma, lymphangioma, fibroma, elastofibroma, superficial fibromatosis, fibrous histiocytoma, fibrosarcoma, fibromatosis, dermatofibrosarcoma protuberans (DFSP), malignant fibrous histiocytoma (MFH), myxoma, granular cell tumor, malignant mesenchymomas, alveolar soft-part sarcoma, epithelioid sarcoma, clear cell sarcoma, and desmoplastic small cell tumor. In a particular embodiment, the soft tissue cancer is a sarcoma selected from the group consisting of a fibrosarcoma, a gastrointestinal sarcoma, a leiomyosarcoma, a dedifferentiated liposarcoma, a pleomorphic liposarcoma, a malignant fibrous histiocytoma, a round cell sarcoma, and a synovial sarcoma.

In another embodiment, the cancer being treated by the disclosed methods is a cancer of the breast, colon or ovaries.

In some embodiments, the present teachings provide methods of inhibiting the growth of tumor-initiating cells or reducing the likelihood of recurrence of a cancer in a subject who is undergoing an anti-cancer therapy. The method comprises the steps of:

- a) assessing the subject to determine whether the cancer is in remission; and
- b) if the cancer is in remission; then administering to the subject an effective amount of a TTK inhibitor (*e.g.*, a compound represented by Structural Formula (I) or (Ia)). If the cancer is not in remission, the method optionally further comprises the step of continuing the anti-cancer therapy until the cancer goes into remission and then the step b) of administering an effective amount of a TTK inhibitor (*e.g.*, a compound represented by Structural Formula (I) or (Ia)).

As used herein, the term “tumor-initiating cells” or “TICs” refer to cells present within some tumors that possess the ability to self-renew and proliferate. These cells are sometimes called cancer stem cells (CSCs) and may be observed to share certain characteristics with normal stem cells, including a stem cell-like phenotype and function. In some embodiments, TICs are characterized by their ability to form tumors after xenotransplantation in immunodeficient mice.

In some embodiments, the present teachings provide methods of inhibiting the growth of tumor-initiating cells or reducing the likelihood of recurrence of a cancer in a subject whose cancer is in remission comprising administering to the subject an effective amount of a TTK inhibitor (*e.g.*, a compound represented by Structural Formula (I) or (Ia)).

In some embodiments, *e.g.*, where the subject is being treated to reduce the likelihood of recurrence of a cancer, the subject has already been treated with an anti-cancer therapy. Alternatively, the subject has already been treated with an anti-cancer therapy and the subject is in remission.

In some embodiments, the present teachings provide methods of treating a subject with a cancer comprising administering to the subject an effective amount of a compound represented by Structural Formula (I) or (Ia) in combination with an effective anti-cancer therapy. In one embodiment, the cancer is a metastatic cancer. A “metastatic cancer” is a cancer that has spread from its primary site to other parts of the body.

In another embodiment, the present teachings are directed to a method of treating a subject with a drug-resistant cancer. A “drug-resistant cancer” is a cancer that is not responsive to one, two, three, four, five or more drugs that are typically used for the treatment of the cancer. In one embodiment, the drug-resistant cancer is mediated by the growth of tumor-initiating cells.

Suitable methods known in the art can be used for assessing a subject to determine whether the cancer is in remission. For example, the size of the tumor and/or tumor markers, usually proteins associated with tumors, can be monitored to determine the state of the cancer. Size of the tumor can be monitored with imaging devices, such as X-ray, MRI, CAT scans, ultrasound, mammography, PET and the like or via biopsy.

For methods described herein, *e.g.*, coadministration methods, the anti-cancer therapy is selected from the group consisting of surgery, radiation therapy, immunotherapy, endocrine therapy, gene therapy and administration of an anti-cancer agent. Alternatively, the anti-cancer therapy is radiation therapy. In another alternative, the anti-cancer therapy is immunotherapy. In another alternative, the anti-cancer therapy is administration of an anti-cancer agent. In yet another alternative, the anti-cancer therapy is surgery.

Radiation therapy is the use of radiation to kill, destroy or treat the cancers. Exemplary radiation therapy includes, but is not limited to, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and radioisotope therapy (*i.e.*, systemic radioactive isotopes therapy).

An endocrine therapy is a treatment that adds, blocks or removes hormones. For example, chemotherapeutic agents that can block the production or activity of estrogen have been used for treating breast cancer. In addition, hormonal stimulation of the immune system has been used to treat specific cancers, such as renal cell carcinoma and melanoma. In one embodiment, the endocrine therapy comprises administration of natural hormones, synthetic hormones or other synthetic molecules that may block or increase the production of the body's natural hormones. In another embodiment, the endocrine therapy includes removal of a gland that makes a certain hormone.

As used herein, a gene therapy is the insertion of genes into a subject's cell and biological tissues to treat diseases, such as cancer. Exemplary gene therapy includes, but is not limited to, a germ line gene therapy and a somatic gene therapy.

Immunotherapy (also called biological response modifier therapy, biologic therapy, biotherapy, immune therapy, or biological therapy) is treatment that uses parts of the immune system to fight disease. Immunotherapy can help the immune system recognize cancer cells, or enhance a response against cancer cells. Immunotherapies include active and passive immunotherapies. Active immunotherapies stimulate the body's own immune system while passive immunotherapies generally use immune system components created outside of the body.

Examples of active immunotherapies include, but are not limited to vaccines including cancer vaccines, tumor cell vaccines (autologous or allogeneic), dendritic cell vaccines, antigen vaccines, anti-idiotypic vaccines, DNA vaccines, viral vaccines, or Tumor-Infiltrating Lymphocyte (TIL) Vaccine with Interleukin-2 (IL-2) or Lymphokine-Activated Killer (LAK) Cell Therapy.

Examples of passive immunotherapies include but are not limited to monoclonal antibodies and targeted therapies containing toxins. Monoclonal antibodies include naked antibodies and conjugated monoclonal antibodies (also called tagged, labeled, or loaded antibodies). Naked monoclonal antibodies do not have a drug or radioactive material attached whereas conjugated monoclonal antibodies are joined to, for example, a chemotherapy drug (chemolabeled), a radioactive particle (radiolabeled), or a toxin (immunotoxin). Examples of these naked monoclonal antibody drugs include, but are not limited to Rituximab (Rituxan), an antibody against the CD20 antigen used to treat, for example, B cell non-Hodgkin lymphoma; Trastuzumab (Herceptin), an antibody against the HER2 protein used to treat, for example, advanced breast cancer; Alemtuzumab (Campath), an antibody against the CD52 antigen used to treat, for example, B cell chronic lymphocytic leukemia (B-CLL); Cetuximab (Erbix), an antibody against the EGFR protein used, for example, in combination with irinotecan to treat, for example, advanced colorectal cancer and head and neck cancers; and Bevacizumab (Avastin) which is an antiangiogenesis therapy that works against the VEGF protein and is used, for example, in combination with chemotherapy to treat, for example, metastatic colorectal cancer. Examples of the conjugated monoclonal antibodies include, but are not limited to Radiolabeled antibody Ibritumomab tiuxetan (Zevalin) which delivers radioactivity directly to cancerous B lymphocytes and is used to treat, for example, B cell non-Hodgkin lymphoma;

radiolabeled antibody Tositumomab (Bexxar) which is used to treat, for example, certain types of non-Hodgkin lymphoma; and immunotoxin Gemtuzumab ozogamicin (Mylotarg) which contains calicheamicin and is used to treat, for example, acute myelogenous leukemia (AML). BL22 is a conjugated monoclonal antibody for treating, for example, hairy cell leukemia, immunotoxins for treating, for example, leukemias, lymphomas, and brain tumors, and radiolabeled antibodies such as OncoScint for example, for colorectal and ovarian cancers and ProstaScint for example, for prostate cancers.

Alternatively, the anti-cancer therapy described herein includes administration of an anti-cancer agent. An “anti-cancer agent” is a compound, which when administered in an effective amount to a subject with cancer, can achieve, partially or substantially, one or more of the following: arresting the growth, reducing the extent of a cancer (e.g., reducing size of a tumor), inhibiting the growth rate of a cancer, and ameliorating or improving a clinical symptom or indicator associated with a cancer (such as tissue or serum components) or increasing longevity of the subject.

The anti-cancer agent suitable for use in the methods described herein includes any anti-cancer agents that have been approved for the treatment of cancer. In one embodiment, the anti-cancer agent includes, but is not limited to, a targeted antibody, an angiogenesis inhibitor, an alkylating agent, an antimetabolite, a vinca alkaloid, a taxane, a podophyllotoxin, a topoisomerase inhibitor, a hormonal antineoplastic agent and other antineoplastic agents.

In one embodiment, the anti-cancer agents that can be used in methods described herein include, but are not limited to, paclitaxel, docetaxel, 5-fluorouracil, trastuzumab, lapatinib, bevacizumab, letrozole, goserelin, tamoxifen, cetuximab, panitumumab, gemcitabine, capecitabine, irinotecan, oxaliplatin, carboplatin, cisplatin, doxorubicin, epirubicin, cyclophosphamide, methotrexate, vinblastine, vincristine, melphalan, cytarabine, etoposide, daunorubicin, bleomycin, mitomycin and adriamycin and a combination thereof.

In one embodiment, the anti-cancer agent and the compound represented by Structural Formula (I) or (Ia) are administered contemporaneously. When administered contemporaneously, the anti-cancer agent and the compound can be administered in the same formulation or in different formulations. Alternatively, the compound and the additional anti-cancer agent are administered separately at different times.

In one embodiment, the subject in the methods described herein has not been previously treated with a TTK inhibitor (e.g., the compound represented by Structural Formula (I) or (Ia)).

The term an “effective amount” means an amount when administered to the subject which results in beneficial or desired results, including clinical results, e.g., inhibits, suppresses or reduces the cancer (e.g., as determined by clinical symptoms or the amount of cancer cells) in a subject as compared to a control.

The term “inhibiting the growth of tumor-initiating cells” refers to preventing or decreasing the rate of the proliferation and/or survival of the tumor-initiating cells.

As used herein, the term “reducing the likelihood of recurrence of a cancer” means inhibiting or delaying the return of a cancer at or near a primary site and/or at a secondary site after a period of remission. It also means that the cancer is less likely to return with treatment described herein than in its absence.

As used herein, the term “remission” refers to a state of cancer, wherein the clinical symptoms or indicators associated with a cancer have disappeared or cannot be detected, typically after the subject has been successfully treated with an anti-cancer therapy.

As used herein, “treating a subject with a cancer” includes achieving, partially or substantially, one or more of the following: arresting the growth, reducing the extent of the cancer (e.g., reducing size of a tumor), inhibiting the growth rate of the cancer, ameliorating or improving a clinical symptom or indicator associated with the cancer (such as tissue or serum components) or increasing longevity of the subject; and reducing the likelihood of recurrence of the cancer.

Generally, an effective amount of a compound taught herein varies depending upon various factors, such as the given drug or compound, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject or host being treated, and the like, but can nevertheless be routinely determined by one skilled in the art. An effective amount of a compound of the present teachings may be readily determined by one of ordinary skill by routine methods known in the art.

In an embodiment, an effective amount of a compound taught herein ranges from about 0.1 to about 1000 mg/kg body weight, alternatively about 1 to about 500 mg/kg body weight, and in another alternative, from about 20 to about 300 mg/kg body weight. In another embodiment, an effective amount of a compound taught herein ranges from about 0.5 to about 5000 mg/m², alternatively about 5 to about 2500 mg/m², and in another alternative from about 50 to about 1000 mg/m². The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject suffering from cancer or reduce the likelihood of recurrence of a cancer. These factors include, but are not limited to, the severity of the disease or disorder, previous treatments, the general health and/or age of the subject and other diseases present.

Moreover, for methods described herein (including treating a subject with a cancer or reducing the likelihood of recurrence of a cancer), a “treatment” or dosing regime of a subject with an effective amount of the compound of the present teachings may consist of a single administration, or alternatively comprise a series of applications. For example, the compound of the present teachings may be administered at least once a week. However, in another embodiment, the compound may be administered to the subject from about one time per week to once daily for a given treatment. The length of the treatment period depends on a variety of factors, such as the severity of the disease, the

age of the patient, the concentration and the activity of the compounds of the present teachings, or a combination thereof. It will also be appreciated that the effective dosage of the compound used for the treatment may increase or decrease over the course of a particular treatment regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required.

A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

The compounds taught herein can be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the present teachings may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal and topical modes of administration. Parenteral administration can be by continuous infusion over a selected period of time.

The compounds taught herein can be suitably formulated into pharmaceutical compositions for administration to a subject. The pharmaceutical compositions of the present teachings optionally include one or more pharmaceutically acceptable carriers and/or diluents therefor, such as lactose, starch, cellulose and dextrose. Other excipients, such as flavoring agents; sweeteners; and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More complete listings of suitable excipients can be found in the Handbook of Pharmaceutical Excipients (5th Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003 - 20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. The carriers, diluents and/or excipients are "acceptable" in the sense of being compatible with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

Typically, for oral therapeutic administration, a compound of the present teachings may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

Typically for parenteral administration, solutions of a compound of the present teachings can generally be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Typically, for injectable use, sterile aqueous solutions or dispersion of, and sterile powders of, a compound described herein for the extemporaneous preparation of sterile injectable solutions or dispersions are appropriate.

For nasal administration, the compounds of the present teachings can be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

For buccal or sublingual administration, the compounds of the present teachings can be formulated with with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine, as tablets, lozenges or pastilles.

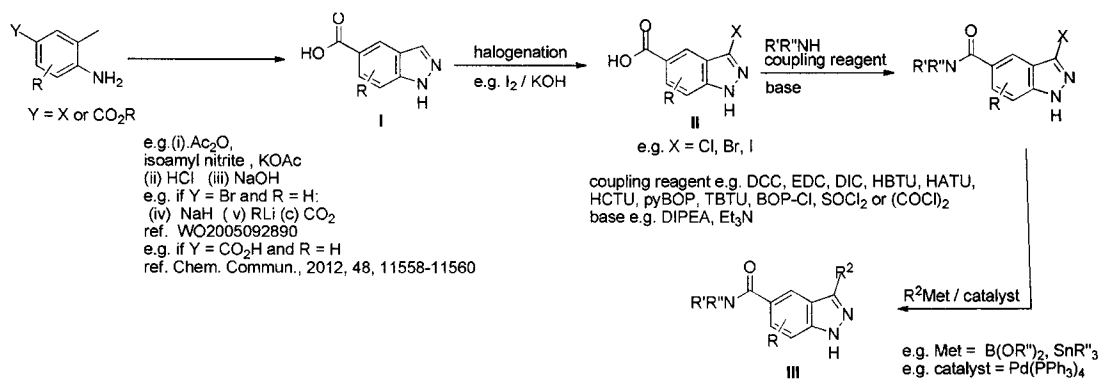
For rectal administration, the compounds described herein can be formulated in the form of suppositories containing a conventional suppository base such as cocoa butter.

The compounds of invention may be prepared by methods known to those skilled in the art, as illustrated by the general schemes and procedures below and by the preparative examples that follow. All starting materials are either commercially available or prepared by methods known to those skilled in the art and the procedures described below.

General synthetic approaches to the 1H-indazole core have been reviewed in literature (Schmidt A. *et al. Eur. J. Org. Chem.* 2008, 4073–4095).

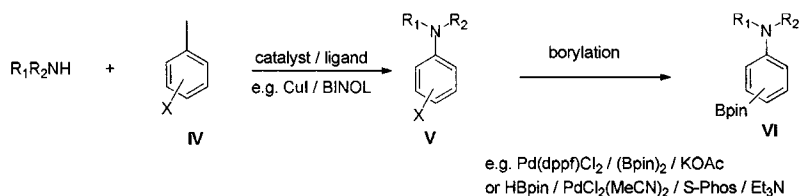
In one general synthetic process, compounds **III** described herein can be prepared according to the following reaction **Scheme 1**, from 3-halo-1H-indazole-5-carboxylic acid **II** in a sequence comprising of an amide formation followed by a cross-coupling reaction with a suitable cross coupling partner, R²Met (e.g. ArB(OR')₂, ArSnR₃) in the presence of a metal catalyst (e.g. PdCl₂(dppf) or Pd(PPh₃)₄).

Scheme 1



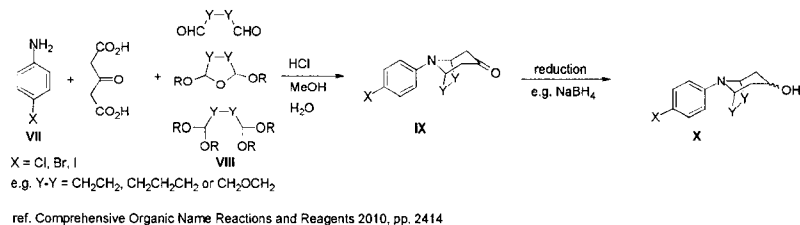
The intermediate boronic esters **VI** described herein can be prepared through a borylation of suitable aniline-based arylhalide **V** which, in turn, can be prepared via meta- catalyzed amination of an appropriately substituted dihalobenzene **IV** (Scheme 2).

Scheme 2



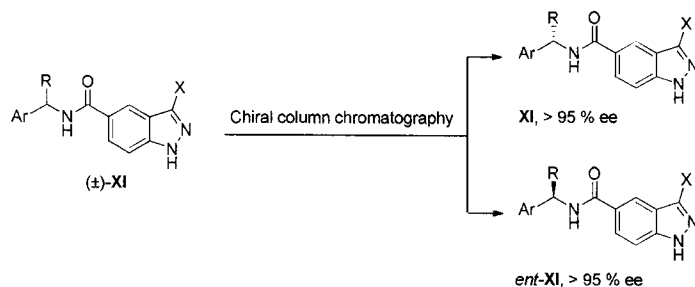
Whereas nortropine and norpseudotropine are commercially available, nortropinone and its analogs can be made through a multicomponent condensation of para-haloaniline **VII**, 3-oxopentanedioic acid and suitable dialdehydes, or their precursors (**VIII**), as shown in **Scheme 3**. Subsequent reduction of thus obtained ketones (**IX**) affords the corresponding bridged bicyclic alcohols **X**.

Scheme 3



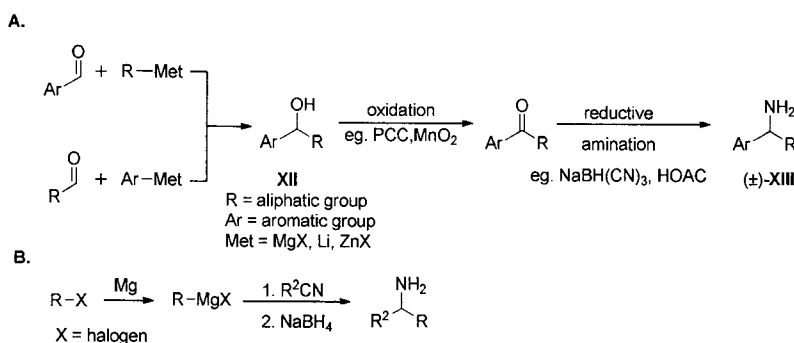
Enantiomerically pure (typically > 98 % ee) 3-iodo-1H-indazole-5-carboxamides described herein can be prepared as outlined in **Scheme 4** by separating racemic compounds (**XI**) using chiral preparative chromatography.

Scheme 4



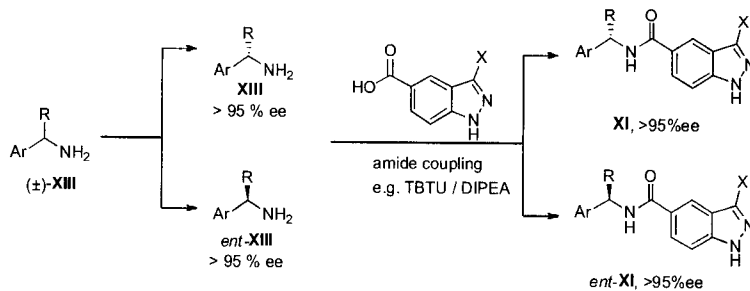
Racemic amines (**XIII**) described herein can be synthesized in three steps as outlined in **Scheme 5A**. Nucleophilic addition to an aldehyde using organometallic reagents such as Grignard, organolithium or organozinc reagents resulted in secondary alcohol **XII**. Subsequent oxidation to the corresponding ketone followed by reductive amination step resulted in the desired racemic amine (**XIII**). Alternatively, the desired racemic amines described herein can be obtained using a one-pot synthesis through a condensation of an organometallic reagent and an organonitrile, followed by reduction of the imine intermediate as shown in **Scheme 5B**.

Scheme 5



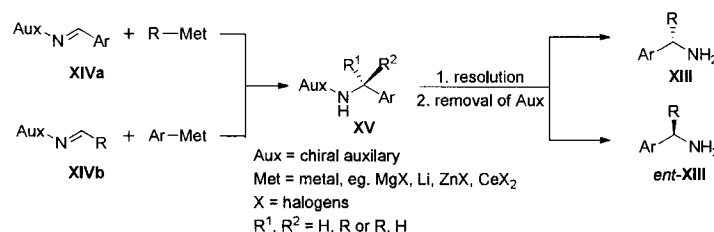
Alternatively, enantiomerically pure 3-iodo-1H-indazole-5-carboxamides **XI** can be prepared via an amide coupling of 3-halo-1H-indazole-5-carboxylic acid and enantiomerically pure amines **XIII** (**Scheme 6**). Such enantiomerically pure amine can be obtained by separating racemic amine using chiral preparative chromatography or recrystallization of its salt with chiral acids such as for example tartaric acid, mandelic acid and dibenzoyl-tartaric acid.

Scheme 6



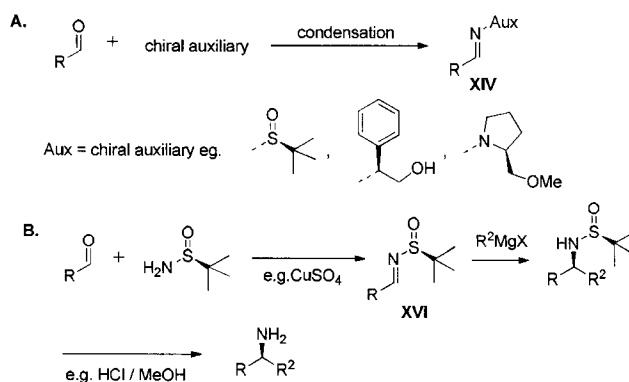
In addition, enantiomerically pure amines described herein can be synthesized using asymmetric nucleophilic addition of carboanions to chiral imines **XIVa,b** (Scheme 7). In this approach, the desired chiral amine can be synthesized in two ways by switching the role of which fragment acts as a nucleophile and which acts as an electrophile in the addition step. The chiral auxiliary serves as a chiral directing group to provide addition product **XV** with high diastereoselectivity in general, or can be further enriched using standard purification methods. Removal of the chiral auxiliary affords the desired optically active amine **XIII**. Enantiomeric excess of the amines described herein can be further improved by recrystallization.

Scheme 7



A variety of chiral auxiliary can be employed in the synthesis of chiral imine **XIVa,b** (Scheme 8A). A method developed by Ellman involved a condensation of tert-butylsulfinyl amide with aldehydes to provide intermediate **XVI** (Scheme 8B; ref: *Chem. Rev.* **2010**, *110*, 3600). Grignard reagents are added diastereoselectively and the auxiliary is removed under mild acidic conditions. Other examples of chiral auxiliaries that are commonly employed in this approach are 1-amino-2-methoxymethylpyrrolidine (ref: *Tetrahedron: Asymmetry* **1997**, *8*, 1895), and phenylglycinol (ref: *J. Org. Chem.* **1991**, *56*, 1340).

Scheme 8



Compounds described herein can be prepared in a manner analogous to the general procedures described above or the detailed procedures described in the examples herein.

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

Example A: Synthesis

General Methods

Commercially available starting materials, reagents, and solvents were used as received. In general, anhydrous reactions were performed under an inert atmosphere such as nitrogen or Argon. PoraPak® Rxn CX refers to a commercial cation-exchange resin available from Waters.

Microwave reactions were performed with a Biotage Initiator microwave reactor. Reaction progress was generally monitored by TLC using Merck silica gel plates with visualization by UV at 254 nm, by analytical HPLC or by LCMS (Bruker Exquire 4000). Flash column chromatographic purification of intermediates or final products was performed using 230-400 mesh silica gel 60 from EMD chemicals or Silicycle, or purified using a Biotage Isolera with KP-SIL or HP-SIL silica cartridges, or KP-NH basic modified silica and corresponding samplelets. Reverse-phase RPHPLC purification was performed on a Varian PrepStar model SD-1 HPLC system with a Varian Monochrom 10u C-18 reverse-phase column using a of about 5-30 % MeCN or MeOH/ 0.05 % TFA - H₂O to 70-90 % MeCN or MeOH/0.05 % TFA - H₂O over a 20-40-min period at a flow rate of 30-50 mL/min. Reverse phase purification was also performed using a Biotage Isolera equipped with a KP-C18-H column using a between 10-95 % MeOH / 0.1 % TFA in H₂O. Proton NMRs were recorded on a Bruker 400 MHz spectrometer, and mass spectra were obtained using a Bruker Esquire 4000 spectrometer. Optical rotations were measured at the sodium D-line (589.44nm) using an AA-55 polarimeter from Optical Activity Ltd with a 2.5x100mm unjacketed stainless steel tube at given sample concentrations (c, units of g/100mL).

Compound names were generated using the software built into CambridgeSoft-PerkinElmer's ChemBioDraw Ultra version 11.0 or 12.0.

Abbreviations:

Ac	Acetyl
aq	aqueous
anh	anhydrous
Ar	argon
BINOL	1,1'-binaphthalene-2,2'-diol
Boc	<i>tert</i> -butoxycarbonyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
br.	broad
calcd	calculated
COMU	(1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate
d	doublet (only when used within ¹ H NMR spectra)
d	day

DBTA	dibenzoyl-L-tartaric acid monhydrate
DCE	1,2-dichloroethane
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCM	dichloromethane
DEA	diethylamine
de	diastereomeric excess
DIPEA	diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'- bis(diphenylphosphino) ferrocene
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
e.e.	enantiomeric excess
h	hour
hal	halogen
HATU	2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
IPA	iso-propanol
LC-MS	liquid chromatography coupled to mass spectrometry
min	minute
m	multiplet
MS ESI	mass spectra, electrospray ionization
NMR	nuclear magnetic resonance
NBS	<i>N</i> -Bromosuccinimide
O/N	overnight
PCC	pyridinium chlorochromate
pin	pinacol
prep	preparative
PTSA	p-toluenesulfonic acid
PyBOP	(benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
RBF	round bottomed flask
rt	room temperature
Rt	retention time
s	singlet
satd	saturated
SMs	starting materials
SPE	solid phase extraction

S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet
TBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
TEA	triethylamine
temp.	temperatureTFA trifluoroacetic acid
TLC	thin layer chromatography
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl
Ts	tosyl
xs	excess

Preparation of Starting Materials

General Method A (amide coupling)

A DMF solution of 3-iodo-1*H*-indazole-5-carboxylic acid (1.0 equiv), DIPEA (3.0-5.0 equiv) and RR'NH (1.00-1.05 equiv) at 0 °C or rt was treated with TBTU or BOP-Cl (1.05 equiv) added in one portion. The reaction was stirred allowing slowly to warm to rt. After several h or overnight stirring the crude reaction was subsequently diluted with H₂O. In the majority of examples a filtration and washing (H₂O) of the precipitate provided the desired material with the required purity or alternatively the material was purified directly by prep-HPLC or/and flash chromatography.

General Method B (Suzuki-Miyaura cross coupling)

A mixture of 3-iodo-1*H*-indazole (1.0 equiv), aryl boronic acid or boronate ester (1.2 equiv), base and palladium catalyst (0.05 equiv e.g. and PdCl₂dppf.DCM, Pd(PPh₃)₄) in solvents was degassed with Ar and heated sealed in a Biotage microwave reactor. The crude material was filtered through Celite using MeOH to rinse the pad. In the majority of examples, purification by prep-HPLC provided the target material.

General Method B2 (Suzuki-Miyaura cross coupling with PdCl₂dppf.DCM-Na₂CO₃)

Aq Na₂CO₃ (2 M, 3-4 mmol) was added to a mixture of 5-substituted-3-iodo-1*H*-indazole (1.0 mmol), aryl boronic acid or boronate ester (1.0-1.4 mmol), and PdCl₂dppf.DCM (0.1 mmol) in PhMe : EtOH (1:1, 20 mL) was heated under Ar in a Biotage microwave reactor, an oil bath or a reaction block at temperatures from 100-130 °C. The crude material was filtered through Celite using MeOH (alternatively, acetone / MeOH or EtOAc) to rinse the pad or partitioned between EtOAc and H₂O followed by drying (Na₂SO₄ or MgSO₄), and evaporated and purified by chromatography.

General Method C (Borylation of aryl halides): using B₂pin₂ / Pd

A mixture of aryl iodide or aryl bromide (1 equiv.), bis(pinacolato)diboron (1.2 to 1.5 equiv.), KOAc (3 equiv.) and DMF or DMSO was purged with Ar for 10 min. [1,1'- PdCl₂dppf*CH₂Cl₂ (3-5 mol%) was added, the vial sealed and heated at 85-100 °C for 2-3 h. The product was partitioned between

EtOAc and satd aq NaHCO₃ solution, washed with brine, dried over Na₂SO₄ or MgSO₄, filtered, and concentrated to dryness. The crude product was purified by flash chromatography to give the title compound.

General Method D (Boronation of aryl halides): using HBpin / Pd

To a solution of aryl iodide or aryl bromide (1.0 mmol) in NEt₃ (3.0 mmol) and dioxane (1.0 mL) was added under Ar and HBpin (1.5 mmol), S-Phos (0.040 mmol) and Cl₂Pd(CH₃CN)₂ (0.010 mmol) and the reaction heated to 110 °C for 3 h. The mixture was then transferred to a separatory funnel with EtOAc (10 mL) and washed with NaHCO₃ (satd) (2 x 10 mL), H₂O (10 mL), and brine (10 mL). The organic layer was dried over MgSO₄, filtered and the solvent removed to yield pinacol boronic esters which were used directly for subsequent steps.

General Method E (Reductive amination)

NaBH₃CN (4 mmol) was added to a solution of aryl alkyl ketone (1 mmol) and NH₄OAc (12 mmol) in MeOH (4-5 mL) under Ar, and the reaction mixture was heated at 60 °C for 14-24 h. Aq. NaOH (2 M, 15 mL) was added and the product was extracted into Et₂O (3x 40 mL). The combined Et₂O layer was washed with H₂O (10 mL) and brine (10 mL), dried (Na₂SO₄), filtered, concentrated to dryness and used crude or purified by chromatography.

General Method F (copper catalyzed amination of aryl-hal)

A microwave vial was charged with 1,4-diiodobenzene or 1-bromo-4-iodobenzene (1.0 equiv), CuI (20 mol%), BINOL (20 mol%), and K₃PO₄ (2 equiv.). The vial was capped and then evacuated and backfilled with Ar. Dialkylamine (1.2 equiv) and DMF were then added. The resulting mixture was stirred at rt for 2 to 4 d. The mixture was diluted with EtOAc, filtered through a cake of Celite and the filtrate was concentrated to give the crude product. Crude product was purified by flash chromatography to give the title compound.

General Method G (One-pot synthesis of cyclopropylmethanamine using aryl nitrile)

To a microwave vial charged with Mg powder (2 equiv.) and THF was added bromocyclopropane (2 equiv.). The resulting mixture was stirred for 30 min at rt before a solution of aryl nitrile (1 equiv.) in THF was added. It was microwaved 10 min at 100 °C, cooled to rt and added dropwise to a cold solution of NaBH₄ (2 equiv.) in MeO at 0 °C. The resulting mixture was stirred for 15 min at rt, quenched with H₂O, extracted with DCM and purified by Biotage SiO₂ column (gradient: MeOH/DCM 0-30%) to give the desired product.

General Method H (Synthesis of t-butylsulfinylimines)

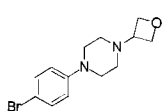
Aryl or alkyl aldehyde (1.2 eq.) was added to a stirred suspension of (S)-t-butylsulfinylamide (1.0 eq.) and flame-dried CuSO₄ (2.2 eq.) in dry CH₂Cl₂. The resulting mixture was stirred at rt for 69 h. The reaction mixture was filtered through a pad of Celite and the pad was extracted with CH₂Cl₂. The combined organic extracts were concentrated under reduced pressure yielding the crude product. Purification by repeated flash chromatography (SiO₂) using EtOAc-cyclohexane as eluent gave the desired product.

General Method I (Deprotection of sulfinamides)

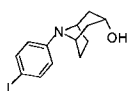
A solution of HCl (2.0 M in Et₂O, 2.0 eq.) was added carefully to a stirred 0 °C solution of sulfinamide (1.0 eq.) in MeOH. After the addition was complete the cooling bath was removed and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure and Et₂O was added and a white precipitation formed. The precipitation was filtered off and washed with Et₂O and dried under reduced pressure yielding the crude product.

General Method J (HCl salt formation)

To a solution of final compound in MeOH at 0 °C was added 1 M HCl in Et₂O (1-2.1 equiv. depending on the number of basic centers). After stirring for 1 min at 0 °C, it was concentrated to remove solvents. MeOH was added and solvents were removed. This was repeated twice to give the desired HCl or 2HCl salts usually as yellow solids.

Intermediates:Synthesis of (1R,3R,5S)-8-(4-iodophenyl)-8-azabicyclo[3.2.1]octan-3-ol

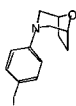
To a solution of 1-(4-bromophenyl)piperazine (24.1 g, 100 mmol) in DCE (400 mL) was added oxetan-3-one (10.8 g, 150 mmol) and precipitates formed immediately. NaBH(OAc)₃ (31.8 g, 150 mmol) was added followed by HOAc (1 mL). The resulting mixture was stirred O/N at rt. It was quenched with sat. NaHCO₃ (100 mL), H₂O (100 mL) and stirred for 5 min before extracting with DCM (200 mL x 2). The combined extracts were washed with H₂O (300 mL) and dried over Na₂SO₄. Removal of solvents gave 1-(4-bromophenyl)-4-(oxetan-3-yl)piperazine as white solid (28.53 g, 96%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.36 (d, J = 9.2 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 4.71 (t, J = 6.4 Hz, 2H), 4.66 (t, J = 5.8 Hz, 2H), 3.56 (quintet, J = 6.4 Hz, 1H), 3.21 (t, J = 5.0 Hz, 4H), 2.50 (t, J = 5.0 Hz, 4H). MS ESI 296.1 [M + H]⁺, calcd for [C₁₃H₁₇BrN₂O+H]⁺ 296.1

Synthesis of (1R,3R,5S)-8-(4-iodophenyl)-8-azabicyclo[3.2.1]octan-3-ol

The title compound was synthesized according to General Method F by utilizing nortropine (2.0 g, 15.7 mmol), 1,4-diiodobenzene (7.78 g, 23.5 mmol), K₃PO₄ (10 g, 47 mmol), BINOL (0.9 g, 3.14 mmol), CuI (0.6 g, 3.14 mmol) and anhyd DMF (48 mL) at 45°C for 18 h. After reaction completion the solid sludge was filtered through Celite and washed with EtOAc and the filtrate was concentrated to give the crude product. Purification by flash chromatography (0-45% EtOAc in hexanes) gave 2.90 gm of crude product. After trituration with MeOH, the title compound was isolated as light pink solid (1.14 g, crop-1). The filtrate was concentrated and repurified by flash chromatography (5-90% MeOH in H₂O) to give a further 1.12 g (crop-2) (Combined yield : 2.26 g, 43.6%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.45-7.48 (m, 2 H), 6.52-6.55 (m, 2H), 4.14 (br. s, 2H), 4.01 (br. s, 1H), 2.29-2.34 (m, 2H), 2.17-2.23 (m, 2H), 2.05-2.07

(m, 2H), 1.56-1.60 (m, 2H), 1.42 (d, $J=2.4$ Hz, 1H); MS ESI 330.0 $[M + H]^+$, calcd for $[C_{13}H_{16}INO+H]^+$ 330.2

Synthesis of (1R,5S)-3-(4-iodophenyl)-8-oxa-3-azabicyclo[3.2.1]octane

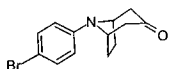


The title compound was synthesized according to General Method F by utilizing 8-oxa-3-azabicyclo[3.2.1]octane HCl salt (100 mg, 0.66 mmol), 1,4-diiodobenzene (330 mg, 1.0 mmol), K_3PO_4 (567 mg, 2.67 mmol), BINOL (38 mg, 0.13 mmol), CuI (26 mg, 0.13 mmol) and anhydrous DMF (6 mL) at 24°C for 48 h. After reaction work up and purification by flash chromatography (0-75 % EtOAc in hexanes) the title compound was isolated as a white solid (95 mg, 45%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.51 (d, $J=8.3$ Hz, 2 H), 6.58 (d, $J=8.3$ Hz, 2 H), 4.49 (br. s, 2 H), 3.28 (d, $J=11.3$ Hz, 2 H), 3.00 (d, $J=11.3$ Hz, 2 H), 1.84 - 2.05 (m, 4 H); MS ESI 316.2 $[M + H]^+$, calcd for $[C_{12}H_{14}INO+H]^+$ 316.0

The following intermediates were synthesized according to General Method F:

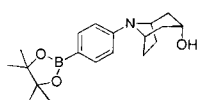
IUPAC name	Structure	MS calculated MS ESI $[M+H]^+$	Yield; Appearance; Salt form
(1R,3S,5S)-8-(4-iodophenyl)-8-azabicyclo[3.2.1]octan-3-ol		$[C_{13}H_{16}INO+H]^+$ 330.0	2.36 g (36%), yellow solid; free base
SMs: (1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (3.27 g, 20 mmol), 1,4-diiodobenzene (6.60 g, 20 mmol)			
^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.52-7.47 (m, 2H), 6.60-6.56 (m, 2H), 4.25-4.11 (m, 3H), 2.11-2.04 (m, 2H), 1.88-1.82 (m, 2H), 1.69-1.61 (m, 2H), 1.18 (d, $J = 6.4$ Hz, 1H).			

Synthesis of (1R,5S)-8-(4-bromophenyl)-8-azabicyclo[3.2.1]octan-3-one



To a solution of 2,5-dimethoxytetrahydrofuran (43.5 g, 330 mmol) and 3-oxopentanedioic acid (16.8 g, 345 mmol) in H_2O (200 mL) was added concentrated HCl (24 mL). The resulting solution was stirred at rt for 30 min, then cooled to 0 °C. A solution of 4-bromoaniline (51.6 g, 300 mmol) in MeOH (250 mL) was added over 20 min. After addition, the resulting mixture was stirred O/N at rt. Conc. HCl (6 mL) was added and reaction was heated at 55 °C for 2h. After quenching with K_2CO_3/H_2O (27.6 g/200 mL) to pH about 7, it was stirred at rt for 45 min. The precipitated were collected by suction filtration, rinsed with H_2O , MeOH and dried to give the title compound as brown solid (73.98 g, 88%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 (d, $J = 8.8$ Hz, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 4.48-4.44 (m, 2H), 2.65 (dd, $J = 15.6, 4.0$ Hz, 2H), 2.33 (d, $J = 15.6$ Hz, 2H), 2.14-2.07 (m, 2H), 1.85-1.78 (m, 2H). MS ESI 279.9 $[M + H]^+$, calcd for $[C_{13}H_{14}BrNO+H]^+$ 280.0

Synthesis of (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-



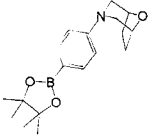
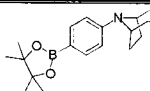
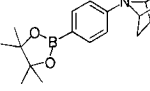
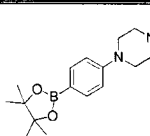
azabicyclo[3.2.1]octan-3-ol

To a suspension of (1R,3r,5S)-8-(4-iodophenyl)-8-azabicyclo[3.2.1]octan-3-ol (13.16 g, 40 mmol), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (987 g, 2.4 mmol, 6 mol%), Pd(CH₃CN)₂Cl₂ (156 mg, 0.6 mmol, 1.5 mol%) in anh. dioxane (120 mL) under Ar, was added Et₃N (16.8 mL, 120 mmol, 3 eq), followed by 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17.4 mL, 3 eq). After addition was complete the resulting mixture was heated in an oil bath at 110 °C for 5 h. After cooling to rt, the reaction mixture was diluted with DCM (100 mL) and slowly quenched with sat. aq NaHCO₃ to pH ~ 8. The reaction mixture was then passed through Celite, rinsed with DCM (200 mL) and the layers were separated. The aq. layer was extracted with DCM (100 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated. Multiple triturations with MeOH gave the title compound as an off white solid (11.619 g). The triturate was purified by Biotage silica gel column (EtOAc/hex 5 to 50%) to give an additional 1.88 g light yellowish off white solid. The total amount of title compound C was 13.50 g (quantitative yield, some pinacol present). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.69 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 4.28-4.23 (m, 2H), 4.03-3.97 (m, 1H), 2.36-2.28 (m, 2H), 2.27-2.19 (m, 2H), 2.11-2.05 (m, 2H), 1.60 (d, J = 14.8 Hz, 2H), 1.33 (s, 12H). MS ESI 330.1 [M + H]⁺, calcd for [C₁₉H₂₈BNO₃+H]⁺ 330.2

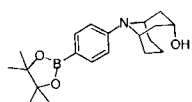
The following intermediates were synthesized according to the synthesis of (1R,5S)-8-(4-bromophenyl)-8-azabicyclo[3.2.1]octan-3-one:

IUPAC name	Structure	MS calculated MS ESI [M+H] ⁺	Yield; Appearance; Salt form
(1R,5S)-9-(4-bromophenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-one		[C ₁₃ H ₁₄ BrNO ₂ +H] ⁺ 296.0 296.0	0.88 g (15%), light brown solid; free base
SMs: 2-(2,2-diethoxyethoxy)-1,1-diethoxyethane (5.00 g, 20 mmol), 3-oxopentanedioic acid (1.61 g, 22 mmol), 4-bromoaniline (3.44 g, 20 mmol)			
¹ H NMR (400 MHz, CDCl ₃) δ ppm 7.42 (d, J = 9.2 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 4.19 (d, J = 5.6 Hz, 1H), 3.94 (d, J = 11.2 Hz, 2H), 3.88 (d, J = 11.2 Hz, 2H), 2.59 (dd, J = 15.6, 5.6 Hz, 2H), 2.48 (d, J = 15.2 Hz, 2H).			
(1R,5S)-9-(4-bromophenyl)-9-azabicyclo[3.3.1]nonan-3-one		[C ₁₄ H ₁₆ BrNO+H] ⁺ 294.0 294.0	2.97 g (10%), brown solid and 6.2 g brown oil (used without further purification); free base
SMs: glutaraldehyde (50%wt in H ₂ O, 20 mL, 110 mmol), 3-oxopentanedioic acid (16.8 g, 115 mmol), 4-bromoaniline (17.2 g, 100 mmol)			
¹ H NMR (400 MHz, CDCl ₃) δ ppm 7.37 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 9.2 Hz, 2H), 4.45-4.38 (m, 2H), 2.65 (dd, J = 16.4, 6.4 Hz, 2H), 2.41 (d, J = 16.4 Hz, 2H), 2.02-1.90 (m, 2H), 1.80-1.73 (m, 2H), 1.70-1.61 (m, 2H).			

The following intermediates were synthesized according to General Method C (or D where indicated):

IUPAC name	Structure	MS calculated MS ESI [M+H] ⁺	Yield; Appearance; Salt form
(1R,5S)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-oxa-3-azabicyclo[3.2.1]octane		[C ₁₈ H ₂₆ BNO ₃ +H] ⁺ 316.2 316.2	58 mg (61%); white solid
SMs: (1R,5S)-3-(4-iodophenyl)-8-oxa-3-azabicyclo[3.2.1]octane (95 mg, 0.30 mmol), B ₂ pin ₂ (115 mg, 0.45 mmol), KOAc (89 mg, 0.90 mmol), PdCl ₂ dppf*CH ₂ Cl ₂ (24 mg, 0.029 mmol)			
¹ H NMR (400 MHz, CDCl ₃) δ ppm 7.71 (d, J=8.5 Hz, 2H), 6.79 (d, J=8.5 Hz, 2H), 4.49 (br. s, 2H), 3.41 (d, J=11.3 Hz, 2H), 3.07 (s, 2H), 1.93 (br. s, 4H), 1.31 - 1.36 (m, 12H)			
(1R,3S,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol		[C ₁₉ H ₂₈ BNO ₃ +H] ⁺ 330.2 330.1	2.05 g (87%), off white solid; free base
SMs: (General Method D) (1R,3s,5S)-8-(4-iodophenyl)-8-azabicyclo[3.2.1]octan-3-ol (2.35 g, 7 mmol), HBpin (3.05 mL, 21 mmol)			
¹ H NMR (400 MHz, CDCl ₃) δ ppm 7.70 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 4.36-4.31 (m, 2H), 4.22-4.11 (m, 1H), 2.11-2.04 (m, 2H), 1.91-1.83 (m, 2H), 1.80-1.74 (m, 2H), 1.70-1.61 (m, 2H), 1.34 (s, 12H), 1.13 (d, J = 6.4 Hz, 1H, OH).			
(1R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-one		[C ₁₉ H ₂₆ BNO ₃ +H] ⁺ 328.2 328.1	550 mg, light yellow; free base
SMs: (General Method D) (1R,5S)-8-(4-bromophenyl)-8-azabicyclo[3.2.1]octan-3-one (840 mg, 3 mmol), HBpin (0.65 mL, 9 mmol)			
1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine		[C ₁₉ H ₂₉ BN ₂ O ₃ +H] ⁺ 345.2 345.1	5.32 g (77%), white solid; free base
SMs: (General Method D) 1-(4-bromophenyl)-4-(oxetan-3-yl)piperazine (5.96 g, 20 mmol), HBpin (4.4 mL, 30 mmol)			
¹ H NMR (400 MHz, CDCl ₃) δ ppm 7.32 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 4.71 (t, J = 6.6 Hz, 2H), 4.67 (t, J = 6.2 Hz, 2H), 3.56 (quintet, J = 6.0 Hz, 1H), 3.32 (t, J = 5.0 Hz, 4H), 2.49 (t, J = 5.0 Hz, 4H), 1.34 (s, 12H).			

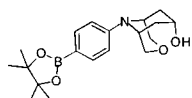
Synthesis of (1R,3R,5S)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-9-azabicyclo[3.3.1]nonan-3-ol



To a solution of (1R,5S)-9-(4-bromophenyl)-9-azabicyclo[3.3.1]nonan-3-one (6.2 g, crude) in DCM (100 mL) and MeOH (60 mL) at 0 °C was added NaBH₄ (5.7 g, 15 mmol). The resulting mixture was stirred at 0 °C for 10 min, then rt for 30 min. After aqueous workup, the residue was purified by flash chromatography (EtOAc/DCM 0 to 10%) to give (1R,3R,5S)-9-(4-bromophenyl)-9-azabicyclo[3.3.1]nonan-3-ol as brown solid (1.30 g). MS ESI 295.9 [M + H]⁺, calcd for [C₁₄H₁₈BrNO+H]⁺ 296.1

The title compound (727 mg, beige solid) was prepared using (1R,,5S)-9-(4-bromophenyl)-9-azabicyclo[3.3.1]nonan-3-ol as brown solid (1.30 g, 4.4 mmol) and HBpin (1.9 mL) according to General Method D. ¹H NMR (400 MHz, *CDCl*₃) δ ppm 7.67 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.36-4.27 (m, 2H), 3.85-3.75 (m, 1H), 2.48-2.38 (m, 2H), 1.83-1.73 (m, 2H), 1.63-1.43 (m, 6H), 1.33 (s, 12H). MS ESI 344.1 [M + H]⁺, calcd for [C₂₀H₃₀BNO₃+H]⁺ 344.2

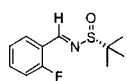
Synthesis of (1R,5S,7S)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-ol



To a solution of (1R,5S)-9-(4-bromophenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-one (0.98 g, 3.34 mmol) in THF (20 mL) and MeOH (0.5 mL) at 0 °C was added NaBH₄ (380 mL, 10 mmol). The resulting mixture was heated at 50 °C for 30 min. After cooling to rt, it was diluted with H₂O and extracted with DCM to give (1R,5S,7S)-9-(4-bromophenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-ol as greenish yellow solid. MS ESI 298.0 [M + H]⁺, calcd for [C₁₃H₁₆BrNO₂+H]⁺ 298.0

The title compound (336 mg, off white solid) was prepared using the above solid (1R,5S)-9-(4-bromophenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-ol and HBpin (1.45 mL, 10 mmol) according to General Method D. ¹H NMR (400 MHz, *CDCl*₃) δ ppm 7.72 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 12.4 Hz, 1H), 4.02-3.92 (m, 6H), 2.32-2.24 (m, 2H), 1.78 (d, J = 14.8 Hz, 2H), 1.34 (s, 12H). MS ESI 346.1 [M + H]⁺, calcd for [C₁₉H₂₈BNO₄+H]⁺ 346.2

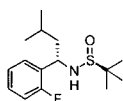
Synthesis of (S)-N-(1-(2-fluorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide



A. (R,E)-N-(2-fluorobenzylidene)-2-methylpropane-2-sulfinamide

The title compound was synthesized by utilizing 2-fluorobenzaldehyde (10.0 g, 80.5 mmol), (S)-t-butylsulfinylamide (12.2 g, 100 mmol), flame-dried CuSO₄ (16 g, 100 mmol) and MgSO₄ (29 g, 240 mmol) in DCM (150 mL). The resulting mixture was stirred at rt for 72 h. The reaction mixture was filtered through a pad of Celite and the pad was rinsed with CH₂Cl₂ (5 x 100 mL). The combined organic extracts were concentrated under reduced pressure yielding pale yellow oil (24 g). Purification by flash chromatography (Biotage Isolera, 100g HP-SIL, 0-15 % EtOAc in hexanes) gave the product (11.3 g, 61% as a clear pale yellow oil. ¹H NMR (300 MHz, *CDCl*₃) δ ppm 8.91 (s, 1H), 8.01 (dt, J = 7.6, 1.6 Hz, 1 H), 7.48-7.54 (m, 1 H), 7.23-7.27 (m, 1 H), 7.14-7.19 (m, 1 H), 1.28 (s, 9 H).

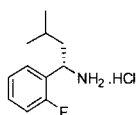
B. (S)-N-((S)-1-(2-fluorophenyl)-3-methylbutyl)-2-methylpropane-2-sulfinamide



Isobutyl magnesium bromide (2.0 M in Et₂O, 8.25 mL, 16.5 mmol) was added carefully to stirred dimethylzinc (1.2 M in toluene, 15.6 mL, 18.7 mmol) at rt. Dry THF (30 mL) was added and the mixture was stirred at rt for 30 min before being added slowly, drop wise over 30 min to a stirred -78°C solution of (R,E)-N-(2-fluorobenzylidene)-2-methylpropane-2-sulfinamide (2.5 g, 11 mmol) in dry THF (30 mL). Once the addition was complete the mixture was stirred at this temperature for 3 h. The reaction was

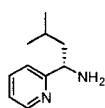
quenched by addition of saturated aq. NH_4Cl (50 mL). H_2O (200 mL) was added and the mixture was extracted with Et_2O (2 x 75 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure yielding the crude product (3.05 g, 97%, 4:1 mixture of product and Me-added side product) as a clear yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.40 (m, 0.25 H), 7.29-7.33 (m, 1 H), 7.22-7.29 (m, 1.25 H), 7.11-7.17 (m, 1.25 H), 7.02-7.06 (m, 1.25 H), 4.79 - 4.82 (m, 0.25 H), 4.56-4.61 (m, 1 H), 3.53 (m, 1.25 H), 1.63-1.68 (m, 0.91 H), 1.55-1.60 (m, 1.50 H), 1.44 - 1.54 (m, 1.30 H), 1.21 (s, 9 H), 0.90-0.95 (m, 6 H), $[\text{C}_{15}\text{H}_{24}\text{FNOS}+\text{H}]^+$

C. (S)-1-(2-fluorophenyl)-3-methylbutan-1-amine



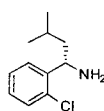
The deprotection of chiral auxiliary carried out by utilizing HCl (2.0 M in Et_2O , 25 mL) and a solution of (S)-N-((S)-1-(2-fluorophenyl)-3-methylbutyl)-2-methylpropane-2-sulfinamide (3.05 g, 10.6 mmol) in MeOH (30 mL). After the addition was complete, the cooling bath was removed and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure and the residue to give crude pale yellow solid (3.0 g). Purification by flash chromatography (Biotage isolera 120 g C18, 5-80% MeOH in H_2O) gave the title compound as a white solid HCl salt (1.52 g, 64%, 97% ee (S)). ^1H NMR (400 MHz, CD_3OD) δ ppm 7.46-7.52 (m, 2H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.22-7.26 (m, 1H), 4.62-4.66 (m, 1H), 1.93-1.98 (m, 1H), 1.79-1.86 (m, 1H), 1.37-1.47 (m, 1H), 0.93-0.98 (m, 6H). The ee of the compound was determined by chiral HPLC, Daicel Chiralpak OD-H, 3:97 v/v 0.5% DEA-IPA:Hexane, 1.0 mL/min, $\lambda = 254$ nm, $R_t = 6.08$ min (R), $R_t = 6.89$ min (S).

Synthesis of (S)-3-Methyl-1-(pyridin-2-yl)butan-1-amine



To a hot solution of (L)-DBTA (7.2 g, 20 mmol) in MeOH (75 mL) with stirring was added a solution of racemic 3-methyl-1-(pyridin-2-yl)butan-1-amine (3.3 g, 20 mmol) in MeOH (30 mL) dropwise. After addition, the resulting suspension was stirred for 5 min under reflux and cooled in air for about 5 min. The resulting precipitate was collected by vacuum filtration, washed with cold MeOH , air-dried and recrystallized from MeOH (200 mL) to give (L)-DBTA salt of (S)-3-methyl-1-(pyridin-2-yl)butan-1-amine as white solid (1.95 g, 95.6 % ee). The ee of the compound was determined by acetylating small samples with acetyl chloride and analyzing the products by chiral HPLC: Daicel Chiralpak AD-H, 90:10 v/v hexanes-IPA (+0.5% Et_3N), 1.0 ml min^{-1} , $\lambda = 254$ nm, $R_t = 5.8$ mins (R), $R_t = 7.5$ min (S).

To a suspension of the above salt (1.9 g) in MeOH (5 mL) was added 4 M NaOH (3 mL). A clear solution was formed. After diluting with H_2O (50 mL), the aq layer was extracted with DCM (30 mL x 2), and the combined organic layers were dried (Na_2SO_4) and solvent was removed to give the desired amine as a colorless oil (705 mg, 21 %).

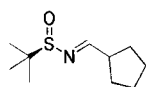
Synthesis of (S)-1-(2-chlorophenyl)-3-methylbutan-1-amine

To a RBF under Ar charged with Me_2Zn (1.2 M in PhMe, 12.5 mmol, 1.5 eq) was carefully added *i*-BuMgBr (2.0 M in Et_2O , 7.5 mL 1.5 eq). The resulting mixture was stirred at rt for 30 min after diluting with THF (10 mL). The mixture was added over 10 min to a stirred solution of (S,E)-N-(2-chlorobenzylidene)-2-methylpropane-2-sulfinamide (2.44 g, 10 mmol, 1 eq) in THF (50 mL) at -78°C . After addition, it was stirred at -78°C for 3 h, before quenching with sat. NH_4Cl and warming to rt. Extraction with Et_2O provided crude 1-((S)-1-((R)-tert-butylsulfinyl)-4-methylpentan-2-yl)-2-chlorobenzene as colorless viscous oil (3.06 g). ^1H NMR indicated about 21% of methylated byproduct.

The mixture was redissolved in MeOH (30 mL), cooled to 0°C and treated with 1 M aq HCl in Et_2O (20 mL, 20 mmol). After stirring for 30 min, it was concentrated to dryness and purified by Biotage reverse phase (MeOH/ H_2O 5 to 90%) to give the title compound as white solid (1.41 g, 60%, HCl salt). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.61 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.55 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.49 (dt, $J = 7.5, 1.5$ Hz, 1H), 7.44 (dt, $J = 7.6, 2.0$ Hz, 1H), 4.93-4.35 (m, 1H, partially buried in H_2O), 2.00-1.91 (m, 1H), 1.90-1.82 (m, 1H), 1.55-1.43 (m, 1H), 1.00 (d, $J = 6.4$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H). MS ESI 181.0 $[\text{M} + \text{H}]^+$, calcd for $[\text{C}_{11}\text{H}_{16}\text{ClN} + \text{H} - \text{NH}_3]^+$ 181.1

The following intermediates were synthesized via reductive amination using General Method E:

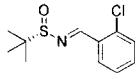
IUPAC name	Structure	MS calculated MS ESI $[\text{M} + \text{H}]^+$	Yield; Appearance; Salt form
cyclopentyl(pyridin-2-yl)methanamine		$[\text{C}_{11}\text{H}_{16}\text{N}_2 + \text{H}]^+$ 177.1 177.1	931 mg (93%); clear oil; free base
Starting material: cyclopentyl-2-pyridyl ketone (1 g, 5.7 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.50 (d, $J = 4.0$ Hz, 1 H), 7.80 (t, $J = 7.9$ Hz, 1 H), 7.41 (d, $J = 8.0$ Hz, 1 H), 7.31 (t, $J = 5.0$ Hz, 1 H), 3.76 (d, $J = 8.8$ Hz, 1 H), 2.14 - 2.27 (m, 1 H), 1.88 - 1.99 (m, 1 H), 1.36 - 1.75 (m, 5 H), 1.25 - 1.35 (m, 1 H), 1.12 - 1.24 (m, 1 H)			
1-(2-chlorophenyl)-2-methylpropan-1-amine		$[\text{C}_{10}\text{H}_{14}\text{ClN} + \text{H}]^+$ 184.1 184.1	348 mg (23%); colourless oil; free base
Starting material: 1-(2-chlorophenyl)-2-methyl-propan-1-one (1.5 g, 8.2 mmol)			
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.38-7.21 (m, 4H), 4.87 (br.s, 2H), 4.16 (d, $J = 8.0$ Hz, 1H), 2.12-2.04 (m, 1H), 1.02 (d, $J = 6.4$ Hz, 3H), 0.82 (d, $J = 6.8$ Hz, 3H)			

(R,E)-N-(Cyclopentylmethylene)-2-methylpropane-2-sulfinamide

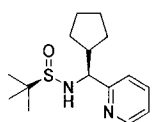
The title compound was synthesized according to General Method H utilizing cyclopentanecarboxaldehyde (15.0 g, 152.8 mmol, 1.0 eq.), (R)-*t*-butylsulfinylamide (24.1 g, 198.7 mmol, 1.3 eq.), and flame-dried CuSO_4 (73.2 g, 458.5 mmol, 3.0 eq.). The resulting mixture was stirred at rt for 71 h. The reaction mixture was filtered through a pad of Celite and the pad was rinsed with CH_2Cl_2 (5 x 100 mL). The combined organic extracts were concentrated under reduced pressure yielding a clear yellow oil (37.2 g). Purification by flash chromatography (SiO_2)

using 1:9 EtOAc-cyclohexane as eluent gave the product (23.8 g, 78% isolated yield) as a clear pale yellow oil. ^1H NMR (300 MHz, CDCl_3) δ ppm 7.99 (d, $J = 5.5$ Hz, 1H), 3.02-2.87 (m, 1H), 1.97-1.78 (m, 2H), 1.78-1.55 (m, 6H), 1.18 (s, 9H).

The following sulfinamides were synthesized according to the synthesis of (*R,E*)-*N*-(cyclopentylmethylene)-2-methylpropane-2-sulfinamide using General Method H:

IUPAC name	Structure	MS calculated MS ESI $[\text{M}+\text{H}]^+$	Yield; Appearance; Salt form
(<i>S,E</i>)- <i>N</i> -(2-chlorobenzylidene)-2-methylpropane-2-sulfinamide		$[\text{C}_{11}\text{H}_{14}\text{ClNOS}+\text{H}]^+$ 244.1 N/A	26.9 g (89%); pale yellow oil; free base
SMs: 2-chlorobenzaldehyde (20.9 g, 149 mmol), (<i>S</i>)- <i>t</i> -butylsulfinylamide (15.0 g, 124 mmol)			
^1H NMR (300 MHz, CDCl_3) δ 9.05 (s, 1H), 8.06 (d, $J = 7.5$ Hz, 1H), 7.48-7.39 (m, 2H), 7.38-7.31 (m, 1H), 1.28 (s, 9H)			

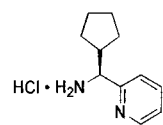
Large scale asymmetric synthesis of (*S*)-1-(Cyclopentyl)-1-(2-pyridinyl)methylamine HCl salt



*A. (*R,S*)-N-((*S*)-cyclopentyl(pyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide*

A solution of 2-bromopyridine (11.5 g, 73 mmol) in dry THF (50 mL) was added carefully to *i*-PrMgCl•LiCl (1.3 M in THF, 56 mL, 73 mmol). The resulting solution was stirred at rt for 2 h after which it was added dropwise, over 30 min, to a -42°C solution of (*R,E*)-*N*-(cyclopentylmethylene)-2-methylpropane-2-sulfinamide (11.3 g, 56 mmol) in dry CH_2Cl_2 (100 mL). The resulting mixture was slowly warmed up to rt and stirred O/N at rt. The reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with CH_2Cl_2 . After removal of solvents, the residue was purified by flash chromatography on silica gel (gradient: EtOAc/hexane 0 to 80%) to give the title compound (2.80 g). The impure fractions were purified again using 5% MeOH in EtOAc followed by trituration with hexane to give additional title compound (497 mg). Total: 3.347 g (yield 21%) (^1H NMR (400 MHz, CDCl_3) δ ppm 8.56 (d, $J = 4.5$ Hz, 1H), 7.63 (dt, $J = 1.0, 7.5$ Hz, 1H), 7.22 (d, $J = 7.5$ Hz, 1H), 7.16 (dd, $J = 4.5, 7.5$ Hz, 1H), 4.26 (dd, $J = 5.0, 8.5$ Hz, 1H), 3.95 (d, $J = 5.0$ Hz, 1H), 2.44-2.31 (m, 1H), 1.94-1.83 (m, 1H), 1.68-1.44 (m, 5H), 1.44-1.32 (m, 1H), 1.30-1.17 (m, 1H), 1.13 (s, 9H).

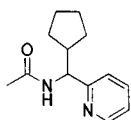
*B. (*S*)-1-(cyclopentyl)-1-(2-pyridinyl)methylamine HCl salt*



The title compound was synthesized according to General Method I utilizing HCl (2.0 M in Et_2O , 31.4 mL, 62.8 mmol) and a solution of (*R,S*)-*N*-(*S*)-cyclopentyl(pyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide (8.8 g, 31.4 mmol) in MeOH (100 mL). After the addition was complete the cooling bath was removed and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was suspended in Et_2O (125 mL). The precipitation was filtered off and washed with Et_2O (2 x 125 mL) and dried under reduced pressure yielding the crude product (7.7 g, 95.0% ee (*S*)) as a white solid. The crude product was recrystallised from *t*-BuOMe (150 mL), EtOH (200 mL) and MeOH (170 mL).

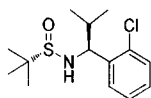
at 80 °C. The crystals formed after the solution cooled down were collected by filtration (3.3 g, 99.0% ee (S)) and the filtrate was concentrated under reduced pressure and was recrystallised again from t-BuOMe (100 mL) and MeOH (150 mL). The second crop of crystals were collected by filtration (1.3 g, 98.0% ee (S)) resulting in a combined yield of 4.6 g, 69% isolated yield). ¹H NMR (400 MHz, D₂O + NaOH) δ ppm 8.81 (d, J = 5.5 Hz, 1H), 8.55 (t, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.99 (t, J = 6.5 Hz, 1H), 4.53 (d, J = 10.5 Hz, 1H), 2.63-2.50 (m, 1H), 2.11-2.01 (m, 1H), 1.84-1.40 (m, 6H), 1.24-1.12 (m, 1H). The ee of the compound was determined by acetylating small samples with AcCl (see example below for the synthesis) and analysing the products, (S)- and (R)-N-(Cyclopentyl(pyridin-2-yl)methyl)acetamides, by chiral HPLC: Daicel Chiralpak AD-H, 80:20 v/v heptane-EtOH (+0.2% Et₃N), 1.0 mL/min, λ = 230 nm, R_t = 9.5 min (R), R_t = 25.4 min (S).

C. (rac)-N-(cyclopentyl(pyridin-2-yl)methyl)acetamide



AcCl (0.10 g, 1.25 mmol) was added to a stirred suspension of Et₃N (0.35 mL, 0.25 g, 2.5 mmol, 2.2 eq.) and (rac)-1-cyclopentyl-1-(2-pyridinyl)methylamine HCl salt (0.25 g, 1.14 mmol) in CH₂Cl₂ (5 mL). The resulting mixture was stirred at rt for 2 h. The reaction mixture was washed with H₂O (10 %, 3 x 3 mL) and was dried over Na₂SO₄ and was concentrated under reduced pressure yielding the crude product (0.20 g) as a clear yellow oil which quickly crystallized. ¹H NMR (300 MHz, CDCl₃) δ ppm 8.53 (d, J = 5.0 Hz, 1H), 7.62 (dt, J = 1.5, 7.5 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 5.0 Hz, 1H), 6.72 (br d, J = 7.0 Hz, 1H), 4.93 (t, J = 9.0 Hz, 1H), 2.37-2.20 (m, 1H), 2.00 (s, 3H), 1.80-1.10 (m, 8H); HPLC: Daicel Chiralpak AD-H, 80:20 v/v heptane-EtOH (+0.2% Et₃NH), 1.0 mL min⁻¹, 210 nm, R_t = 9.5 min, R_t = 19.2 min.

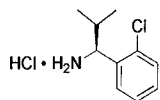
Large scale asymmetric synthesis of (S)-1-(2-chlorophenyl)-1-isopropylmethylamine HCl salt



A. (S_S)-N-((S)-1-(2-chlorophenyl)-2-methylpropyl)-2-methylpropane-2-sulfinamide

i-PrMgCl (2.0 M in THF, 46.2 mL, 92.3 mmol) was added carefully to stirred Me₂Zn (1.2 M in PhMe, 82 mL, 98.4 mmol) at rt. The resulting solution was stirred at rt for 30 min before being added dropwise, over 30 min, to a stirred -78 °C solution of (S,*E*)-N-(2-chlorobenzylidene)-2-methylpropane-2-sulfinamide (15.0 g, 61.5 mmol) in dry THF (350 mL). After the addition was complete the reaction mixture was stirred at -78 °C for 3 h before being quenched by careful addition of satd aq NH₄Cl (200 mL). The mixture was extracted with Et₂O (3 x 100 mL). The combined organic extracts were washed with brine (100 mL) and were dried (Na₂SO₄). The organic layer was concentrated under reduced pressure yielding the crude product (17.9 g, quantitative yield, 16:1 d.r. (S_S,S)- (S_S,R) as a white solid which was used without any further purification. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.38-7.15 (m, 4H), 4.46 (t, J = 8.0 Hz, 1H), 3.75 (br d, J = 8.0 Hz, 1H), 2.28-2.15 (m, 1H), 1.22 (s, 9H), 1.01 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H).

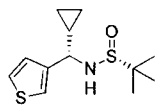
B. (S)-1-(2-chlorophenyl)-1-isopropylmethylamine HCl salt



The title compound was synthesized according to General Method I utilizing HCl (2.0 M in Et₂O, 61.0 mL, 122.0 mmol) and a solution of (S_S)-N-((S)-1-(2-chlorophenyl)-2-methylpropyl)-2-methylpropane-2-sulfinamide (17.8 g, 61.0 mmol)

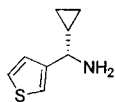
in MeOH (175 mL). After the addition was complete the cooling bath was removed and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure and Et₂O (250 mL) was added and a white precipitation formed. The precipitation was filtered off and washed with Et₂O (2 x 200 mL) and dried under reduced pressure yielding the crude product (11.8 g, 88.7% ee (S)) as a white solid. The crude product was recrystallised from t-BuOMe (300 mL) and MeOH (48 mL) at 80 °C. After having cooled down over night only a small amount of crystals had been formed which were removed by filtration. The filtrate was concentrated under reduced pressure and after roughly half the volume had been removed a second crop of solids appeared which was also removed by filtration. The two crops of crystals were found to be racemic by chiral HPLC. The filtrate was concentrated to dryness and recrystallised again from t-BuOMe (300 mL) and MeOH (33 mL) at 80 °C. Again only a small amount of crystals were formed as the solution cooled down which were removed by filtration, as was a second crop of solids formed when the solution was concentrated under reduced pressure. The remaining filtrate was concentrated to dryness and was suspended in t-BuOMe (200 mL) and filtered off. The resulting white solid was washed with Et₂O (3 x 150 mL) and was dried under reduced pressure yielding the purified product (9.0 g, 67% isolated yield, 97% ee (S)) as a white solid. ¹H NMR (400 MHz, D₂O + NaOH) δ ppm 7.59-7.41 (m, 4H), 4.60 (d, J = 9.5 Hz, 1H), 2.44-2.30 (m, 1H), 1.18 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H; HPLC: Daicel Chiralpak AD-H, 97:3 v/v heptane-EtOH (+0.1% Et₃N), 1.0 mL/min, λ = 280 nm, R_t = 6.0 min (S), R_t = 7.3 min (R)).

Synthesis of (R)-N-((S)-cyclopropyl(thiophen-3-yl)methyl)-2-methylpropane-2-sulfinamide

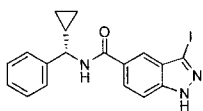


To a anh THF (4 mL) solution of (R)-2-methylpropane-2-sulfinamide (0.242 g, 2.0 mmol) and Ti(Oi-Pr)₄ (0.83 mL, 2.8 mmol) was added cyclopropyl(thiophen-3-yl)methanone (0.29 mL, 2.4 mmol). The reaction was heated overnight at 70 °C under Ar. Later the reaction was cooled to -48 °C and L-Selectride was added (1.0 M in THF, 6.0 mL, 6 mmol). The reaction was allowed to warm to rt and stirred for 4 h. The reaction was quenched by an addition of MeOH, diluted with brine and filtered through Celite followed by rinsing the flask and filter bed with EtOAc. Concentration of the filtrate followed by two separate flash chromatography purifications on SiO₂, first using: DCM:MeOH (97:3) and then Et₂O:hexanes (4:1) afforded (R)-N-((S)-cyclopropyl(thiophen-3-yl)methyl)-2-methylpropane-2-sulfinamide as a white solid (0.175 g, 24 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.27 - 7.32 (m, 2 H), 7.17 (dd, J=4.77, 1.51 Hz, 1 H), 3.81 (dd, J=8.66, 4.14 Hz, 1 H), 3.48 (br. s., 1 H), 1.24 (s, 9 H), 1.13-1.26 (m., 1 H), 0.67 - 0.78 (m, 1 H), 0.46 - 0.64 (m, 2 H), 0.30 (s, 1 H);

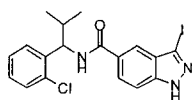
MS ESI 258.0 [M + H]⁺, calcd for [C₁₂H₁₉INOS₂ + H]⁺ 258.1.

Synthesis of (S)-cyclopropyl(thiophen-3-yl)methanamine

To a solution of (R)-N-((S)-cyclopropyl(thiophen-3-yl)methyl)-2-methylpropane-2-sulfonamide (0.125 g, 0.49 mmol) in MeOH (1 mL) was added HCl (1.0 M in Et₂O, 0.98 mL, 0.98 mmol) at rt. The reaction was stirred at the temperature for 2 h, concentrated under reduced pressure and taken into hexanes:Et₂O (1:1 v/v). Formed precipitate was filtered off and rinsed with hexanes:Et₂O (1:1 v/v) to afford (S)-cyclopropyl(thiophen-3-yl)methanamine as an HCL salt (white solid, 0.069 g, 74 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.48 - 7.58 (m, 2 H), 7.25 (dd, *J*=4.77, 1.51 Hz, 1 H), 3.73 (d, *J*=10.04 Hz, 1 H), 1.29 - 1.43 (m, 1 H), 0.66 - 0.86 (m, 2 H), 0.51 - 0.61 (m, 1 H), 0.37 - 0.50 (m, 1 H); MS ESI 136.9 [M - NH₂]⁺, calcd for [C₈H₁₁NS - NH₂]⁺ 137.0

Synthesis of (S)-N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide

The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (79 mg, 0.79 mmol), (S)-cyclopropylphenylmethanamine · HCl (50 mg, 0.27 mmol), TBTU (87 mg, 0.27 mmol), DIPEA (0.14 mL, 0.81 mmol), and DMF (4 mL) to give the title compound (orange solid, 110 mg, 98 %). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.09 (s, 1 H), 7.95 (dd, *J*=8.9, 1.6 Hz, 1 H), 7.56 (d, *J*=8.8 Hz, 1 H), 7.43 - 7.50 (m, 2 H), 7.33 (t, *J*=7.6 Hz, 2 H), 7.24 (t, *J*=7.3 Hz, 1 H), 4.46 (d, *J*=9.5 Hz, 1 H), 1.34 - 1.46 (m, 1 H), 0.66 (d, *J*=8.0 Hz, 2 H), 0.48 (m, 2 H); MS ESI 418.1 [M + H]⁺, calcd for [C₁₈H₁₆IN₃O + H]⁺ 418.0.

Synthesis of N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamideA. 1-(2-chlorophenyl)-2-methylpropan-1-ol

A solution of 2-chlorobenzaldehyde (2.75 g) in Et₂O (30 mL) was slowly added to a solution of isopropyl magnesium bromide (obtained from 0.98 g of magnesium and 4.85 g 2-bromopropane in 70 mL anhydrous Et₂O) at 0°C. The reaction mixture was stirred for 1 h at 0°C, and then quenched with aq. 25 % NH₄Cl (100 mL). The organic layer was separated and the aq. layer was extracted with EtOAc (50 mL). The combined organic layer was washed with H₂O and brine, dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-25 % EtOAc in Hexane) gave the title compound (clear colorless oil, 1.5 g, 41 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.52 (d, *J*=7.2 Hz, 1H), 7.37-7.31 (m, 2H), 7.25-7.21 (m, 1H), 5.27 (d, *J*=4.4 Hz, 1H), 4.68 (dd, *J*=5.2 Hz, 1H), 1.88-1.80 (m, 1H), 0.86 (dd, *J*=17.2 Hz, *J*=6.8 Hz, 6H).

B. 1-(2-chlorophenyl)-2-methyl-propan-1-one

A solution of 1-(2-chlorophenyl)-2-methylpropan-1-ol (1.5 g in 15 mL DCM) was added to a suspension of PCC (2.62 g in 30 mL DCM) at 25°C, monitoring the reaction by TLC. The reaction was complete in 2 h. Et₂O (120 mL) was added and the reaction mixture was stirred for 15 min. The supernatant was decanted, dried (Na₂SO₄) and concentrated under vacuum. Purification by flash

chromatography (SiO₂, 0-10 % EtOAc in Hexane) gave the title compound (clear colorless oil, 1.24 g, 82 %). ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.27 (m, 4H), 3.37-3.30 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 6H).

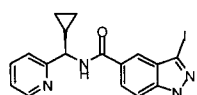
C. 1-(2-chlorophenyl)-2-methylpropan-1-amine

The title compound was prepared using General Method E from 1-(2-chlorophenyl)-2-methylpropan-1-one (1.5 g, 8.2 mmol) at 65°C for 24 h. Evaporation of MeOH and addition of 3M aq NaOH (100 mL), extraction using EtOAc (2x 100 mL), and *purification by flash chromatography* (SiO₂, 0-25 % DCM in MeOH) to give the title compound (colorless oil, 348 mg, 23 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.38-7.21 (m, 4H), 4.87 (br.s, 2H), 4.16 (d, *J* = 8.0 Hz, 1H), 2.12-2.04 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); MS ESI 184.08. [M + H]⁺, calcd for [C₁₀H₁₄ClN + H]⁺ 184.08.

D. N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide

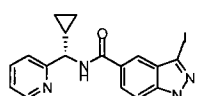
The title compound was synthesized according to General Method A by using 1-(2-chlorophenyl)-2-methylpropan-1-amine (0.55 g, 2.99 mmol), DMF (11 mL), 3-iodo-1H-indazole-5-carboxylic acid (863 mg, 2.99 mmol), DIPEA (2.09 mL, 11.98 mmol) and TBTU (960 mg, 2.99 mmol). The resultant reaction mass stirred at 25°C for 12 h and then quenched it in H₂O (440 mL). The solid collected by filtration and was washed with H₂O to provide the title compound (cream color solid, 1.29 g, 95%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.76 (s, 1H), 8.91 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.74-7.66 (m, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.46-7.22 (m, 4H), 5.27 (t, *J* = 9.2 Hz, 1H), 2.20-2.15 (m, 1H), 1.08 (d, *J* = 6.0 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H); MS ESI 454 [M + H]⁺, calcd for [C₁₈H₁₇ClIN₃O + H]⁺ 454.

Synthesis of (R)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide

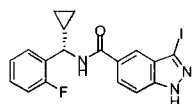


The title compound was synthesized according to General Method A utilizing (R)-cyclopropyl(pyridin-2-yl)methanamine and obtained as a light yellow solid (334 mg, 80% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51-8.55 (m, 1 H), 8.13-8.16 (m, 1 H), 7.95-8.00 (m, 1 H), 7.81-7.86 (m, 1 H), 7.53-7.61 (m, 2 H), 7.30-7.36 (m, 1 H), 4.49-4.53 (m, 1 H), 1.38-1.48 (m, 1 H), 0.68 - 0.75 (m, 1 H), 0.51 - 0.64 (m, 3 H); MS ESI [M + H]⁺ 419.0, calcd for [C₁₇H₁₅INO₄ + H]⁺ 419.04.

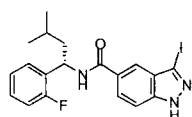
Synthesis of (S)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide



The title compound was synthesized according to General Method A utilizing (S)-cyclopropyl(pyridin-2-yl)methanamine and obtained as a yellow solid (874 mg, 77% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51-8.55 (m, 1 H), 8.13-8.16 (m, 1 H), 7.95-8.00 (m, 1 H), 7.81-7.86 (m, 1 H), 7.53-7.61 (m, 2 H), 7.30-7.36 (m, 1 H), 4.49-4.53 (m, 1 H), 1.38-1.48 (m, 1 H), 0.68 - 0.75 (m, 1 H), 0.51-0.64 (m, 3 H); MS ESI [M + H]⁺ 419.0, calcd for [C₁₇H₁₅INO₄ + H]⁺ 419.04.

Synthesis of (S)-N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide

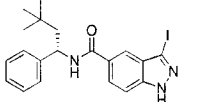
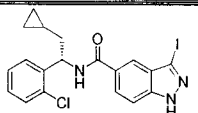
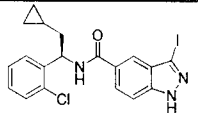
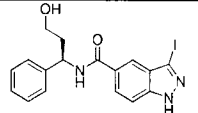
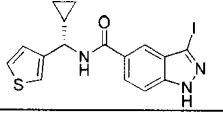
The title compound was synthesized according to General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (358 mg, 1.23 mmol), (S)-cyclopropyl(2-fluorophenyl) methanamine hydrochloride (250 mg, 1.23 mmol), BOP-Cl (576 mg, 1.3 mmol), DIPEA (1.08 mL, 6.19 mmol) and DMF (5 mL) at 0°C. The reaction was stirred and slowly warmed to rt and stirred at 24°C for 3 h. The reaction was concentrated and purified by flash chromatography (Biotage isolera 60 g C18-HS, 5-90% MeOH in 0.1% TFA.H₂O) to give the title compound as an off white solid (405 mg, 75%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.08 (s, 1 H), 7.95 (dd, *J*=8.8, 1.6 Hz, 1 H), 7.56-7.58 (m, 2 H), 7.26-7.31 (m, 1 H), 7.17 (t, *J*=7.6 Hz, 1 H), 7.09 (t, *J*=10 Hz, 1 H), 4.76 (d, *J*=9.2 Hz, 1 H), 1.41-1.50 (m, 1 H), 0.66-0.72 (m, 1 H), 0.58-0.62 (m, 1 H), 0.50-0.56 (m, 2 H); MS ESI 436.2 [M + H]⁺, calcd for [C₁₈H₁₅FIN₃O+H]⁺ 436.

Synthesis of (S)-N-(1-(2-fluorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide

The title compound was synthesized according to General Method A by utilizing (S)-1-(2-fluorophenyl)-3-methylbutan-1-amine HCl salt (1.0 g, 0.46 mmol), 3-iodo-1H-indazole-5-carboxylic acid (1.32 g, 0.46 mmol), TBTU (1.55 g, 0.48 mmol), DIPEA (3.01 mL, 1.84 mmol) and DMF (15 mL). After stirring for 4h, the crude reaction was subsequently diluted with H₂O, filtered and washed with H₂O to give the title compound as a cream solid (1.8 g, 87%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.95 (d, *J* = 8.4 Hz, 1H), 8.08 (s, 1 H), 7.93 (d, *J* = 8.8 Hz, 1H), (m, 1 H), 7.60-7.50 (m, 1 H), 7.47-7.56 (m, 1 H), 7.23-7.31 (m, 1 H), 7.13-7.21 (m, 2 H), 5.41-5.53 (m, 1 H), 1.84-1.92 (m, 1 H), 1.60-1.72 (m, 1 H), 1.47-1.58 (m, 1 H), 0.89-0.99 (m, 6 H); MS ESI 452.2 [M + H]⁺, calcd for [C₁₉H₁₉FIN₃O+H]⁺ 452.06

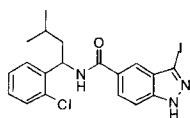
The following intermediates were synthesized according to General Method A:

IUPAC name	Structure	MS calculated MS ESI [M+H] ⁺	Yield; Appearance; Salt form
(R)-3-iodo-N-(3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide		[C ₁₈ H ₁₉ IN ₃ O+H] ⁺ 435.1 435.1	1.21 g, yellow solid; free base
SMs: (R)-3-methyl-1-(pyridin-2-yl)butan-1-amine (705 mg), 3-iodo-1H-indazole-5-carboxylic acid (1.008 g, 3.5 mmol).			
¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 13.69 (s, 1H), 8.94 (d, <i>J</i> = 8.4 Hz, 1H), 8.53-8.50 (m, 1H), 8.14-8.12 (m, 1H), 7.98 (dd, <i>J</i> = 8.8, 1.6 Hz, 1H), 7.75 (dd, <i>J</i> = 7.6, 2.0 Hz, 1H), 7.59 (d, <i>J</i> = 8.8, Hz, 1H), 7.43 (d, <i>J</i> = 8.0 Hz, 1H), 7.27-7.22 (m, 1H), 5.26-5.16 (m, 1H), 1.91-1.83 (m, 1H), 1.76-1.65 (m, 2H), 0.95 (d, <i>J</i> = 6.8 Hz, 3H), 0.93 (d, <i>J</i> = 6.4 Hz, 3H).			
(S)-3-iodo-N-(3-methyl-1-phenylbutyl)-1H-indazole-5-carboxamide		[C ₁₉ H ₂₀ IN ₃ O+H] ⁺ 434.3 34.1 434.3	424 mg (39%); white solid; free base
SMs: 3-iodo-1H-indazole-5-carboxylic acid (0.721 g, 2.5mmol), (S)-3-methyl-1-phenylbutan-1-amine HCl salt (0.5 g, 2.5 mmol)			
¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 13.68 (s, 1 H), 8.90 (d, <i>J</i> =8.5 Hz, 1 H), 8.03 - 8.09 (m, 1 H), 7.94 (dd, <i>J</i> =8.8, 1.5 Hz, 1 H), 7.58 (dd, <i>J</i> =8.8, 0.8 Hz, 1 H), 7.38 - 7.43 (m, 2 H), 7.28 - 7.35 (m, 2 H), 7.18 -			

IUPAC name	Structure	MS calculated MS ESI [M+H] ⁺	Yield; Appearance; Salt form
7.24 (m, 1 H), 5.15 (dd, <i>J</i> =8.7, 4.4 Hz, 1 H), 1.88 (dd, <i>J</i> =10.0, 8.0 Hz, 1 H), 1.50 - 1.68 (m, 2 H), 0.93 (t, <i>J</i> =6.5 Hz, 6 H)			
(S)-N-(3,3-dimethyl-1-phenylbutyl)-3-iodo-1H-indazole-5-carboxamide		[C ₂₀ H ₂₂ IN ₃ O+H] ⁺ 448.1 448.3	534 mg (51%); off white solid; free base
SMs: 3-iodo-1H-indazole-5-carboxylic acid (647 mg, 2.3 mmol), (S)-3,3-dimethyl-1-phenylbutan-1-amine HCl salt (500 mg, 2.3 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.06 (s, 1 H), 7.92 (d, <i>J</i> =1.5 Hz, 1 H), 7.58 (d, <i>J</i> =8.5 Hz, 1 H), 7.42 (d, <i>J</i> =7.5 Hz, 2 H), 7.33 (t, <i>J</i> =7.7 Hz, 2 H), 7.23 (s, 1 H), 5.30 - 5.37 (m, 1 H), 2.03 - 2.13 (m, 1 H), 1.70 - 1.79 (m, 1 H), 1.05 (s, 9 H)			
(S)-N-(1-(2-chlorophenyl)-2-cyclopropylethyl)-3-iodo-1H-indazole-5-carboxamide		[C ₁₉ H ₁₇ ClIN ₃ O+H] ⁺ 466.0 466.4	4.77 g (crude); yellow solid; free base
SMs: (S)-1-(2-chlorophenyl)-2-cyclopropylethanamine hydrochloride (2.32 g, 10 mmol), 3-iodo-1H-indazole-5-carboxylic acid (2.88 g, 10 mmol).			
¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 13.71 (s, 1H), 9.06 (d, <i>J</i> = 8.0 Hz, 1H), 8.12 (s, 1H), 7.95 (dd, <i>J</i> = 8.8, 1.2 Hz, 1H), 7.60 (d, <i>J</i> = 8.8 Hz, 1H), 7.55 (dd, <i>J</i> = 7.6, 1.2 Hz, 1H), 7.40 (d, <i>J</i> = 8.0 Hz, 1H), 7.32 (t, <i>J</i> = 6.8 Hz, 1H), 7.24 (dt, <i>J</i> = 7.6, 1.2 Hz, 1H), 5.55-5.45 (m, 1H), 1.98-1.88 (m, 1H), 1.48-1.38 (m, 1H), 0.90-0.81 (m, 1H), 0.50-0.36 (m, 2H), 0.27-0.18 (m, 1H), 0.13-0.60 (m, 1H).			
(R)-N-(1-(2-chlorophenyl)-2-cyclopropylethyl)-3-iodo-1H-indazole-5-carboxamide		[C ₁₉ H ₁₇ ClIN ₃ O+H] ⁺ 466.0 466.4	4.74 g (crude); yellow solid; free base
SMs: (R)-1-(2-chlorophenyl)-2-cyclopropylethanamine hydrochloride (2.32 g, 10 mmol), 3-iodo-1H-indazole-5-carboxylic acid (2.88 g, 10 mmol).			
¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) Spectral data was identical for that obtained in (S)-N-(1-(2-chlorophenyl)-2-cyclopropylethyl)-3-iodo-1H-indazole-5-carboxamide			
(R)-N-(3-hydroxy-1-phenylpropyl)-3-iodo-1H-indazole-5-carboxamide		[C ₁₇ H ₁₆ IN ₃ O ₂ + H] ⁺ 422.0 422.1	247 mg (59%); white solid; free base
SMs: 3-iodo-1H-indazole-5-carboxylic acid (288 mg, 1 mmol), (R)-3-phenyl-beta-alaninol (151 mg, 1 mmol)			
¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 13.70 (s, 1 H), 8.93 (d, <i>J</i> =8.3 Hz, 1 H), 8.06 (s, 1 H), 7.94 (d, <i>J</i> =9.0 Hz, 1 H), 7.59 (d, <i>J</i> =8.5 Hz, 1 H), 7.40 (d, <i>J</i> =7.5 Hz, 2 H), 7.33 (t, <i>J</i> =7.5 Hz, 2 H), 7.22 (t, <i>J</i> =7.5 Hz, 1 H), 5.15 - 5.24 (m, 1 H), 4.59 (br. s., 1 H), 3.45 (br. s., 2 H), 2.02 - 2.15 (m, 1 H), 1.86 - 1.98 (m, 1 H), 1.22 - 1.29 (m, 1 H)			
(S)-N-(cyclopropyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide		[C ₁₆ H ₁₄ IN ₃ OS + H] ⁺ 424.0 424.0	106 mg (69%); white solid; free base
SMs: 3-iodo-1H-indazole-5-carboxylic acid (105 mg, 0.36 mmol), (S)-cyclopropyl(thiophen-3-yl)methanamine*HCl (69 mg, 0.36 mmol)			
¹ H NMR (400 MHz, CDCl ₃) δ ppm 10.72 (br. s, 1 H), 7.91 - 8.02 (m, 2 H), 7.53 (d, <i>J</i> = 9.03 Hz, 1 H), 7.30 - 7.40 (m, 2 H), 7.20 (d, <i>J</i> =4.77 Hz, 1 H), 6.59 (br. s., 1 H), 4.80 (t, <i>J</i> =8.66 Hz, 1 H), 1.31 - 1.46 (m, 1 H), 0.73-0.83 (m, 1 H), 0.72-0.58 (m, 2 H), 0.47 - 0.59 (m, 1 H)			

Synthesis of N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide

A. 1-(2-chlorophenyl)-3-methylbutan-1-amine



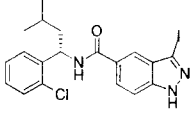
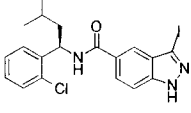
Using General Method G: a RBF charged with Mg powder (7.20 g, 300 mmol) in

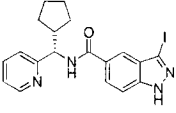
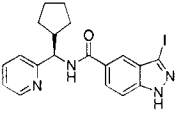
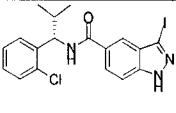
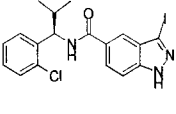
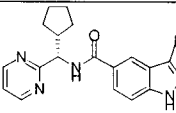
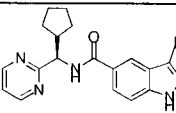
Et₂O (100 mL) was added *i*-BuBr (32.6 mL, 300 mmol) portionwise. After addition, it was stirred at rt for 1 h before 2-chlorobenzonitrile (20.63 g, 150 mmol) in PhMe (100 mL) was added slowly. The resulting mixture was refluxed (oil Temp 70 °C) for 3 h and cooled to rt. The mixture was added slowly to a cold solution of NaBH₄ in MeOH at -78 °C. After addition, cold bath was removed and the mixture was stirred for 45 min before quenching at 0 °C with 2 M aq HCl and adjusting to pH 2 and diluting with H₂O. After extracting with EtOAc, the aqueous layer was basified with 4 M NaOH to pH 12 and extracted with DCM to give 1-(2-chlorophenyl)-3-methylbutan-1-amine as dark orange oil (12.90 g). MS ESI 181.0 [M + H]⁺, calcd for [C₁₁H₁₆ClN+H-NH₃]⁺ 181.1

B. N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide

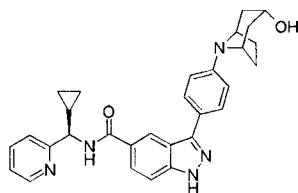
The title compound (2.78 g, pale yellow solid) was prepared using 1-(2-chlorophenyl)-3-methylbutan-1-amine (1.98 g, 10 mmol), 3-iodo-1H-indazole-5-carboxylic acid (2.88 g, 10 mmol) according to General Method A. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.70 (s, 1H), 9.01 (d, J = 8.4 Hz, 1H), 8.12-8.09 (m, 1H), 7.96 (dd, J = 8.8, 1.6 Hz, 1H), 7.62-7.57 (m, 2H), 7.41 (dd, J = 8.0, 1.2 Hz, 1H), 7.34 (dt, J = 8.0, 1.2 Hz, 1H), 7.24 (dt, J = 7.6, 1.6 Hz, 1H), 5.60-5.52 (m, 1H), 1.88-1.72 (m, 2H), 1.49-1.41 (m, 1H), 0.97 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H). MS ESI 468.4 [M + H]⁺, calcd for [C₁₉H₁₉ClIN₃O+H]⁺ 468.0

The following enantiomerically pure intermediates were prepared by separating racemic compounds using preparative, chiral supercritical fluid chromatography (SFC):

IUPAC name	Structure	MS calculated MS ESI [M+H] ⁺	Yield; Appearance; Salt form
(S)-N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide		[C ₁₉ H ₁₉ ClIN ₃ O+H] ⁺ 468.0 As racemate	16.5 g (39%), pale yellow solid; free base
SMs: crude N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide (42.4 g)			
Preparative HPLC method: OJ-H (2 x 25 cm); 30% EtOH(0.1%DEA)/CO ₂ , 100 bar; 70 mL/min, 220 nm			
Analytic HPLC method: OJ-H (25 x 0.46 cm); 40% EtOH(DEA)/CO ₂ , 100 bar; 3 mL/min, 220 and 254 nm; R _t 1.33 min, 100 % ee			
(R)-N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide		[C ₁₉ H ₁₉ ClIN ₃ O+H] ⁺ 468.0 As racemate	17.0 g (40%), pale yellow solid; free base
SMs: crude N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide (42.4 g)			
Preparative HPLC method: OJ-H (2 x 25 cm); 30% EtOH(0.1%DEA)/CO ₂ , 100 bar; 70 mL/min, 220 nm			
Analytic HPLC method: OJ-H (25 x 0.46 cm); 40% EtOH(DEA)/CO ₂ , 100 bar; 3 mL/min, 220 and 254 nm; R _t 2.67 min, 100 % ee			

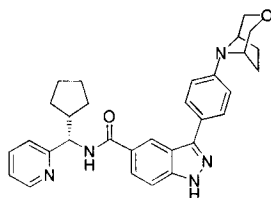
(S)-N-(cyclopentyl (pyridin-2-yl)methyl)-3- iodo-1H-indazole-5- carboxamide		$[C_{19}H_{19}IN_4O + H]^+$ 447.1 447.1	3.6 g (46%); yellow solid; free base
SMs: N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (7.9 g, 18 mmol)			
Preparative HPLC method: AD-H (2 x 15 cm); 25% EtOH(0.1%DEA)/CO ₂ , 100 bar; 65 mL/min, 220 nm			
Analytic HPLC method: AD-H (15 x 0.46 cm); 40% EtOH(DEA)/CO ₂ , 100 bar; 3 mL/min, 220, 254, and 280 nm; R _t 2.14 min, > 99 % ee			
(R)-N-(cyclopentyl (pyridin-2-yl)methyl)-3- iodo-1H-indazole-5- carboxamide		$[C_{19}H_{19}IN_4O + H]^+$ 447.1 447.1	3.5 g (44%); yellow solid; free base
SMs: N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (7.9 g, 18 mmol)			
Preparative HPLC method: AD-H (2 x 15 cm); 25% EtOH(0.1%DEA)/CO ₂ , 100 bar; 65 mL/min, 220 nm			
Analytic HPLC method: AD-H (15 x 0.46 cm); 40% EtOH(DEA)/CO ₂ , 100 bar; 3 mL/min, 220, 254, and 280 nm; R _t 1.36 min, > 99 % ee			
(S)-N-(1-(2-chlorophenyl)- 2-methylpropyl)-3-iodo- 1H-indazole-5- carboxamide		$[C_{18}H_{17}ClIN_3O + H]^+$ 454.0 454.0	454 mg (46%); yellow solid; free base
SMs: N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide (1.0 g, 2.2 mmol)			
Preparative HPLC method: IC (2 x 15 cm); 30% i-PrOH/CO ₂ , 100 bar; 65 mL/min, 220 nm			
Analytic HPLC method: IC (15 x 0.46 cm); 30% i-PrOH(DEA)/CO ₂ , 100 bar; 3 mL/min, 220, 254, and 280 nm; R _t 4.57 min, > 99 % ee			
(R)-N-(1-(2- chlorophenyl)-2- methylpropyl)-3-iodo-1H- indazole-5-carboxamide		$[C_{18}H_{17}ClIN_3O + H]^+$ 454.0 454.0	454 mg (46%); yellow solid; free base
SMs: N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide (1.0 g, 2.2 mmol)			
Preparative HPLC method: IC (2 x 15 cm); 30% i-PrOH/CO ₂ , 100 bar; 65 mL/min, 220 nm			
Analytic HPLC method: IC (15 x 0.46 cm); 30% i-PrOH(DEA)/CO ₂ , 100 bar; 3 mL/min, 220, 254, and 280 nm; R _t 6.32 min, > 99 % ee			
(S)-N-(cyclopentyl (pyrimidin-2-yl)methyl)-3- iodo-1H-indazole-5- carboxamide		$[C_{18}H_{18}IN_5O + H]^+$ 448.1 448.1	468 mg (44%); yellow solid; free base
SMs: N-(cyclopentyl(pyrimidin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (1.1 g, 2.4 mmol)			
Preparative HPLC method: AD-H (2 x 25 cm); 30% EtOH(0.1%DEA)/CO ₂ , 100 bar; 65 mL/min, 220 nm			
Analytic HPLC method: AD-H (25 x 0.46 cm) 40% EtOH(DEA)/CO ₂ , 100 bar; 3 mL/min, 220 and 254 nm; R _t 2.95 min, > 99 % ee			
(R)-N-(cyclopentyl (pyrimidin-2-yl)methyl)-3- iodo-1H-indazole-5- carboxamide		$[C_{18}H_{18}IN_5O + H]^+$ 448.1 448.4	475 mg (45%); yellow solid; free base
SMs: N-(cyclopentyl(pyrimidin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (1.1 g, 2.4 mmol)			
Preparative HPLC method: AD-H (2 x 25 cm); 30% EtOH(0.1%DEA)/CO ₂ , 100 bar; 65 mL/min, 220 nm			
Analytic HPLC method: AD-H (25 x 0.46 cm); 40% EtOH(DEA)/CO ₂ , 100 bar; 3 mL/min, 220 and 254 nm; R _t 2.29 min, > 99 % ee			

Example A1: *N*-(*(R)*-cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1*R*,3*R*,5*S*)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1*H*-indazole-5-carboxamide



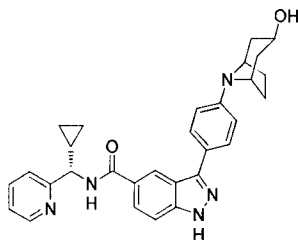
A mixture of crude, prior to amid hydrolysis, (*R*)-*N*-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1*H*-indazole-5-carboxamide (4.954 g, 11.85 mmol) and (1*R*,5*S*)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1] octan-3-ol (4.29 g, 13.04 mmol, 1.1 eq) was treated with EtOH/PhMe (100 mL/50 mL), 1 M aq Na₂CO₃ (23.7 mL, 2.7 mmol, 2 eq), followed by Pd(PPh₃)₄ (685 mg, 0.593 mmol, 5 mol%). The resulting mixture was refluxed (oil bath temperature at 110 °C) under Ar for 1.5 d; LCMS showed the reaction was incomplete. Additional 1 M aq Na₂CO₃ (14.2 mL, 1.2 eq) and Pd(PPh₃)₄ (685 mg, 0.593 mol) were added and the resulting mixture was refluxed (oil bath temperature at 110 °C) for 1 d. LCMS indicated the completion of reaction, H₂O (100 mL) and brine (50 mL) were added, followed by EtOAc (300 mL). Upon separation, the aqueous layer was extracted with EtOAc (60 mL x 2) and the combined organic layers were dried over Na₂SO₄ and concentrated. The resulting dark brown oil which was purified by flash chromatography using two Biotage 100g SiO₂ columns (gradient: EtOAc/hex 10 to 100 %, then MeOH/DCM 0 to 10 %). The impure fractions were combined and purified by flash chromatography for a second time. All clean fractions were combined and dried to give the title compound (2.64 g, 45%) as light brown foam. ¹H NMR (400 MHz, MeOH-*d*₄) δ ppm 8.67 (s, 1H), 8.51 (d, *J* = 4.8 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.80 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 5.2, 2.0 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 4.50 (d, *J* = 9.2 Hz, 1H), 4.25 (br, s, 2H), 3.93 (t, *J* = 4.8 Hz, 1H), 2.39-2.36 (m, 2H), 2.26-2.18 (m, 2H), 2.07-2.02 (m, 2H), 1.63 (d, *J* = 14.8 Hz, 2H), 1.46-1.36 (m, 1H), 0.71-0.66 (m, 1H), 0.61-0.50 (m, 3H); MS ESI [*M* + *H*]⁺ 494.2, calcd for [C₃₀H₃₂N₂O₅+H]⁺ 494.2. It was converted to 2HCl salt (3.018 g, quantitative yield) using General Method J. ¹H NMR (400 MHz, MeOH-*d*₄) δ ppm 8.23 (s, 1H), 7.96 (s, 1H), 7.72 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.32-7.27 (m, 3H), 6.49 (br, s, 1H, NH), 6.40 (t, *J* = 6.2 Hz, 1H, NH), 4.08-4.02 (m, 2H), 3.44 (t, *J* = 11.8 Hz, 2H), 3.33 (t, *J* = 6.4 Hz, 2H), 2.97-2.89 (m, 1H), 2.10-1.97 (m, 1H), 1.81-1.75 (m, 2H), 1.53-1.42 (m, 2H), 0.92-0.86 (m, 2H), 0.67-0.62 (m, 2H). HPLC (2HCl salt, > 99%ee, eluted at 7.9 min): Daicel Chiralpak IA, 60:40 v/v hexane-*i*PrOH (+0.5% Et₂NH), 1.0 mL min⁻¹, 254 nm, *R*_t (R) = 7.9 min, *R*_t (S) = 10.6 min. [α]_D²⁴ (2HCl salt) = -75.3° (c = 0.46, MeOH).

Example A2: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((S)-cyclopentyl(pyridin-2-yl)methyl)-1H-indazole-5-carboxamide



A mixture of crude, prior to amid hydrolysis, (S)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (200 mg, 0.44 mmol) and (1R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (138 mg, 0.44 mmol, 1 eq) was treated with EtOH/PhMe (2 mL/2 mL), satd aq Na₂CO₃ (2 mL), followed by Pd(PPh₃)₄ (26 mg, 0.022 mmol, 5 mol%). The resulting mixture was heated under Ar in a Biotage microwave reactor at 125°C for 3 h; LCMS indicated the completion of reaction. H₂O (10 mL) and brine (5 mL) were added, followed by EtOAc (20 mL). Upon separation, the aqueous layer was extracted with EtOAc (10 mL x 3) and the combined organic layers were dried over Na₂SO₄ and concentrated. The resulting yellow oil was purified by flash chromatography using a Biotage 50 g SiO₂ column (gradient: EtOAc/hex 0 to 100 %). The purest fractions were combined and purified again by reverse phase chromatography using a Biotage 50g C18 column (gradient: ACN/water 10 to 90 %). All pure fractions were combined and dried to give a light yellow solid. Using General Method J, the title compound was converted to 2HCl salt; yellow solid (99 mg, 39%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.78 (d, J=6.0 Hz, 1 H), 8.61 (s, 1 H), 8.55 (t, J=7.9 Hz, 1 H), 8.09 (d, J=8.0 Hz, 1 H), 7.81 - 7.98 (m, 4 H), 7.60 (d, J=8.3 Hz, 1 H), 7.08 (br. s., 2 H), 5.01 (d, J=10.8 Hz, 1 H), 4.25 (br. s., 2 H), 3.94 (d, J=11.0 Hz, 2 H), 3.58 (br. s., 2 H), 2.55 - 2.68 (m, 1 H), 2.15 - 2.26 (m, 1 H), 2.00 - 2.14 (m, 4 H), 1.67 - 1.84 (m, 3 H), 1.53 - 1.67 (m, 2 H), 1.39 - 1.49 (m, 1 H), 1.18 - 1.29 (m, 1 H); MS ESI 330.1 [M + H]⁺ 508.4, calcd for [C₃₁H₃₃N₅O₂+H]⁺ 508.3. HPLC (2HCl salt, > 99% ee, eluted at 16.6 min): Daicel Chiralpak IA, 60:40 v/v hexane-iPrOH (+0.5% Et₂NH), 1.0 mL min⁻¹, 254 nm, R_t (R) = 9.7 min, R_t (S) = 16.6 min. [α]_D²⁴ (2 HCl salt) = +90.9° (c = 0.48, MeOH).

Example A3: N-((S)-cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1R,3R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide



A mixture of (R)-N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (600 mg, 1.44 mmol) and (1R,3S,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-

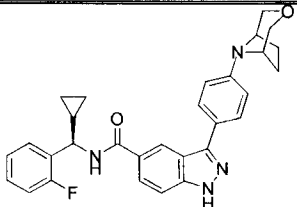
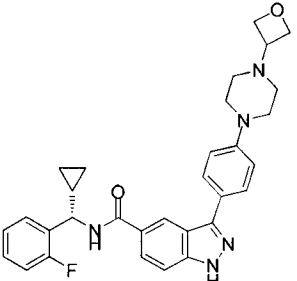
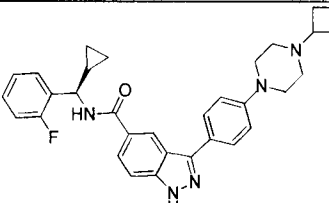
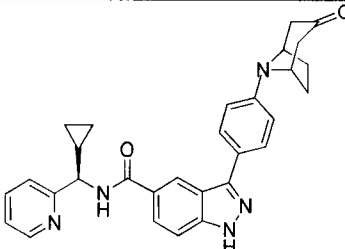
azabicyclo[3.2.1]octan-3-ol (520 mg, 1.58 mmol, 1.1 eq.) was treated with EtOH/PhMe (10 mL/5 mL), 1 M aq Na₂CO₃ (2.87 mL, 2.87 mmol, 2 eq), followed by Pd(PPh₃)₄ (83 mg, 0.072 mmol, 5 mol%). The resulting mixture was heated in microwave for 4 h at 125 °C; This reaction was repeated 4 times on the same scale (1.44 mmol) and one time on 0.48 mmol scale.

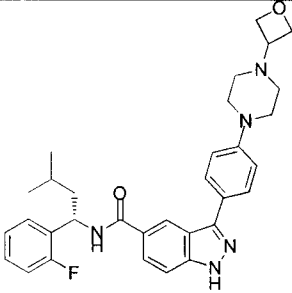
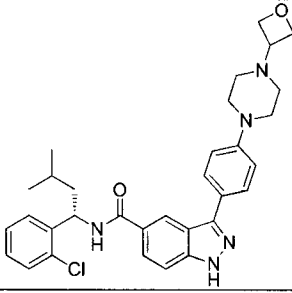
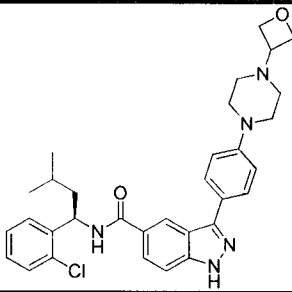
All 6 reactions were combined, passed thru Ceilte, diluted with EtOAc and washed with H₂O and brine. After drying and evaporation of solvents, it was concentrated and purified on by flash chromatography using Biotage 100g SiO₂ columns (gradient: EtOAc/hex 0 to 100 %, then MeOH/DCM 0 to 20%). It was then purified by prep-HPLC and passed through porapak to give the tile compound as a yellow solid (free base, 1.97 g, 53%). ¹H NMR (400 MHz, MeOH-*d*₄) δ ppm 8.66 (s, 1H), 8.52 (d, *J* = 5.0 Hz, 1H), 7.95 (dd, *J* = 8.8, 1.0 Hz, 1 H), 7.91-7.77 (m, 3H), 7.56 (dd, *J* = 13.2, 8.4 Hz, 2H), 7.32 (dd, *J* = 7.2, 5.4 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 4.52 (d, *J* = 9.3 Hz, 1H), 4.37 (br, s, 2H), 4.21-4.10 (m, 1H), 2.14 - 2.02 (m, 2H), 1.89-1.69 (m, 6H), 1.47-1.34 (m, 1H), 0.70 (d, *J* = 2.3 Hz, 1H), 0.63-0.47 (m, 3H).

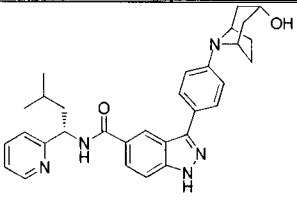
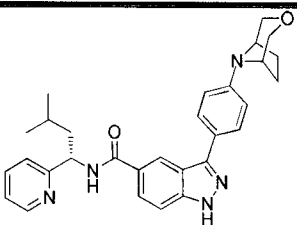
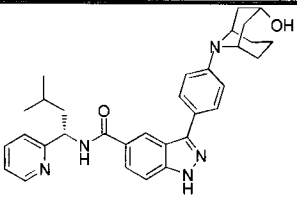
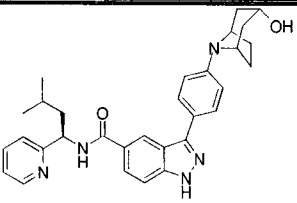
To a solution of the above compound (free base, 1.97 g, 4.00 mmol) in MeOH (15 mL) at -10 °C was added 1 M HCl in Et₂O (8.2 mL, 8.2 mmol, 2.05 eq.) dropwise. After stirring for 2 mins at -10 °C, it was concentrated to remove solvents. MeOH was added and solvents were removed. This was repeated twice to give the desired 2HCl salt (2.30 g, quantitate yield) as yellow solid. ¹H NMR (400 MHz, MeOH-*d*₄) δ ppm 8.81 (br, s, 2H), 8.67 (t, *J* = 7.5 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 2H), 8.04-8.02 (m, 2H), 7.78-7.64 (m, 3H), 4.73 (br,s, 2H), 4.52 (d, *J* = 10.0 Hz, 1H), 4.34-4.19 (m, 1H), 2.37-2.01 (m, 8H), 1.61 (br, s, 1H), 0.94 (br. s., 1H), 0.84-0.61 (m, 3H); MS ESI [M + H]⁺ 494.3, calcd for [C₃₀H₃₂N₂O₅+H]⁺ 494.2. HPLC (2HCl salt, > 99% ee, eluted at 16.1 min): Daicel Chiralpak IA, 60:40 v/v hexane-iPrOH (+0.5% Et₂NH), 1.0 mL min⁻¹, 254 nm, R_f (R) = 10.7 min, R_f (S) = 16.1 min. [α]_D²⁴ (2 HCl salt) = +82° (c = 0.30, MeOH).

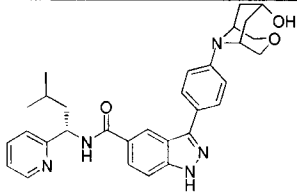
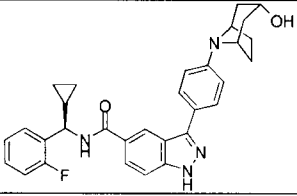
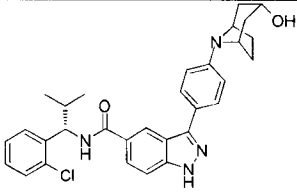
The following compound examples were prepared according to the syntheses described for Example A1, A2 and A3 and using General Methods B or B2:

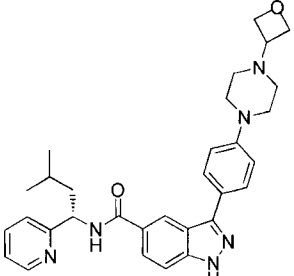
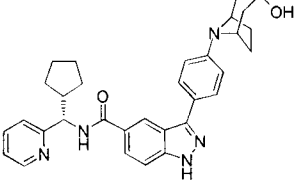
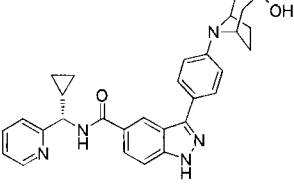
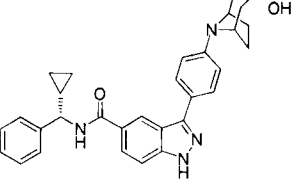
Example/ IUPAC name	Structure	MS calculated MS ESI [M+H] ⁺	Yield; Appearance; Salt form
A4: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((S)-cyclopropyl(2-fluorophenyl)methyl)-1H-indazole-5-carboxamide		[C ₃₀ H ₂₉ FN ₄ O ₂ +H] ⁺ 497.2 497.4	54 mg (59%); yellow solid; HCl salt
SMs: (S)-N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (75 mg, 0.17 mmol), (1R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (55 mg, 0.17 mmol), Pd(PPh ₃) ₄ (15 mg, 0.012 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.62 (s, 1 H), 8.27 (d, <i>J</i> =8.4 Hz, 2 H), 7.99 (d, <i>J</i> =8.8 Hz, 1			

H), 7.81 (d, $J=8.4$ Hz, 2 H), 7.68 (d, $J=8.4$ Hz, 1 H), 7.58 (t, $J=6.4$ Hz, 1 H), 7.26-7.31 (m, 1 H), 7.17 (t, $J=7.6$ Hz, 1 H), 7.06-7.11 (m, 1 H), 4.77 (d, $J=9.6$ Hz, 1 H), 4.71 (br.s, 2 H), 4.25 (d, $J=12.4$ Hz, 2 H), 3.99 (d, $J=12.8$ Hz, 2 H), 2.35-2.37 (m, 2 H), 2.19-2.22 (m, 2 H), 1.46-1.48 (m, 1 H), 0.70-0.73 (br. m, 1 H), 0.59-0.69 (m, 1 H), 0.45-0.54 (m, 2 H)			
A5: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((R)-cyclopropyl(2-fluorophenyl)methyl)-1H-indazole-5-carboxamide		$[C_{30}H_{29}FN_4O_2 + H]^+$ 497.2 497.4	13 mg (12%); yellow solid; TFA salt
SMs: (R)-N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (80 mg, 0.18 mmol), (1R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (65 mg, 0.2 mmol), Pd(PPh ₃) ₄ (10 mg, 0.009 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.61 (s, 1 H), 7.97 - 7.84 (m, 3 H), 7.63 - 7.50 (m, 2 H), 7.31 - 7.22 (m, 1 H), 7.16 (t, $J = 7.2$ Hz, 1 H), 7.12 - 7.03 (m, 2 H), 4.75 (d, $J = 9.5$ Hz, 1 H), 4.24 (br. s., 2 H), 3.93 (d, $J = 11.0$ Hz, 2 H), 3.57 (br. s., 2 H), 2.15 - 1.97 (m, 4 H), 1.48-1.40 (m, 1 H), 0.72 - 0.62 (m, 1 H), 0.62 - 0.53 (m, 1 H), 0.53 - 0.38 (m, 2 H)			
A6: (S)-N-(cyclopropyl(2-fluorophenyl)methyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{31}H_{32}FN_5O_2 + H]^+$ 526.2 526.8	60 mg (54%); off-white solid; TFA salt
SMs: (S)-N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (75 mg, 0.17 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (60 mg, 0.17 mmol), Pd(PPh ₃) ₄ (15 mg, 0.012 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.58 (d, $J=0.4$ Hz, 1 H), 7.95 (dd, $J=8.8$, 2.4 Hz, 3 H), 7.54-7.61 (m, 2 H), 7.25-7.30 (m, 1 H), 7.11-7.25 (m, 3 H), 7.06-7.09 (m, 1 H), 4.76 (d, $J=9.6$ Hz, 1 H), 4.48-7.51 (m, 1 H), 3.58 (br.s, 4 H), 3.40 (br.s, 4 H), 1.41-1.47 (m, 1 H), 0.65-0.72 (m, 1 H), 0.53-0.61 (m, 1 H), 0.42-0.51 (m, 2 H), 4H-merged with solvent peak.			
A7: (R)-N-(cyclopropyl(2-fluorophenyl)methyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{31}H_{32}FN_5O_2 + H]^+$ 526.2 526.8	20 mg (18%); yellow powder; TFA salt
SMs: (R)-N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (80 mg, 0.18 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (65 mg, 0.2 mmol), Pd(PPh ₃) ₄ (15 mg, 0.012 mmol)			
¹ H NMR (400 MHz, CD ₃ OD): Identical to the spectrum for Example A269.			
A8: N-((R)-cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1R,5S)-3-oxo-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{30}H_{29}N_5O_2 + H]^+$ 492.2 492.2	330 mg (45%); pale yellow solid; free base
SMs: (R)-N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (624 mg, 1.5 mmol), (1R,5S)-8-(4-bromophenyl)-8-azabicyclo[3.2.1]octan-3-one (550 mg, 1.7 mmol),			

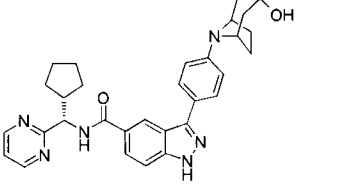
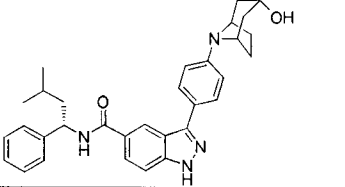
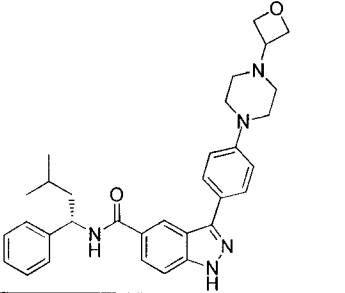
Pd(PPh ₃) ₄ (87 mg, 0.075 mmol)			
¹ H NMR (400 MHz, CD ₃ OD): δ ppm 8.67 (s, 1H), 8.52 (d, J = 4.4 Hz, 1H), 7.98-7.93 (m, 3H), 7.85-7.79 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.34-7.29 (m, 1H), 7.16 (d, J = 8.8 Hz, 2H), 4.68-4.62 (m, 2H), 4.52 (d, J = 9.2 Hz, 1H), 2.79-2.71 (m, 2H), 2.31 (d, J = 15.2 Hz, 2H), 2.26-2.18 (m, 2H), 1.85-1.77 (m, 2H), 1.46-1.37 (m, 1H), 0.73-0.67 (m, 1H), 0.62-0.51 (m, 3H).			
A9: (S)-N-(1-(2-fluorophenyl)-3-methylbutyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₆ FN ₅ O ₂ +H] ⁺ 542.2 542.5	82 mg (56%); yellow solid; TFA salt
SMs: (S)-N-(1-(2-fluorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (76 mg, 0.22 mmol), Pd(PPh ₃) ₄ (13 mg, 0.011 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.58 (s, 1 H), 7.91-7.95 (m, 3 H), 7.59-7.62 (m, 1 H), 7.44-7.48 (m, 1 H), 7.25 - 7.29 (m, 1 H) 7.06 - 7.18 (m, 4 H), 5.55-5.59 (m, 1 H), 4.46-4.53 (m, 1 H), 3.57 (br. s, 4 H), 3.40 (br. s, 4 H), 1.89-1.96 (m, 1 H), 1.63-1.75 (m, 2 H), 1.02 (d, J=5.6 Hz, 6 H), 4H merged with solvent peak.			
A10: (S)-N-(1-(2-chlorophenyl)-3-methylbutyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₆ ClN ₅ O ₂ +H] ⁺ 558.3 558.6	368 mg (68%), yellow solid; TFA salt
SMs: (S)-N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide (374 mg, 0.8 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (276 mg, 0.8 mmol)			
Spectral data was identical for that obtained in (R)-N-(1-(2-chlorophenyl)-3-methylbutyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide			
A11: (R)-N-(1-(2-chlorophenyl)-3-methylbutyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₆ ClN ₅ O ₂ +H] ⁺ 558.3 559.5	6.508 g (60%), yellow solid; TsOH salt
SMs: (R)-N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide (7.02 g, 15 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (5.16 g, 15 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.59 (s, 1H), 7.90-7.50 (m, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.8 Hz, 1H), 7.80-7.40 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 7.25-7.19 (m, 3H), 7.16 (d, J = 8.4 Hz, 2H), 5.71 (dd, J = 10.0, 4.8 Hz, 1H), 4.96-4.85 (m, 4H, partially buried in H ₂ O), 4.31 (quintet, J = 6.0 Hz, 1H), 4.10-3.10 (m, 8H), 2.34 (s, 3H), 1.91-1.78 (m, 2H), 1.68-1.58 (m, 2H), 1.06 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H). HPLC (pTSA salt, > 99%ee, eluted at 35.9 min): Daicel Chiralpak AD-H, 80:20 v/v hexane-			

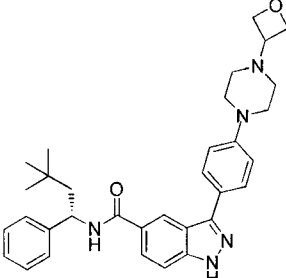
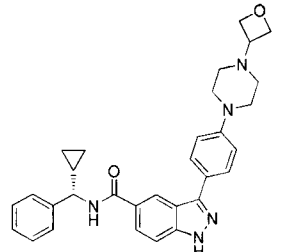
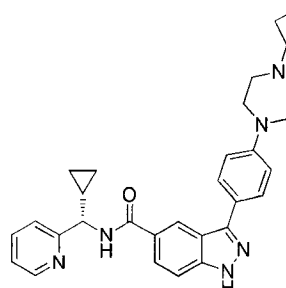
iPrOH (+0.5% Et ₂ NH), 1.0 mL min ⁻¹ , 254 nm, R _t (R) = 34.9 min, R _t (S) = 30.7 min. [α] _D ²⁴ (pTSA salt) = -52.3° (c = 2.3, MeOH).			
A12: 3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((S)-3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₅ N ₅ O ₂ +H] +510.3 510.4	44 mg (25%), yellow solid; 2xHCl salt
SMs: (S)-3-iodo-N-(3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide (133 mg, 0.3 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (120 mg, 0.36 mmol)			
Spectral data was identical for that obtained in 3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((R)-3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide.			
A13: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((S)-3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide		[C ₃₀ H ₃₃ N ₅ O ₂ +H] +496.3 496.3	79 mg (46%), yellow solid; 2xHCl salt
SMs: (S)-3-iodo-N-(3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide (130 mg, 0.3 mmol), (1R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (95 mg, 0.3 mmol)			
¹ H NMR (free base, 400 MHz, CD ₃ OD) δ ppm 8.68 (s, 1H), 8.51-8.48 (m, 1H), 7.97 (dd, J = 8.8, 1.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.74 (dt, J = 7.6, 1.6 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.27-7.22 (m, 1H), 6.89 (d, J = 8.8 Hz, 2H), 5.37-5.32 (m, 1H), 4.12-4.02 (m, 2H), 3.81 (d, J = 10.8 Hz, 2H), 3.44 (d, J = 10.8 Hz, 2H), 2.03-1.85 (m, 5H), 1.78-1.65 (m, 2H), 0.97 (t, J = 5.6 Hz, 6H).			
A14: 3-(4-((1R,3S,5S)-3-hydroxy-9-azabicyclo[3.3.1]nonan-9-yl)phenyl)-N-((S)-3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₇ N ₅ O ₂ +H] +524.3 524.3	36 mg (20%), yellow solid; 2xHCl salt
SMs: (S)-3-iodo-N-(3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide (130 mg, 0.3 mmol), (1R,3R,5S)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-9-azabicyclo[3.3.1]nonan-3-ol (113 mg, 0.33 mmol)			
¹ H NMR (free base, 400 MHz, CD ₃ OD) δ ppm 8.66 (d, J = 0.4 Hz, 1H), 8.52-8.48 (m, 1H), 7.95 (dd, J = 9.0, 1.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.76 (dd, J = 7.8, 1.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.29-7.25 (m, 1H), 7.98 (d, J = 8.8 Hz, 2H), 5.38-5.32 (m, 1H), 4.35-4.27 (m, 2H), 3.75-3.66 (m, 1H), 2.47-2.37 (m, 2H), 2.30-2.15 (m, 1H), 1.95-1.85 (m, 1H), 1.85-1.77 (m, 4H), 1.68-1.40 (m, 5H), 1.05-0.97 (m, 6H).			
A15: 3-(4-((1R,3R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((R)-3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₅ N ₅ O ₂ +H] +510.3 510.3	52 mg (30%), yellow solid; 2xHCl salt
SMs: (R)-3-iodo-N-(3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide (130 mg, 0.3 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (109 mg, 0.33 mmol)			

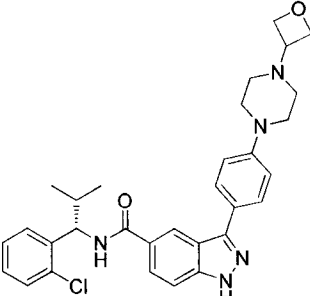
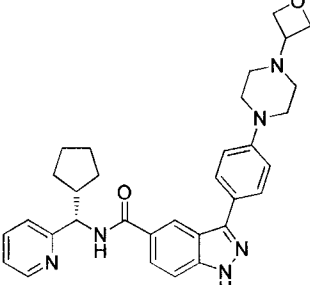
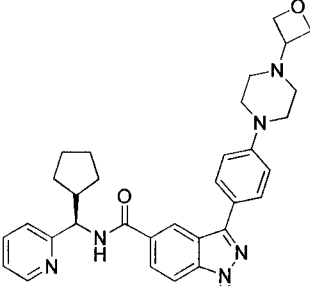
¹ H NMR (free base, 400 MHz, CD ₃ OD) δ ppm 8.66 (d, J = 0.8 Hz), 8.52-8.49 (m, 1H), 7.95 (dd, J = 8.8, 1.6 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.77 (dt, J = 7.6, 1.7 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.29-7.25 (m, 1H), 6.91 (d, J = 8.8 Hz, 2H), 5.35 (dd, J = 10.0, 5.2 Hz, 1H), 4.25-4.18 (m, 2H), 3.91 (t, J = 4.6 Hz, 1H), 2.38-2.31 (m, 2H), 2.23-2.16 (m, 2H), 2.06-1.98 (m, 2H), 1.96-1.85 (m, 1H), 1.80-1.66 (m, 2H), 1.61 (d, J = 14.4 Hz, 2H), 1.02-0.97 (m, 6H).			
A16: 3-(4-((1R,5S,7R)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)phenyl)-N-((S)-3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₅ N ₅ O ₃ +H] ⁺ 526.3 526.4	59 mg (33%), yellow solid; 2xHCl salt
SMs: (S)-3-iodo-N-(3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide (130 mg, 0.3 mmol), (1R,5S,7R)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-ol (99 mg, 0.3 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.88 (s, 1H), 8.32 (d, J = 4.8 Hz, 1H), 8.70-8.62 (m, 1H), 8.28 (d, J = 6.4 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.08-7.98 (m, 3H), 7.76 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 6.4 Hz, 2H), 5.53-5.45 (m, 1H), 4.19 (brs, 2H), 4.07-3.95 (m, 4H), 3.92-3.87 (m, 1H), 2.40-2.31 (m, 3H), 1.91-1.78 (m, 4H), 1.08 (d, J = 5.2 Hz, 3H), 1.06 (d, J = 5.2 Hz, 3H).			
A17: N-((R)-cyclopropyl(2-fluorophenyl)methyl)-3-(4-((1R,3R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₁ FN ₄ O ₂ +H] ⁺ 511.2 511.4	20 mg (40%); yellow powder; TFA salt
SMs: (R)-N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (40 mg, 0.09 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (36 mg, 0.1 mmol), Pd(PPh ₃) ₄ (5 mg, 0.009 mmol)			
¹ H NMR (400MHz, CD ₃ OD) δ 8.61 (s, 1 H), 8.09 (d, J = 8.5 Hz, 2 H), 8.02 - 7.91 (m, 1 H), 7.63 (d, J = 8.8 Hz, 1 H), 7.57 (t, J = 6.8 Hz, 1 H), 7.48 (d, J = 7.5 Hz, 2 H), 7.34 - 7.22 (m, 1 H), 7.22 - 7.12 (m, 1 H), 7.12 - 7.00 (m, 1 H), 4.76 (d, J = 9.5 Hz, 1 H), 4.53 (br. s., 2 H), 4.08 (br. s., 1 H), 2.59 (d, J = 7.8 Hz, 2 H), 2.48-2.39 (m, 2 H), 2.19 - 2.10 (m, 2 H), 2.05-1.97 (m, 2 H), 1.54 - 1.33 (m, 1 H), 0.75 - 0.63 (m, 1 H), 0.61-0.54 (m, 1 H), 0.53 - 0.38 (m, 2 H)			
A18: N-((S)-1-(2-chlorophenyl)-2-methylpropyl)-3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₃ ClN ₄ O ₂ +H] ⁺ 529.2 529.6	15 mg (19%); yellow solid; free base
SMs: (S)-N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide (69mg, 0.15 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (50 mg, 0.15 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.55 (dd, J=1.6, 0.9 Hz, 1 H), 7.87 (dd, J=8.8, 1.5 Hz, 1 H), 7.78 (d, J=8.8 Hz, 2 H), 7.50 - 7.58 (m, 2 H), 7.36 (dd, J=8.0, 1.3 Hz, 1 H), 7.23 - 7.30 (m, 1 H), 7.20 (dd, J=8.0, 1.8 Hz, 1 H), 6.89 (d, J=8.8 Hz, 2 H), 5.38 (d, J=9.8 Hz, 1 H), 4.21 (br. s., 2 H), 3.91 (s, 1 H), 2.35 (d, J=7.0 Hz, 2 H), 2.23 - 2.31 (m, 1 H), 2.19 (d, J=14.8 Hz, 2 H), 1.98 - 2.06 (m, 2 H), 1.61 (d, J=14.6 Hz, 2 H), 1.14 (d, J=6.5 Hz, 3 H), 0.85 (d, J=6.8 Hz, 3 H)			

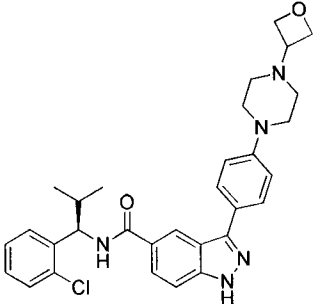
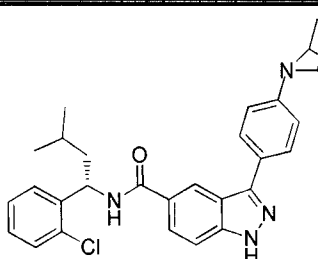
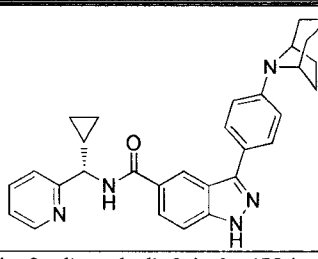
A19: (S)-N-(3-methyl-1-(pyridin-2-yl)butyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₆ N ₆ O ₂ +H] ⁺ 525.3 525.3	70 mg (51%); yellow solid; free base
SMs: (S)-3-iodo-N-(3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide (115 mg, 0.26 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (100 mg, 0.58 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.64 - 8.70 (m, 1 H), 8.46 - 8.51 (m, 1 H), 7.94 - 8.01 (m, 1 H), 7.83 (d, J=8.8 Hz, 2 H), 7.72 (td, J=7.8, 1.8 Hz, 1 H), 7.58 (dd, J=8.9, 0.6 Hz, 1 H), 7.46 (d, J=7.8 Hz, 1 H), 7.23 (ddd, J=7.5, 4.9, 1.1 Hz, 1 H), 6.94 (d, J=9.0 Hz, 2 H), 5.36 (dd, J=9.9, 5.4 Hz, 1 H), 4.59 - 4.68 (m, 2 H), 4.50 - 4.58 (m, 2 H), 3.36 - 3.43 (m, 1 H), 3.04 - 3.19 (m, 4 H), 2.21 - 2.48 (m, 4 H), 1.82 - 1.95 (m, 1 H), 1.60 - 1.80 (m, 2 H), 0.89 - 1.01 (m, 6 H)			
A20: N-((S)-cyclopentyl(pyridin-2-yl)methyl)-3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₅ N ₅ O ₂ +H] ⁺ 522.3 522.3	33 mg (33%); white solid; free base
SMs: (S)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (86 mg, 0.19 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (70 mg, 0.21 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.61 (dd, J=1.5, 0.8 Hz, 1 H), 8.48 - 8.54 (m, 1 H), 7.91 (dd, J=8.8, 1.5 Hz, 1 H), 7.73 - 7.84 (m, 3 H), 7.56 (dd, J=8.9, 0.6 Hz, 1 H), 7.45 - 7.50 (m, 1 H), 7.28 (ddd, J=7.5, 5.0, 1.3 Hz, 1 H), 6.90 (d, J=8.8 Hz, 2 H), 5.01 (d, J=10.3 Hz, 1 H), 4.22 (br. s., 2 H), 3.91 (t, J=4.5 Hz, 1 H), 2.53 (m, J=9.8 Hz, 1 H), 2.29 - 2.40 (m, 2 H), 2.19 (d, J=11.0 Hz, 2 H), 1.88 - 2.07 (m, 3 H), 1.43 - 1.74 (m, 7 H), 1.19 - 1.40 (m, 2 H)			
A21: N-((S)-cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₀ H ₃₁ N ₅ O ₂ +H] ⁺ 494.3 494.2	13 mg (10%); yellow solid; free base
SMs: (S)-N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (106 mg, 0.25 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (100 mg, 0.3 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.67 (d, J=0.8 Hz, 1 H), 8.51 (d, J=4.0 Hz, 1 H), 7.95 (dd, J=8.8, 1.5 Hz, 1 H), 7.76 - 7.88 (m, 3 H), 7.57 (d, J=8.5 Hz, 1 H), 7.53 (d, J=8.0 Hz, 1 H), 7.25 - 7.33 (m, 1 H), 6.94 (d, J=8.8 Hz, 2 H), 4.51 (d, J=9.5 Hz, 1 H), 4.25 (br. s., 2 H), 3.93 (s, 1 H), 2.36 (d, J=7.3 Hz, 2 H), 2.22 (d, J=14.3 Hz, 2 H), 2.00 - 2.09 (m, 2 H), 1.63 (d, J=14.6 Hz, 2 H), 1.34 - 1.49 (m, 1 H), 0.63 - 0.72 (m, 1 H), 0.45 - 0.61 (m, 3 H)			
A22: N-((S)-cyclopropyl(phenyl)methyl)-3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₂ N ₄ O ₂ +H] ⁺ 493.3 493.5	40 mg (29%); yellow solid; free base
SMs: (S)-N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (115 mg, 0.28			

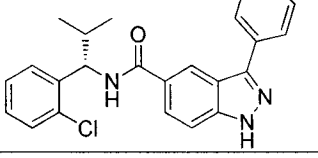
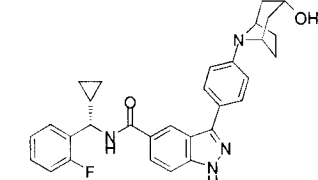
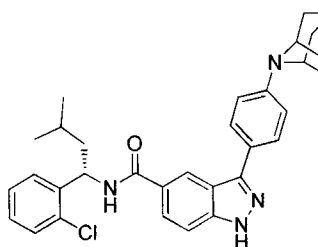
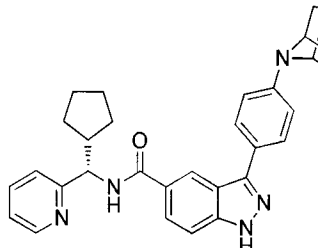
mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (100 mg, 0.3 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.64 (d, J=0.8 Hz, 1 H), 7.95 (dd, J=8.9, 1.4 Hz, 1 H), 7.82 (d, J=8.5 Hz, 2 H), 7.56 (d, J=8.8 Hz, 1 H), 7.47 (d, J=7.5 Hz, 2 H), 7.30 (t, J=7.5 Hz, 2 H), 7.21 (m, J=7.5 Hz, 1 H), 6.90 (d, J=8.8 Hz, 2 H), 4.47 (d, J=9.5 Hz, 1 H), 4.20 (br. s., 2 H), 3.87 - 3.92 (m, 1 H), 2.34 (m, J=7.0 Hz, 2 H), 2.13 - 2.23 (m, 2 H), 1.97 - 2.06 (m, 2 H), 1.60 (d, J=14.3 Hz, 2 H), 1.31 - 1.45 (m, 1 H), 0.56 - 0.67 (m, 2 H), 0.36 - 0.51 (m, 2 H)			
A23: N-((R)-cyclopentyl(pyridin-2-yl)methyl)-3-(4-((1R,3R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₅ N ₅ O ₂ +H] ⁺ 522.3 522.5	34 mg (24%); yellow solid; free base
SMs: (R)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (123 mg, 0.28 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (100 mg, 0.3 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.61 (dd, J=1.5, 0.8 Hz, 1 H), 8.48 - 8.54 (m, 1 H), 7.91 (dd, J=8.8, 1.5 Hz, 1 H), 7.73 - 7.85 (m, 3 H), 7.56 (dd, J=8.8, 0.5 Hz, 1 H), 7.48 (d, J=7.8 Hz, 1 H), 7.28 (ddd, J=7.5, 4.9, 1.1 Hz, 1 H), 6.90 (d, J=8.8 Hz, 2 H), 5.01 (d, J=10.3 Hz, 1 H), 4.22 (br. s., 2 H), 3.91 (t, J=4.5 Hz, 1 H), 2.53 (m, J=9.5 Hz, 1 H), 2.30 - 2.40 (m, 2 H), 2.12 - 2.23 (m, 2 H), 1.84 - 2.06 (m, 3 H), 1.43 - 1.76 (m, 7 H), 1.19 - 1.41 (m, 2 H)			
A24: N-((S)-cyclopropyl(thiophen-3-yl)methyl)-3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		[C ₂₉ H ₃₀ N ₄ O ₂ S+H] ⁺ 499.2 499.4	30 mg (25%); yellow solid; free base
SMs: (S)-N-(cyclopropyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (78 mg, 0.24 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.64 (d, J=0.8 Hz, 1 H), 7.95 (dd, J=8.8, 1.5 Hz, 1 H), 7.84 (d, J=8.8 Hz, 2 H), 7.58 (d, J=8.8 Hz, 1 H), 7.27 (dd, J=5.1, 1.1 Hz, 1 H), 7.12 (dt, J=3.5, 1.1 Hz, 1 H), 6.88 - 7.00 (m, 3 H), 4.76 (d, J=9.5 Hz, 1 H), 4.24 (br. s., 2 H), 3.93 (s, 1 H), 2.36 (d, J=7.0 Hz, 2 H), 2.17 - 2.25 (m, 2 H), 1.99 - 2.09 (m, 2 H), 1.63 (d, J=14.6 Hz, 2 H), 1.44 - 1.57 (m, 1 H), 0.71 - 0.81 (m, 1 H), 0.59 - 0.70 (m, 1 H), 0.42 - 0.58 (m, 2 H)			
A25: N-((R)-cyclopentyl(pyrimidin-2-yl)methyl)-3-(4-((1R,3R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₄ N ₆ O ₂ +H] ⁺ 523.27 523.5	19 mg (23%); yellow solid; free base
SMs: (R)-N-(cyclopentyl(pyrimidin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (70 mg, 0.16 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (52 mg, 0.16 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.76 (d, J=5.0 Hz, 2 H), 8.63 (d, J=0.5 Hz, 1 H), 7.92 (dd, J=8.9, 1.6 Hz, 1 H), 7.83 (d, J=8.8 Hz, 2 H), 7.57 (d, J=8.8 Hz, 1 H), 7.35 (t, J=4.9 Hz, 1 H), 6.93 (d, J=8.8 Hz, 2 H), 5.18 (d, J=9.5 Hz, 1 H), 4.24 (br. s., 2 H), 3.92 (t, J=4.4 Hz, 1 H), 2.57 (m, J=9.0 Hz, 1 H), 2.31 - 2.40 (m, 2 H), 2.21 (d, J=15.1 Hz, 2 H), 2.00 - 2.08 (m, 2 H), 1.92 (d, J=7.3 Hz, 1 H), 1.47 - 1.75 (m, 7 H), 1.36 - 1.45 (m, 2 H)			

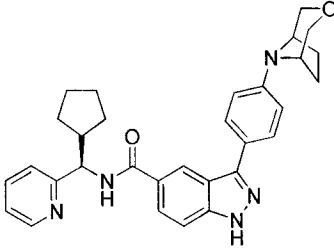
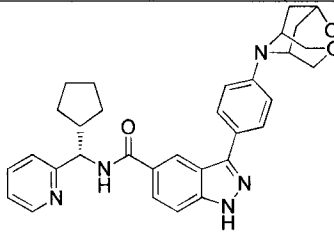
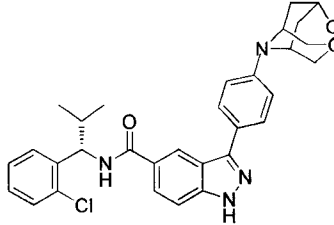
A26: N-((S)-cyclopentyl(pyrimidin-2-yl)methyl)-3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{31}H_{34}N_6O_2 + H]^+$ 523.3 523.4	30 mg (37%); yellow solid; free base
SMs: (S)- N-(cyclopentyl(pyrimidin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (70 mg, 0.16 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (52 mg, 0.16 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.72 - 8.80 (m, 2 H), 8.60 - 8.65 (m, 1 H), 7.92 (dd, $J=8.8$, 1.5 Hz, 1 H), 7.84 (d, $J=8.8$ Hz, 2 H), 7.57 (d, $J=8.8$ Hz, 1 H), 7.36 (t, $J=4.9$ Hz, 1 H), 6.94 (d, $J=8.8$ Hz, 2 H), 5.18 (d, $J=9.8$ Hz, 1 H), 4.25 (br. s., 2 H), 3.93 (s, 1 H), 2.48 - 2.66 (m, 1 H), 2.36 (d, $J=7.3$ Hz, 2 H), 2.21 (d, $J=14.6$ Hz, 2 H), 2.00 - 2.08 (m, 2 H), 1.88 - 1.98 (m, 1 H), 1.47 - 1.75 (m, 7 H), 1.33 - 1.46 (m, 2 H)			
A27: 3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((S)-3-methyl-1-phenylbutyl)-1H-indazole-5-carboxamide		$[C_{32}H_{36}N_4O_2 + H]^+$ 509.3 509.4	83 mg (77%); yellow solid; free base
SMs: (S)-3-iodo-N-(3-methyl-1-phenylbutyl)-1H-indazole-5-carboxamide (92 mg, 0.21 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (70 mg, 0.21 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.62 (s, 1 H), 7.92 (dd, $J=8.8$, 1.3 Hz, 1 H), 7.80 (d, $J=8.5$ Hz, 2 H), 7.54 (d, $J=8.8$ Hz, 1 H), 7.41 (d, $J=7.3$ Hz, 2 H), 7.30 (t, $J=7.7$ Hz, 2 H), 7.21 (d, $J=7.5$ Hz, 1 H), 6.88 (d, $J=8.8$ Hz, 2 H), 5.18 - 5.29 (m, 1 H), 4.19 (br. s., 2 H), 3.90 (br. s., 1 H), 2.33 (d, $J=7.0$ Hz, 2 H), 2.12 - 2.23 (m, 2 H), 1.97 - 2.06 (m, 2 H), 1.83 - 1.96 (m, 1 H), 1.50 - 1.72 (m, 4 H), 0.96 (d, $J=6.3$ Hz, 6 H)			
A28: (S)-N-(3-methyl-1-phenylbutyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{32}H_{37}N_5O_2 + H]^+$ 524.3 524.5	62 mg (69%); white solid; free base
SMs: (S)-3-iodo-N-(3-methyl-1-phenylbutyl)-1H-indazole-5-carboxamide (75 mg, 0.17 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (60 mg, 0.17 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.64 (s, 1 H), 7.95 (dd, $J=8.8$, 1.5 Hz, 1 H), 7.81 (d, $J=8.8$ Hz, 2 H), 7.55 (d, $J=8.8$ Hz, 1 H), 7.40 (d, $J=7.3$ Hz, 2 H), 7.27 (t, $J=7.5$ Hz, 2 H), 7.12 - 7.22 (m, 1 H), 6.91 (d, $J=8.8$ Hz, 2 H), 5.26 (dd, $J=9.3$, 5.8 Hz, 1 H), 4.57 - 4.67 (m, 2 H), 4.48 - 4.56 (m, 2 H), 3.34 - 3.42 (m, 1 H), 3.02 - 3.17 (m, 4 H), 2.25 - 2.40 (m, 4 H), 1.76 - 1.96 (m, 1 H), 1.54 - 1.71 (m, 2 H), 0.83 - 1.01 (m, 6 H)			

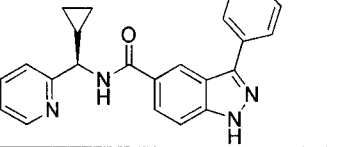
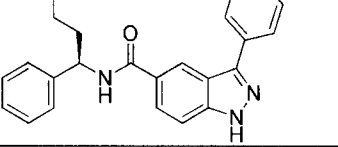
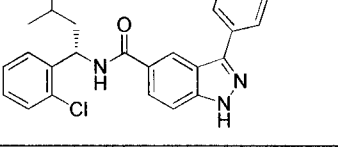
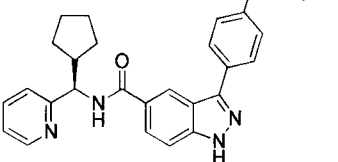
A29: (S)-N-(3,3-dimethyl-1-phenylbutyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₃ H ₃₉ N ₅ O ₂ +H] ⁺ 538.3 538.6	72 mg (64%); white solid; free base
SMs: (S)-N-(3,3-dimethyl-1-phenylbutyl)-3-iodo-1H-indazole-5-carboxamide (95mg, 0.21 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (80mg, 0.23 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.58 (s, 1 H), 7.91 (d, J=8.8 Hz, 1 H), 7.86 (d, J=4.5 Hz, 2 H), 7.57 (d, J=8.8 Hz, 1 H), 7.41 (d, J=7.8 Hz, 2 H), 7.31 (t, J=6.9 Hz, 2 H), 7.16 - 7.25 (m, 1 H), 6.98 - 7.13 (m, 2 H), 5.35 (dd, J=9.5, 3.3 Hz, 1 H), 4.71 (d, J=6.3 Hz, 2 H), 4.59 - 4.66 (m, 2 H), 3.52 (br. s., 1 H), 3.27 (br. s., 4 H), 2.49 (br. s., 4 H), 2.07 (dd, J=14.4, 9.4 Hz, 1 H), 1.73 (dd, J=14.3, 2.8 Hz, 1 H), 0.98 - 1.07 (m, 9 H)			
A30: (S)-N-(cyclopropyl(phenyl)methyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₃ N ₅ O ₂ +H] ⁺ 508.3 508.4	50 mg (52%); white solid; free base
SMs: (S)-N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (78 mg, 0.19 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (64 mg, 0.19 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.62 (s, 1 H), 7.91 - 7.98 (m, 1 H), 7.87 (d, J=8.8 Hz, 2 H), 7.59 (s, 1 H), 7.47 (d, J=7.3 Hz, 2 H), 7.31 (t, J=7.5 Hz, 2 H), 7.22 (t, J=7.5 Hz, 1 H), 7.07 (d, J=8.8 Hz, 2 H), 4.71 (t, J=6.8 Hz, 2 H), 4.63 (t, J=6.3 Hz, 2 H), 4.47 (d, J=9.5 Hz, 1 H), 3.48 - 3.56 (m, 1 H), 3.23 - 3.29 (m, 4 H), 2.45 - 2.54 (m, 4 H), 1.33-1.45 (m, 1 H), 0.64 (d, J=8.0 Hz, 2 H), 0.39 - 0.51 (m, 2 H)			
A31: (S)-N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₀ H ₃₂ N ₆ O ₂ +H] ⁺ 509.3 509.2	26 mg (20%); white solid; free base
SMs: (S)-N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (103 mg, 0.25 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (85 mg, 0.25 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.66 (s, 1 H), 8.50 (d, J=4.0 Hz, 1 H), 7.95 (dd, J=8.9, 1.4 Hz, 1 H), 7.88 (d, J=8.8 Hz, 2 H), 7.76 - 7.82 (m, 1 H), 7.58 (d, J=8.8 Hz, 1 H), 7.52 (d, J=7.8 Hz, 1 H), 7.26 - 7.32 (m, 1 H), 7.07 (d, J=8.8 Hz, 2 H), 4.70 (t, J=6.5 Hz, 2 H), 4.62 (t, J=5.8 Hz, 2 H), 4.50 (d, J=9.5 Hz, 1 H), 3.51 (quin, J=6.3 Hz, 1 H), 3.23 - 3.29 (m, 4 H), 2.45 - 2.51 (m, 4 H), 1.33 - 1.45 (m, 1 H), 0.63 - 0.71 (m, 1 H), 0.48 - 0.60 (m, 3 H)			

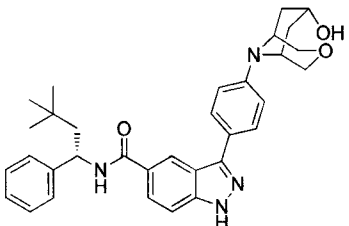
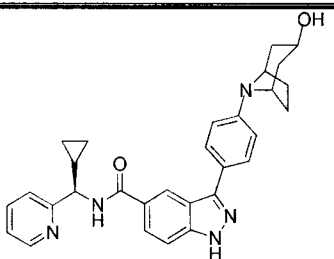
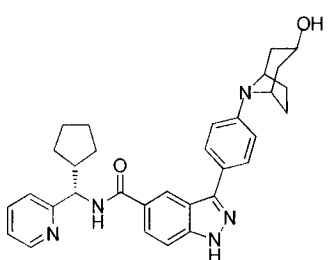
A32: (S)-N-(1-(2-chlorophenyl)-2-methylpropyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{31}H_{34}ClN_5O_2+H]^+$ 544.2 544.5	51 mg (43%); white solid; free base
SMs: (S)-N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (76 mg, 0.22 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.54 (s, 1 H), 7.81 - 7.90 (m, 3 H), 7.51 - 7.58 (m, 2 H), 7.37 (dd, $J=7.8, 1.0$ Hz, 1 H), 7.25 - 7.31 (m, 1 H), 7.18 - 7.23 (m, 1 H), 7.06 (d, $J=8.8$ Hz, 2 H), 5.37 (d, $J=9.8$ Hz, 1 H), 4.72 (t, $J=6.8$ Hz, 2 H), 4.63 (t, $J=6.3$ Hz, 2 H), 3.49 - 3.57 (m, 1 H), 3.25 - 3.30 (m, 4 H), 2.47 - 2.53 (m, 4 H), 2.21 - 2.33 (m, 1 H), 1.15 (d, $J=6.8$ Hz, 3 H), 0.86 (d, $J=6.5$ Hz, 3 H)			
A33: (S)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{32}H_{36}N_6O_2+H]^+$ 537.3 537.3	49 mg (42%); white solid; free base
SMs: (S)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (76 mg, 0.22 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.60 (s, 1 H), 8.52 (d, $J=4.3$ Hz, 1 H), 7.92 (d, $J=8.8$ Hz, 1 H), 7.87 (d, $J=8.3$ Hz, 2 H), 7.79 (t, $J=7.8$ Hz, 1 H), 7.59 (d, $J=8.8$ Hz, 1 H), 7.50 (d, $J=7.3$ Hz, 1 H), 7.25 - 7.33 (m, 1 H), 7.07 (d, $J=8.3$ Hz, 2 H), 5.02 (d, $J=10.3$ Hz, 1 H), 4.72 (t, $J=6.5$ Hz, 2 H), 4.63 (t, $J=6.0$ Hz, 2 H), 3.45 - 3.56 (m, 1 H), 3.28 (br. s., 4 H), 2.42 - 2.59 (m, 5 H), 1.91 - 2.02 (m, 1 H), 1.45 - 1.77 (m, 5 H), 1.23 - 1.40 (m, 2 H). HPLC (pTSA salt, > 99% ee, eluted at 33 min): Daicel Chiracel OZ-H, 70:30 v/v hexane-iPrOH (+0.5% Et_2NH), 1.0 mL min^{-1} , 254 nm, R_t (R) = 15 min, R_t (S) = 33 min. $[\alpha]_D^{24}$ (pTSA salt) = +27.4° (c = 0.58, MeOH).			
A34: (R)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{32}H_{36}N_6O_2+H]^+$ 537.3 537.3	52 mg (44%); white solid; free base
SMs: (R)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (76 mg, 0.22 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.59 (s, 1 H), 8.52 (d, $J=4.0$ Hz, 1 H), 7.91 (dd, $J=9.0, 1.3$ Hz, 1 H), 7.86 (d, $J=8.8$ Hz, 2 H), 7.75 - 7.82 (m, 1 H), 7.58 (d, $J=8.8$ Hz, 1 H), 7.49 (d, $J=8.0$ Hz, 1 H), 7.25 - 7.32 (m, 1 H), 7.08 (d, $J=8.8$ Hz, 2 H), 5.01 (d, $J=10.0$ Hz, 1 H), 4.72 (t, $J=6.5$ Hz, 2			

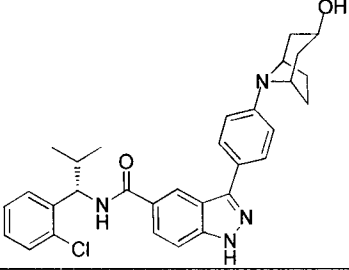
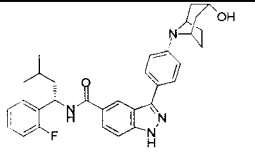
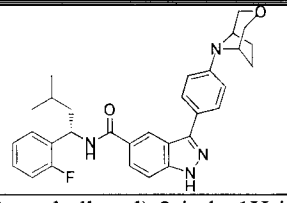
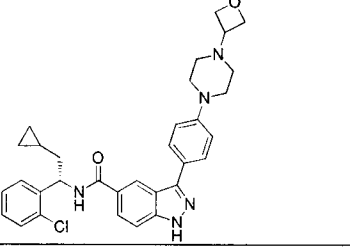
H), 4.63 (t, $J=6.0$ Hz, 2 H), 3.49 - 3.57 (m, 1 H), 3.28 (s, 4 H), 2.46 - 2.58 (m, 5 H), 1.92 - 2.01 (m, 1 H), 1.46 - 1.75 (m, 5 H), 1.23 - 1.40 (m, 2 H)			
A35: (R)-N-(1-(2-chlorophenyl)-2-methylpropyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{31}H_{34}ClN_5O_2 + H]^+$ 544.2 544.4	278 mg (51%); yellow solid; HCl salt
SMs: (R)-N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide (453 mg, 1 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (344 mg, 1 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.52 (s, 1 H), 7.87 - 7.95 (m, 3 H), 7.59 (d, $J=8.8$ Hz, 1 H), 7.52 - 7.57 (m, 1 H), 7.37 - 7.41 (m, 1 H), 7.27 - 7.33 (m, 1 H), 7.20 - 7.25 (m, 1 H), 7.19 (d, $J=8.8$ Hz, 2 H), 5.37 (d, $J=9.5$ Hz, 1 H), 4.88 - 4.97 (m, 4 H), 4.48 - 4.56 (m, 1 H), 3.98 (br. s, 2 H), 3.62 (br. s, 2 H), 3.24 (br. s, 4 H), 2.22 - 2.35 (m, 1 H), 1.16 (d, $J=7.3$ Hz, 3 H), 0.87 (d, $J=6.8$ Hz, 3 H)			
A36: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((S)-1-(2-chlorophenyl)-3-methylbutyl)-1H-indazole-5-carboxamide		$[C_{31}H_{33}ClN_4O_2]$ 529.2 529.5	53 mg (39%); yellow solid; TFA salt
SMs: (S)-N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.21 mmol), 8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (66 mg, 0.21 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.61 (s, 1 H), 7.89 - 7.98 (m, 3 H), 7.60 (d, $J=8.8$ Hz, 1 H), 7.50 (dd, $J=7.8$, 1.8 Hz, 1 H), 7.37 (dd, $J=7.8$, 1.5 Hz, 1 H), 7.27 (td, $J=7.3$, 1.5 Hz, 1 H), 7.20 (td, $J=7.5$, 1.8 Hz, 1 H), 7.16 (br. s, 2 H), 5.66 - 5.73 (m, 1 H), 4.28 (br. s, 2 H), 3.95 (d, $J=11.0$ Hz, 2 H), 3.57 - 3.66 (m, 2 H), 2.01 - 2.16 (m, 4 H), 1.77 - 1.88 (m, 2 H), 1.62 (s, 1 H), 1.04 (d, $J=6.5$ Hz, 3 H), 1.00 (d, $J=6.5$ Hz, 3 H)			
A37: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((S)-cyclopropyl(pyridin-2-yl)methyl)-1H-indazole-5-carboxamide		$[C_{29}H_{29}N_5O_2 + H]^+$ 480.2 480.2	64 mg (38%); yellow solid; 2TFA salt
SMs: (S)-N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), 8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (76 mg, 0.24 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.64 - 8.73 (m, 2 H), 8.40 (td, $J=7.9$, 1.8 Hz, 1 H), 8.05 (d, $J=8.0$ Hz, 1 H), 7.96 (dd, $J=8.8$, 1.5 Hz, 1 H), 7.87 (d, $J=8.0$ Hz, 2 H), 7.77 - 7.83 (m, 1 H), 7.60 (d, $J=8.8$ Hz, 1 H), 7.02 (br. s, 2 H), 4.48 (d, $J=10.0$ Hz, 1 H), 4.19 (br. s, 2 H), 3.90 (d, $J=10.8$ Hz, 2 H), 3.53 (br. s, 2 H), 1.96 - 2.12 (m, 4 H), 1.42 - 1.54 (m, 1 H), 0.80 - 0.89 (m, 1 H), 0.56 - 0.75 (m, 3 H)			

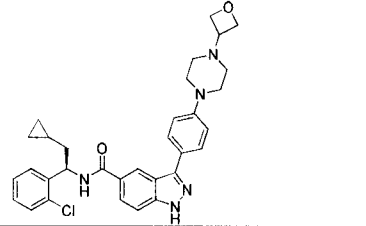
A38: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((S)-1-(2-chlorophenyl)-2-methylpropyl)-1H-indazole-5-carboxamide		$[C_{30}H_{31}ClN_4O_2+H]^+$ 515.2 515.6	51 mg (37%); yellow solid; TFA salt
SMs: (S)-N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), 8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (69 mg, 0.22 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.54 (s, 1 H), 7.93 (br. s., 2 H), 7.86 - 7.90 (m, 1 H), 7.58 (d, $J=8.5$ Hz, 1 H), 7.54 (dd, $J=7.7, 1.6$ Hz, 1 H), 7.38 (dd, $J=7.9, 1.4$ Hz, 1 H), 7.27 - 7.32 (m, 1 H), 7.13 - 7.25 (m, 3 H), 5.37 (d, $J=9.8$ Hz, 1 H), 4.32 (br. s., 2 H), 3.95 - 4.0 (m, 2 H), 3.64 (br. s., 2 H), 2.22 - 2.33 (m, 1 H), 2.02 - 2.18 (m, 4 H), 1.16 (d, $J=6.8$ Hz, 3 H), 0.86 (d, $J=6.5$ Hz, 3 H)			
A39: N-((S)-cyclopropyl(2-fluorophenyl)methyl)-3-(4-((1R,3R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{31}H_{31}FN_4O_2+H]^+$ 511.2 511.4	38 mg (40%); yellow solid; HCl salt
SMs: (S)-N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (75 mg, 0.17 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (57 mg, 0.17 mmol), $Pd(PPh_3)_4$ (15 mg, 0.012 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.60 (s, 1 H), 8.27 (d, $J=8.4$ Hz, 2 H), 7.98 (d, $J=8.8$ Hz, 1 H), 7.58 (d, $J=8.4$ Hz, 2 H), 7.67 (d, $J=8.4$ Hz, 1 H), 7.58 (t, $J=7.2$ Hz, 1 H), 7.26-7.31 (m, 1 H), 7.17 (t, $J=7.6$ Hz, 1 H), 7.06-7.11 (m, 1 H), 4.77 (d, $J=9.6$ Hz, 1 H), 4.71 (br. s., 2 H), 4.17 (s, 1 H), 2.71-2.73 (m, 2 H), 2.63-2.59 (m, 2 H), 2.23-2.27 (m, 4 H), 1.46-1.48 (br. m, 1 H), 0.62-0.69 (br. m, 1 H), 0.56-0.60 (m, 1 H), 0.45-0.54 (m, 2 H)			
A40: 3-(4-((1R,5S)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)phenyl)-N-((S)-1-(2-chlorophenyl)-3-methylbutyl)-1H-indazole-5-carboxamide		$[C_{32}H_{35}ClN_4O_2+H]^+$ 543.2 543.7	22 mg (16%); yellow solid; TFA salt
SMs: (S)-N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.21 mmol), (1R,5S)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-9-azabicyclo[3.3.1]nonane (69 mg, 0.21 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.63 (s, 1 H), 7.94 (dd, $J=8.8, 1.5$ Hz, 1 H), 7.88 (d, $J=8.5$ Hz, 2 H), 7.60 (d, $J=8.5$ Hz, 1 H), 7.50 (dd, $J=7.9, 1.6$ Hz, 1 H), 7.38 (d, $J=6.5$ Hz, 1 H), 7.25 - 7.31 (m, 1 H), 7.18 - 7.24 (m, 1 H), 6.99 - 7.13 (m, 2 H), 5.65 - 5.72 (m, 1 H), 3.95 - 4.09 (m, 4 H), 3.92 (br. s., 2 H), 2.57 - 2.71 (m, 1 H), 1.99 - 2.12 (m, 2 H), 1.70 - 1.90 (m, 4 H), 1.57 - 1.67 (m, 2 H), 1.05 (d, $J=6.5$ Hz, 3 H), 1.01 (d, $J=6.5$ Hz, 3 H)			
A41: 3-(4-((1R,5S)-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)phenyl)-N-((S)-cyclopentyl(pyridin-2-yl)methyl)-1H-indazole-5-carboxamide		$[C_{32}H_{35}N_5O_2+H]^+$ 522.3 522.4	49 mg (30%); yellow solid; 2xTFA salt
SMs: (S)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22			

mmol), (1R,5S)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-9-azabicyclo[3.3.1]nonane (74 mg, 0.22 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.78 (d, J=5.8 Hz, 1 H), 8.61 (s, 1 H), 8.56 (t, J=7.3 Hz, 1 H), 8.09 (d, J=8.0 Hz, 1 H), 7.95 (t, J=6.8 Hz, 1 H), 7.82 - 7.92 (m, 3 H), 7.59 (d, J=8.8 Hz, 1 H), 7.04 (d, J=8.5 Hz, 2 H), 5.01 (d, J=10.8 Hz, 1 H), 4.05 (d, J=11.0 Hz, 2 H), 3.98 (d, J=11.3 Hz, 2 H), 3.92 (br. s., 2 H), 2.55 - 2.70 (m, 2 H), 2.15 - 2.25 (m, 1 H), 1.99 - 2.12 (m, 2 H), 1.69 - 1.84 (m, 5 H), 1.54 - 1.67 (m, 3 H), 1.39 - 1.49 (m, 1 H), 1.16 - 1.30 (m, 1 H)			
A42: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((R)-cyclopentyl(pyridin-2-yl)methyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₃ N ₅ O ₂ +H] ⁺ 508.3 508.3	93 mg (58%); yellow solid; 2TFA salt
SMs: (R)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), 8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (69 mg, 0.22 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.76 (d, J=6.0 Hz, 1 H), 8.60 (s, 1 H), 8.46 - 8.53 (m, 1 H), 8.05 (d, J=8.3 Hz, 1 H), 7.83 - 7.93 (m, 4 H), 7.60 (d, J=8.8 Hz, 1 H), 7.01 - 7.10 (m, 2 H), 5.01 (d, J=10.8 Hz, 1 H), 4.24 (br. s., 2 H), 3.93 (d, J=11.3 Hz, 2 H), 3.57 (d, J=11.5 Hz, 2 H), 2.55 - 2.66 (m, 1 H), 2.13 - 2.23 (m, 1 H), 2.10 (br. s., 4 H), 1.67 - 1.84 (m, 3 H), 1.54 - 1.67 (m, 2 H), 1.38 - 1.48 (m, 1 H), 1.19 - 1.30 (m, 1 H)			
A43: N-((S)-cyclopentyl(pyridin-2-yl)methyl)-3-(4-((1R,5S,7R)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₅ N ₅ O ₃ +H] ⁺ 538.3 538.5	68 mg (40%); yellow solid; 2TFA salt
SMs: (S)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), (1R,5S,7R)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxabicyclo[3.3.1]nonan-7-ol (76 mg, 0.22 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.76 (d, J=5.0 Hz, 1 H), 8.60 (s, 1 H), 8.48 (td, J=7.9, 1.5 Hz, 1 H), 8.04 (d, J=8.0 Hz, 1 H), 7.84 - 7.93 (m, 4 H), 7.59 (d, J=8.8 Hz, 1 H), 7.05 (d, J=8.5 Hz, 2 H), 5.01 (d, J=10.8 Hz, 1 H), 4.03 - 4.09 (m, 2 H), 3.91 - 4.02 (m, 4 H), 3.88 (br. s., 1 H), 2.54 - 2.66 (m, 1 H), 2.27 - 2.37 (m, 2 H), 2.13 - 2.22 (m, 1 H), 1.67-1.82 (br.m, 5 H), 1.53 - 1.66 (m, 2 H), 1.38 - 1.48 (m, 1 H), 1.18 - 1.29 (m, 1 H)			
A44: N-((S)-1-(2-chlorophenyl)-2-methylpropyl)-3-(4-((1R,5S,7R)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₁ H ₃₃ ClN ₅ O ₃ +H] ⁺ 545.2 545.6	68 mg (47%); yellow solid; TFA salt
SMs: (S)-N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), (1R,5S,7R)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxabicyclo[3.3.1]nonan-7-ol (76 mg, 0.22 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.55 (s, 1 H), 7.81 - 7.91 (m, 3 H), 7.52 - 7.59 (m, 2 H), 7.38 (dd, J=7.8, 1.3 Hz, 1 H), 7.29 (td, J=7.5, 1.4 Hz, 1 H), 7.21 (td, J=7.7, 1.6 Hz, 1 H), 7.02 (br. s., 2 H), 5.34 - 5.40 (m, 1 H), 3.82 - 4.07 (m, 7 H), 2.21 - 2.37 (m, 3 H), 1.74 (d, J=15.6 Hz, 2 H), 1.15 (d, J=6.5 Hz, 3 H), 0.86 (d, J=6.8 Hz, 3 H)			

A45: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((R)-cyclopropyl(pyridin-2-yl)methyl)-1H-indazole-5-carboxamide		[C ₂₉ H ₂₉ N ₅ O ₂ +H] +480.2 480.2	68 mg (51%); yellow solid; 2HCl salt
SMs: (R)-N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), 8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (76 mg, 0.24 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.78 - 8.83 (m, 2 H), 8.66 (t, J=8.4 Hz, 1 H), 8.32 (d, J=8.0 Hz, 1 H), 8.28 (d, J=8.5 Hz, 2 H), 8.00 - 8.05 (m, 2 H), 7.75 (d, J=8.5 Hz, 2 H), 7.69 (d, J=8.8 Hz, 1 H), 4.68 (br. s., 2 H), 4.51 (d, J=10.3 Hz, 1 H), 4.21 (d, J=12.5 Hz, 2 H), 3.93 (d, J=12.0 Hz, 2 H), 2.30 - 2.38 (m, 2 H), 2.16 - 2.24 (m, 2 H), 1.56 - 1.65 (m, 1 H), 0.89 - 0.98 (m, 1 H), 0.62 - 0.82 (m, 3 H)			
A46: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((R)-3-hydroxy-1-phenylpropyl)-1H-indazole-5-carboxamide		[C ₂₉ H ₃₀ N ₄ O ₃ +H] +483.2 483.4	48 mg (39%); yellow solid; HCl salt
SMs: (R)-N-(3-hydroxy-1-phenylpropyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), 8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (75 mg, 0.24 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.61 (s, 1 H), 8.25 (d, J=8.5 Hz, 2 H), 7.96 (dd, J=8.9, 1.1 Hz, 1 H), 7.79 (d, J=7.0 Hz, 2 H), 7.67 (d, J=9.0 Hz, 1 H), 7.45 (d, J=7.5 Hz, 2 H), 7.35 (t, J=7.7 Hz, 2 H), 7.25 (t, J=7.3 Hz, 1 H), 5.31 - 5.37 (m, 1 H), 4.71 (br. s., 2 H), 4.21 (d, J=12.0 Hz, 2 H), 3.97 (d, J=12.8 Hz, 2 H), 3.60 - 3.72 (m, 2 H), 2.32 - 2.40 (m, 2 H), 2.10 - 2.24 (m, 4 H)			
A47: N-((S)-1-(2-chlorophenyl)-3-methylbutyl)-3-(4-((1R,5S,7R)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₅ ClN ₄ O ₃ +H] +559.2 559.6	28 mg (34%); yellow solid; HCl salt
SMs: (S)-N-(1-(2-chlorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide (68 mg, 0.14 mmol), (1R,5S,7R)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxabicyclo[3.3.1]nonan-7-ol (50 mg, 0.14 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.68 (s, 1 H), 8.09 (d, J=8.8 Hz, 1 H), 7.91 (d, J=8.8 Hz, 2 H), 7.70 (d, J=9.0 Hz, 1 H), 7.50 (d, J=7.5 Hz, 1 H), 7.38 (d, J=7.8 Hz, 1 H), 7.28 (t, J=7.8 Hz, 1 H), 7.22 (t, J=6.3 Hz, 1 H), 7.12 (d, J=9.0 Hz, 2 H), 5.66 - 5.73 (m, 1 H), 4.12 (br. s., 2 H), 3.92 - 4.05 (m, 4 H), 3.86 - 3.91 (m, 1 H), 2.27 - 2.37 (m, 2 H), 1.75 - 1.89 (m, 4 H), 1.59 - 1.68 (m, 1 H), 1.05 (d, J=6.3 Hz, 3 H), 1.01 (d, J=6.3 Hz, 3 H)			
A48: N-((R)-cyclopentyl(pyridin-2-yl)methyl)-3-(4-((1R,5S,7R)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₅ N ₅ O ₃ +H] +538.3 538.4	55 mg (56%); yellow solid; 2xHCl salt

SMs: (R)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (70 mg, 0.16 mmol), (1R,5S,7R)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxabicyclo[3.3.1]nonan-7-ol (54 mg, 0.16 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.81 (d, J=6.0 Hz, 1 H), 8.73 (s, 1 H), 8.65 (t, J=7.8 Hz, 1 H), 8.23 (d, J=7.8 Hz, 1 H), 7.99 - 8.08 (m, 2 H), 7.96 (d, J=8.3 Hz, 2 H), 7.69 (d, J=8.8 Hz, 1 H), 7.16 (d, J=8.0 Hz, 2 H), 5.04 (d, J=10.8 Hz, 1 H), 4.15 (br. s., 2 H), 3.93 - 4.05 (m, 4 H), 3.90 (br. s., 1 H), 2.65 - 2.77 (m, 1 H), 2.29 - 2.41 (m, 2 H), 2.17 - 2.28 (m, 1 H), 1.69 - 1.88 (m, 5 H), 1.53 - 1.68 (m, 2 H), 1.39 - 1.50 (m, 1 H), 1.17 - 1.30 (m, 1 H)			
A49: N-((S)-3,3-dimethyl-1-phenylbutyl)-3-(4-((1R,5S,7R)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₃ H ₃₈ N ₄ O ₃ +H] ⁺ 539.3 539.5	38 mg (41%); yellow solid; HCl salt
SMs: (S)-N-(3,3-dimethyl-1-phenylbutyl)-3-iodo-1H-indazole-5-carboxamide (70 mg, 0.16 mmol), (1R,5S,7R)-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxabicyclo[3.3.1]nonan-7-ol (54 mg, 0.16 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.63 (s, 1 H), 8.05 (dd, J=9.0, 1.5 Hz, 1 H), 7.89 (d, J=8.8 Hz, 2 H), 7.67 (d, J=8.8 Hz, 1 H), 7.41 (d, J=7.3 Hz, 2 H), 7.32 (t, J=7.5 Hz, 2 H), 7.21 (t, J=7.5 Hz, 1 H), 7.11 (d, J=8.8 Hz, 2 H), 5.34 (dd, J=9.5, 3.5 Hz, 1 H), 4.11 (br. s., 2 H), 3.91 - 4.03 (m, 4 H), 3.86 - 3.90 (m, 1 H), 2.27 - 2.37 (m, 2 H), 2.02 - 2.11 (m, 1 H), 1.70 - 1.84 (m, 3 H), 1.03 (s, 9 H)			
A50: N-((R)-cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₀ H ₃₁ N ₅ O ₂ +H] ⁺ 494.4 494.5	58 mg (53%); yellow solid; free base
SMs: (R)-N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (0.092 g, 0.22 mmol), (1R,3S,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (0.080 g, 0.24 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.68 (d, J=0.8 Hz, 1 H), 8.45 - 8.53 (m, 1 H), 7.95 (dd, J=8.9, 1.4 Hz, 1 H), 7.84 (d, J=8.5 Hz, 2 H), 7.76 (td, J=7.8, 1.8 Hz, 1 H), 7.56 (d, J=8.8 Hz, 1 H), 7.50 (d, J=7.8 Hz, 1 H), 7.26 (ddd, J=7.5, 5.0, 1.0 Hz, 1 H), 6.92 (d, J=8.8 Hz, 2 H), 4.51 (d, J=9.3 Hz, 1 H), 4.29 (br. s., 2 H), 4.04 - 4.19 (m, 1 H), 1.97 - 2.07 (m, 2 H), 1.65 - 1.84 (m, 6 H), 1.28 - 1.48 (m, 1 H), 0.62 - 0.70 (m, 1 H), 0.46 - 0.59 (m, 3 H)			
A51: N-((S)-cyclopentyl(pyridin-2-yl)methyl)-3-(4-((1R,3R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₅ N ₅ O ₂ +H] ⁺ 522.3 522.5	66 mg (57%); yellow solid; free base
SMs: (S)-N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (0.099 g, 0.22 mmol), (1R,3S,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (0.080 g, 0.24 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.59 (s, 1 H), 8.53 (d, J=4.0 Hz, 1 H), 7.91 (d, J=8.8 Hz, 1 H), 7.86 (d, J=8.8 Hz, 2 H), 7.80 (m, J=1.8 Hz, 1 H), 7.58 (d, J=8.8 Hz, 1 H), 7.51 (d, J=7.8 Hz, 1 H), 7.27 - 7.35 (m, 1 H), 7.01 (d, J=8.8 Hz, 2 H), 5.02 (d, J=10.3 Hz, 1 H), 4.38 (br. s., 1 H), 4.10 -			

4.23 (m, 1 H), 2.47 - 2.64 (m, 1 H), 2.09 (d, $J=5.5$ Hz, 2 H), 1.93 - 2.04 (m, 1 H), 1.48 - 1.89 (m, 12 H), 1.24 - 1.43 (m, 2 H)			
A52: N-((S)-1-(2-chlorophenyl)-2-methylpropyl)-3-(4-((1R,3R,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{31}H_{33}ClN_4O_2 + H]^+$ 529.2 529.6	70 mg (60%); yellow solid; free base
SMs: (S)-N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide (0.100 g, 0.22 mmol), (1R,3S,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (0.080 g, 0.24 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.55 (s, 1 H), 7.79 - 7.91 (m, 3 H), 7.56 (d, $J=8.3$ Hz, 2 H), 7.39 (dd, $J=7.8, 1.3$ Hz, 1 H), 7.27 - 7.34 (m, 1 H), 7.22 (m, $J=7.8, 1.8$ Hz, 1 H), 7.00 (d, $J=9.0$ Hz, 2 H), 5.32 - 5.44 (m, 1 H), 4.38 (br. s., 2 H), 4.08 - 4.23 (m, 1 H), 2.21 - 2.34 (m, 1 H), 2.04 - 2.13 (m, 2 H), 1.70 - 1.89 (m, 6 H), 1.17 (d, $J=6.8$ Hz, 3 H), 0.87 (d, $J=6.8$ Hz, 3 H)			
A53: N-((S)-1-(2-fluorophenyl)-3-methylbutyl)-3-(4-((1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{32}H_{35}FN_4O_2 + H]^+$ 527.28 527.5	31 mg (25 %); Yellow solid; HCl salt
SMs: (S)-N-(1-(2-fluorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), (1R,3R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (73 mg, 0.22 mmol), $Pd(PPh_3)_4$ (13 mg, 0.011 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.61 (s, 1H), 8.25 (br. s, 2H), 7.98 (d, $J=8.8$ Hz, 1H), 7.83 (br. s, 2 H), 7.67 (d, $J=8.4$ Hz, 1H), 7.46-7.49 (m, 1H), 7.24-7.29 (m, 1 H), 7.14-7.17 (m, 1 H), 7.06-7.11 (m, 1 H), 5.57-5.59 (m, 1 H), 4.71 (br. s, 2 H), 4.16 (s, 1 H), 2.71-2.73 (br. m, 2 H), 2.58-2.62 (br. m, 2 H), 2.23-2.26 (br. m, 4 H), 1.92-1.96 (m, 1 H), 1.70 (br. m, 2 H), 1.02 (d, $J=5.6$ Hz, 6 H)			
A54: 3-(4-((1R,5S)-3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl)-N-((S)-1-(2-fluorophenyl)-3-methylbutyl)-1H-indazole-5-carboxamide		$[C_{31}H_{33}FN_4O_2 + H]^+$ 513.26 513.5	43 mg (35 %); yellow solid; HCl salt
SMs: (S)-N-(1-(2-fluorophenyl)-3-methylbutyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), (1R,5S)-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (69.6 mg, 0.22 mmol), $Pd(PPh_3)_4$ (13 mg, 0.011 mmol)			
^1H NMR (400 MHz, CD_3OD) δ ppm 8.61 (s, 1 H), 8.20 (br. s, 2 H), 7.98 (d, $J=8.4$ Hz, 1 H), 7.64-7.71 (m, 3 H), 7.45-7.49 (m, 1 H), 7.24-7.29 (m, 1 H), 7.06-7.17 (m, 2 H), 5.57-5.59 (m, 1 H), 4.67 (br. s, 2 H), 4.16-4.17 (br. m, 2 H), 3.91-3.92 (br. s, 2 H), 2.32-2.33 (m, 2 H), 2.19 (br. s, 2 H), 1.92-1.96 (m, 1 H), 1.65-1.70 (m, 2 H), 1.02 (d, $J=6.0$ Hz, 6 H)			
A55: (S)-N-(1-(2-chlorophenyl)-2-cyclopropylethyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		$[C_{32}H_{34}ClN_5O_2 + H]^+$ 556.2 556.7	100 mg (37%), yellow solid; TFA salt
SMs: (S)-N-(1-(2-chlorophenyl)-2-cyclopropylethyl)-3-iodo-1H-indazole-5-carboxamide (187 mg, 0.4 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-			

yl)phenyl)piperazine (138 mg, 0.4 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) δ ppm 8.59 (d, J = 0.4 Hz, 1H), 7.94 (dd, J = 8.8, 1.6 Hz, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.51 (dd, J = 7.6, 1.6 Hz, 1H), 7.34 (dd, J = 7.6, 1.2 Hz, 1H), 7.23 (dt, J = 7.2, 1.2 Hz, 1H), 7.19 (dt, J = 7.6, 1.6 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 5.66 (dd, J = 9.2, 5.2 Hz, 1H), 4.93-4.84 (m, 4H), 4.45 (quintet, J = 6.4 Hz, 1H), 3.70-3.10 (m, 8H), 1.95-1.86 (m, 1H), 1.66-1.58 (m, 1H), 0.89-0.78 (m, 1H), 0.50-0.38 (m, 2H), 0.24-0.17 (m, 1H), 0.13-0.50 (m, 1H).			
A56: (R)-N-(1-(2-chlorophenyl)-2-cyclopropylethyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide		[C ₃₂ H ₃₄ ClN ₅ O ₂ +H] ⁺ 556.2 556.7	116 mg (43%), yellow solid; TFA salt
SMs: (R)-N-(1-(2-chlorophenyl)-2-cyclopropylethyl)-3-iodo-1H-indazole-5-carboxamide (187 mg, 0.4 mmol), 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (138 mg, 0.4 mmol)			
¹ H NMR (400 MHz, CD ₃ OD) Spectral data was identical for that obtained in (S)-N-(1-(2-chlorophenyl)-2-cyclopropylethyl)-3-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)-1H-indazole-5-carboxamide			

Example B: TTK Inhibition Assay

Active TTK was purchased from Invitrogen as an amino terminal GST fusion of full length human TTK. Amino terminal 6 histidine, sumo tagged human TTK (residues 1-275) was expressed in *E. coli*, and purified to >95% homogeneity by Ni²⁺ agarose, gel filtration, and ion exchange chromatography.

TTK activity was measured using an indirect ELISA detection system. GST-TTK (0.68 nM) was incubated in the presence of 16 μM ATP (Sigma cat# A7699), 50mM Hepes pH 7.2, 1mM EGTA, 10mM MgCl₂, and 0.1% Pluronic in a 96 well microtitre plate pre-coated with amino terminal 6 histidine, sumo tagged TTK (amino acid residues 1-275). The reaction was allowed to proceed for 30 minutes, followed by 5 washes of the plate with Wash Buffer (phosphate buffered saline supplemented with 0.2% Tween 20), and incubation for 30 minutes with a 1:3000 dilution of primary antibody (Cell Signaling cat# 9381). The plate was washed 5 times with Wash Buffer, incubated for 30 minutes in the presence of secondary antibody coupled to horse radish peroxidase (BioRad cat# 1721019, 1:3000 concentration), washed an additional 5 times with Wash Buffer, and incubated in the presence of TMB substrate (Sigma cat# T0440). The colourimetric reaction was allowed to continue for 5 minutes, followed by addition of stop solution (0.5 N sulphuric acid), and quantified by detection at 450 nm with either a monochromatic or filter based plate reader (Molecular Devices M5 or Beckman DTX880, respectively).

Compound inhibition was determined at either a fixed concentration (10 μM) or at a variable inhibitor concentration (typically 0.5 μM to 0.001 μM in a 10 point dose response titration). Compounds were pre-incubated in the presence of enzyme for 5 minutes prior to addition of ATP and the activity remaining quantified using the above described activity assay. The % Inhibition of a compound was determined using the following formula; % Inhibition = 100 x (1 – (experimental

value – background value)/(high activity control – background value)). The IC_{50} value was determined using a non-linear 4 point logistic curve fit (XLfit4, IDBS) with the formula; $(A+(B/(1+((x/C)^D))))$, where A = background value, B = range, C = inflection point, D = curve fit parameter.

In Table 1 below, IC_{50} value ranges for exemplary compounds are given. The IC_{50} ranges are indicated as "A," "B," and "C," for values less than or equal to 0.1 μ M; those greater than 0.1 μ M and less than or equal to 0.5 μ M; and those greater than 0.5 μ M, respectively.

Example C: Cancer Cell Line Data on Exemplary Compounds of the Invention

Breast cancer cells (MDA-MB-231), colon cancer cells (HCT116) and ovarian cancer cells (PA-1) were seeded (1000 to 4000 in 80 μ l per well depending on the cell growth rate) into 96 well plates 24 hours before compound overlay. Compounds were prepared as 10 mM stock solutions in 100% DMSO which were diluted with DMEM (Dulbecco's Modified Eagle's Medium) cell growth Medium (Invitrogen, Burlington, ON, Canada) containing 10% FBS (Fetal Bovine Serum) to concentrations ranging from 50 nM to 250 μ M. Aliquots (20 μ l) from each concentration were overlaid to 80 μ l of the pre-seeded cells in the 96 well plates to make final concentrations of 10 nM to 50 μ M. The cells were cultured for 5 days before the Sulforhodamine B assay (SRB) was performed to determine the compound's cell growth inhibition activity.

Sulforhodamine B (purchased from Sigma, Oakville, ON, Canada) is a water-soluble dye that binds to the basic amino acids of the cellular proteins. Thus, colorimetric measurement of the bound dye provides an estimate of the total protein mass that is related to the cell number. the cells are fixed in situ by gently aspirating off the culture media and adding 50 μ l ice cold 10% Trichloroacetic Acid (TCA) per well and incubate at 4°C for 30-60 min, The plates are washed with H₂O five times and allowed to air dry for 5 min. Addition of 50 μ l 0.4%(w/v) SRB solution in 1% (v/v) acetic acid to each well and incubation for 30 min at RT completes the staining reaction. Following staining, plates are washed four times with 1% acetic acid to remove unbound dye and then allowed to air dry for 5 min. The stain is solubilized with 100 μ l of 10 mM Tris pH 10.5 per well. Absorbance is read at 570 nm.

The percentage (%) of relative growth inhibition was calculated by comparing to DMSO treated only cells (100%). GI_{50} 's were determined for compounds with cytotoxic activity. The GI_{50} was calculated using GraphPad PRISM software (GraphPad Software, Inc., San Diego, CA, USA). GI_{50} (growth inhibition) is the compound concentration that causes 50% inhibition of cell growth.

In Table 1 below, GI_{50} value ranges for compound examples against breast cancer cell lines (MDA-MB-231), colon cancer cell lines (HCT116) and ovarian cancer cell lines (PA-1) are given. The example compounds demonstrated varying growth inhibition/cell killing activity against cells of breast cancer, colon cancer, and ovarian cancer. The GI_{50} ranges are indicated as "A," "B," and "C," for values less than or equal to 0.1 μ M; those greater than 0.1 μ M and less than or equal to 0.5 μ M; and those greater than 0.5 μ M, respectively.

Example D: Colon and Ovarian Cancer Tumor-Initiating Cell Data of Exemplary Compounds

Materials and Methods: Non-tissue or tissue cultured treated T-75 flask and 96-well plates were purchased from VWR. Vitamin B-27 supplement, MEM NEAA (minimum essential medium non essential amino acids), sodium pyruvate, L-glutamine, N2 supplement, penicillin-streptomycin and fungizone/amphotericin B were obtained from Invitrogen. Lipid mixture, heparin and EGF were purchased from Sigma; bFGF from BD Biosciences. Tumor Initiating Cells (TICs) from colon were routinely maintained using non-tissue cultured treated T-75 flasks in DMEM:F12 medium containing 0.2XB-27 supplement, 4ug/ml heparin, 1XMEM NEAA, 1Xsodium pyruvate, 1 mM glutamine, 10 pg/ul bFGF, 20 pg/ul EGF, 1X N2 supplement, lipid mixture, penicillin-streptomycin and fungizone/amphotericin B. Ovarian TICs were routinely maintained using tissue cultured treated T-75 flasks in DMEM:F12 medium containing 1XB-27 supplement, 4ug/ml heparin, 20 pg/ul bFGF, 20 pg/ul EGF and penicillin-streptomycin.

Assay Protocol: Compounds described herein were dissolved in DMSO and further diluted in cell culture medium for GI₅₀ determination. Colon TICs were trypsinized and seeded into non-tissue cultured treated 96-well plates with 4,000 cells/well. After 24 h, compound was added into the cell culture at different concentrations, and the final concentration of DMSO was adjusted to 0.1%. Cells were then cultured at 37°C for 9 days. Ovarian TICs were trypsinized and seeded into tissue cultured treated 96-well plates with 1,000 cells/well. After 24 h, compound was added into the cell culture at different concentrations, and the final concentration of DMSO was adjusted to 0.1%. Cells were then cultured at 37°C for 6 days. Cell viability was assessed by Alamar Blue assay: 10 ul of Alamar Blue was added into each well. After 4 hours incubation at 37°C, fluorescence was recorded at excitation 544 and emission 590. GI₅₀ (Growth inhibition) was calculated using GraphPad Prism 4.0 software. Cell growth inhibition data for compounds described herein is tabulated below.

In Table 1 below, GI₅₀ value ranges for compound examples against TICs (Colon 12 and Ovarian 2393A) are given. The GI₅₀ ranges are indicated as "A," "B," and "C," for values less than or equal to 0.1 μM; those greater than 0.1 μM and less than or equal to 0.5 μM; and those greater than 0.5 μM, respectively.

Table 1: *In vitro* activity of Compound Examples

Example #	TTK IC ₅₀ Range	Cancer Cell Line GI ₅₀ Range			Tumor Initiating Cell GI ₅₀ Range	
		HCT116	MDA-MB-468	PA-1	Ovarian 2393A	Colon 12
A1	A	A	A	A	A	A
A2	A	A	A	A	A	A
A3	A	A	A	A	B	B
A4	A	A	A	A	A	A
A5	A	A	A	A	A	A
A6	A	A	A	A	A	A

Example #	TTK IC ₅₀ Range	Cancer Cell Line GI ₅₀ Range			Tumor Initiating Cell GI ₅₀ Range	
		HCT116	MDA-MB-468	PA-1	Ovarain 2393A	Colon 12
A7	A	A	B	A	NA	NA
A8	A	NA	NA	NA	NA	NA
A9	A	A	A	A	NA	NA
A10	A	A	A	A	A	A
A11	A	A	A	A	B	A
A12	A	A	A	A	A	A
A13	A	A	A	A	A	A
A14	A	B	B	B	NA	NA
A15	A	A	A	A	A	A
A16	A	A	A	A	NA	NA
A17	A	A	A	A	A	A
A18	A	A	A	A	A	A
A19	A	A	A	A	NA	NA
A20	A	A	A	A	A	A
A21	A	A	NA	A	A	A
A22	A	A	A	A	A	A
A23	A	A	A	A	NA	A
A24	A	A	A	A	NA	NA
A25	A	A	A	A	NA	A
A26	A	A	A	A	NA	A
A27	A	A	B	A	B	A
A28	A	A	B	A	NA	NA
A29	A	A	B	A	NA	NA
A30	A	A	NA	B	NA	NA
A31	A	A	NA	A	NA	NA
A32	A	A	A	A	A	A
A33	A	A	NA	A	A	A
A34	A	A	A	A	A	A
A35	A	A	B	A	NA	NA
A36	A	A	B	A	NA	NA
A37	A	A	A	A	NA	A
A38	A	A	A	A	A	A
A39	A	A	A	A	A	A
A40	A	B	B	B	NA	NA
A41	A	A	A	A	A	A

Example #	TTK IC ₅₀ Range	Cancer Cell Line GI ₅₀ Range			Tumor Initiating Cell GI ₅₀ Range	
		HCT116	MDA-MB-468	PA-1	Ovarain 2393A	Colon 12
A42	A	A	A	A	A	A
A43	A	A	A	A	A	A
A44	A	A	A	A	A	A
A45	A	A	NA	A	B	A
A46	A	A	A	A	NA	NA
A47	A	A	A	A	NA	NA
A48	A	A	A	A	NA	NA
A49	A	NA	NA	NA	NA	NA
A50	A	A	B	A	NA	NA
A51	A	A	A	A	NA	NA
A52	A	A	A	A	NA	NA
A53	A	NA	NA	NA	NA	NA
A54	A	NA	NA	NA	NA	NA
A55	A	NA	NA	NA	NA	NA
A56	A	NA	NA	NA	NA	NA

NA: Not Available

Example E: Selectivity against a panel of 270 human kinases

The inhibitory activity of selected compounds of the invention (A32, A33, A1 and A11) was evaluated against a panel of 270 different human kinase enzymes by Millipore Corporation. The % Inhibition was determined by the formula; % Inhibition = 100 x (1 - (experimental value - background value)/(high activity control - background value)). Only seven kinases were > 80% inhibited at 1 uM, as shown in the table below.

Table 2: % Inhibition Values for Examples A32, A33, A1 and A11 at 1.0 µM

Kinase	% Inhibition @ 1.0 µM			
	A32	A33	A1	A11
Aurora-B	94	92	75	69
cKit (V560G)	65	86	48	76
JNK3	81	81	90	48
MAPK2	11	-8	90	5
MELK	92	95	80	51
Met(Y1248C)	44	88	23	40
MUSK	94	96	53	54

From the inhibition data in Table 2 it is apparent that certain kinases, e.g. Aurora-B, cKit(V560G), JNK3, MAPK2, MELK, Met(Y1248C) and MUSK are potently inhibited by compounds of the invention at 1 μ M concentration, which is > 2 orders of magnitude above their measured TTK IC₅₀s. Other kinases, including AKT (also known as PKB), PKA, PDK1, p70S6K, ROCK-I, ROCK-II and JNK2, were inhibited < or = 50% at this concentration.

Example F: PLK4 Inhibition Assay

Active PLK4 was purified from an *E. coli* expression system as an amino terminal GST fusion of residues 1-391 of human PLK4. The protein was purified from clarified cell extracts after induction at 15°C overnight using glutathione sepharose, gel permeation chromatography, and ion exchange (Resource Q). The resulting protein was dephosphorylated with lambda phosphatase (NEB cat# P0753), and resolved from the phosphatase using glutathione sepharose. The dephosphorylated GST-PLK4 was stored in aliquots at -80°C until use.

PLK4 activity was measured using an indirect ELISA detection system. Dephosphorylated GST-PLK4 (4 nM) was incubated in the presence of 15 μ M ATP (Sigma cat# A7699), 50 mM HEPES-Na²⁺ pH 7.4, 10 mM MgCl₂, 0.01% Brij 35 (Sigma cat# 03-3170), in a 96 well microtitre plate pre-coated with MBP (Millipore cat# 30-011). The reaction was allowed to proceed for 30 minutes, followed by 5 washes of the plate with Wash Buffer (50 mM TRIS-Cl pH 7.4 and 0.2% Tween 20), and incubation for 30 minutes with a 1:3000 dilution of primary antibody (Cell Signaling cat# 9381). The plate was washed 5 times with Wash Buffer, incubated for 30 minutes in the presence of secondary antibody coupled to horse radish peroxidase (BioRad cat# 1721019, 1:3000 concentration), washed an additional 5 times with Wash Buffer, and incubated in the presence of TMB substrate (Sigma cat# T0440). The colourimetric reaction was allowed to continue for 5 minutes, followed by addition of stop solution (0.5 N sulphuric acid), and quantified by detection at 450 nm with either a monochromatic or filter based plate reader (Molecular Devices M5 or Beckman DTX880, respectively).

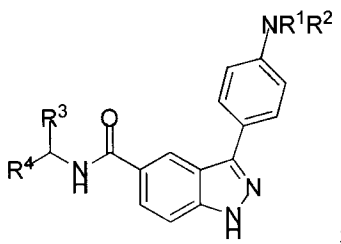
Compound inhibition was determined at either a fixed concentration (10 μ M) or at a variable inhibitor concentration (typically 50 μ M to 0.1 μ M in a 10 point dose response titration). Compounds were pre-incubated in the presence of enzyme for 15 minutes prior to addition of ATP and the activity remaining quantified using the above described activity assay. The % Inhibition of a compound was determined using the following formula; % Inhibition = 100 x (1 – (experimental value – background value)/(high activity control – background value)). The IC₅₀ value was determined using a non-linear 4 point logistic curve fit (XLfit4, IDBS) with the formula; (A+(B/(1+((x/C)^D)))), where A = background value, B = range, C = inflection point, D = curve fit parameter.

Certain compounds of the invention displayed PLK4 inhibition, with IC₅₀ values less 0.05 μ M, and are listed here: A9, A10, A11, A16, A19, A29, A46, A47, A48, A49 A55 and A56.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

-NR¹R² taken together forms a bridged bicyclic group optionally comprising one ring oxygen atom and optionally substituted with alkyl, haloalkyl, hydroxyl, alkoxy, halo, hydroxyalkyl or alkoxyalkyl; or -NR¹R² taken together forms a piperazinyl group *N*-substituted with oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, hydroxyethyl or alkoxyethyl and optionally *C*-substituted with alkyl; and

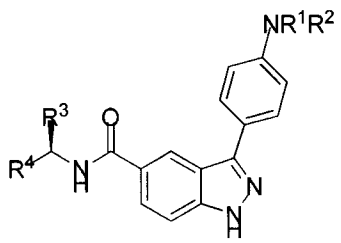
R³ is i) (C₂-C₆) alkyl optionally substituted with hydroxyl, alkoxy or halo; or ii) cycloalkyl optionally substituted with alkyl, haloalkyl, hydroxyl, alkoxy or halo; and

R⁴ is phenyl or monocyclic heteroaryl, each optionally substituted with one to three groups represented by R⁵;

each R⁵ is independently selected from halo, alkyl, haloalkyl, hydroxyl, alkoxy, -CN, -NO₂, -haloalkoxy and -NRᵃRᵃ; and

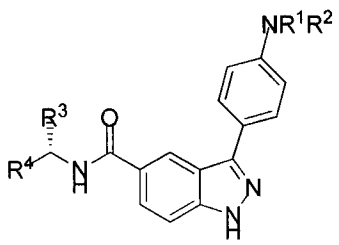
each Rᵃ is independently hydrogen or alkyl.

2. The compound of Claim 1, wherein the compound is represented by the following structural formula:



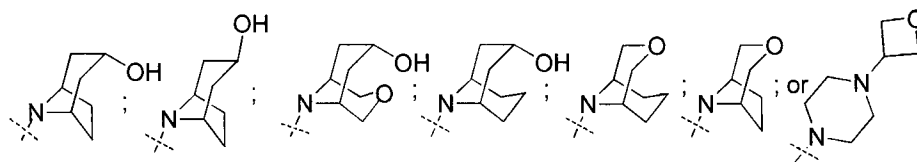
or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1, wherein the compound is represented by the following structural formula:

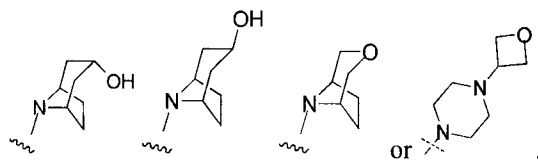


or a pharmaceutically acceptable salt thereof.

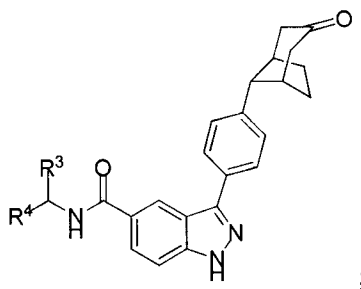
4. The compound of any one of Claims 1-3, wherein the bridged bicyclic group formed by -NR¹R² is a [3.3.1] or a [3.2.1] bridged bicyclic group.
5. The compound of any one of Claims 1-3, wherein -NR¹R² is piperazinyl -N-substituted with oxetanyl, tetrahydrofuryl, tetrahydropyryl, hydroxyethyl or alkoxyethyl and optionally C-substituted with alkyl.
6. The compound of any one of Claims 1-3, wherein R⁴ is phenyl, pyridyl, pyrimidyl or thienyl, each optionally substituted with one to three groups represented by R⁵.
7. The compound of any one of Claims 1-4 or 6, wherein -NR¹R² is:



8. The compound of any one of Claims 1-7, wherein R³ is cyclopropyl, isopropyl, cyclopentyl, isobutyl, cyclopropylmethyl or 2,2-dimethylpropan-1-yl.
9. The compound of Claim 8, wherein R³ is cyclopropyl, cyclopentyl or isobutyl.
10. The compound of any one of Claims 1-9, wherein R⁴ is pyrid-2-yl or 2-chlorophenyl.
11. The compound of any one of Claims 1-3 or 6-10, wherein -NR¹R² is



12. The compound of any one of Claims 1-10, wherein R^5 is chloro or fluoro.
13. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

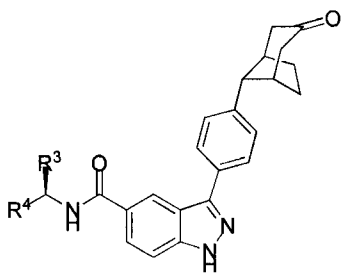
R^3 is i) (C_2-C_6) alkyl optionally substituted with hydroxyl, alkoxy or halo; or ii) cycloalkyl optionally substituted with alkyl, haloalkyl, hydroxyl, alkoxy or halo; and

R^4 is phenyl or monocyclic heteroaryl, each optionally substituted with one to three groups represented by R^5 ;

each R^5 is independently selected from halo, alkyl, haloalkyl, hydroxyl, alkoxy, -CN, -NO₂, -haloalkoxy and -NR^aR^a; and

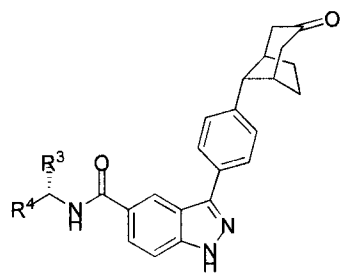
each R^a is independently hydrogen or alkyl.

14. The compound of Claim 13, wherein the compound is represented by the following structural formula:



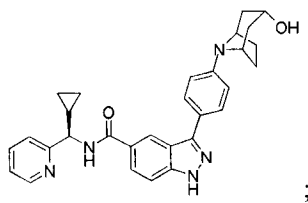
or a pharmaceutically acceptable salt thereof.

15. The compound of Claim 13, wherein the compound is represented by the following structural formula:



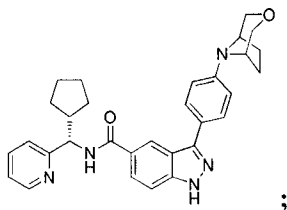
or a pharmaceutically acceptable salt thereof.

16. The compound of any one of Claims 13-15, wherein R⁴ is phenyl, pyridyl, pyrimidyl or thienyl, each optionally substituted with one to three groups represented by R⁵.
17. The compound of any one of Claims 13-16, wherein R³ is cyclopropyl, isopropyl, cyclopentyl, isobutyl, cyclopropylmethyl or 2,2-dimethylpropan-1-yl.
18. The compound of Claim 17, wherein R³ is cyclopropyl, cyclopentyl or isobutyl.
19. The compound of any one of Claims 13-18, wherein R⁴ is pyrid-2-yl or 2-chlorophenyl.
20. A compound represented by the following structural formula:



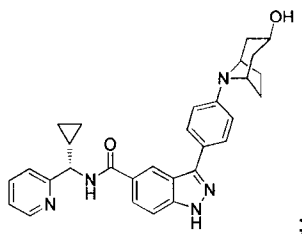
or a pharmaceutically acceptable salt thereof.

21. A compound represented by the following structural formula:



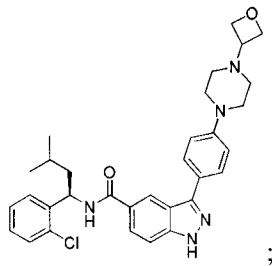
or a pharmaceutically acceptable salt thereof.

22. A compound represented by the following structural formula:



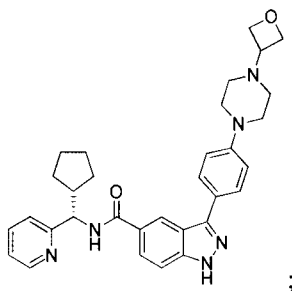
or a pharmaceutically acceptable salt thereof.

23. A compound represented by the following structural formula:



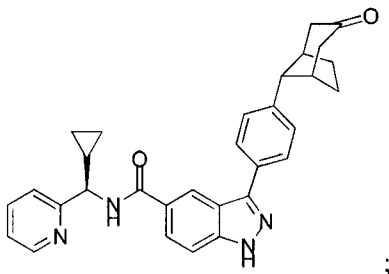
or a pharmaceutically acceptable salt thereof.

24. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

25. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

26. The compound of any one of Claims 1-3, wherein $-NR^1R^2$ taken together forms a bridged bicyclic group optionally comprising one ring oxygen atom and optionally substituted with alkyl, haloalkyl, hydroxyl, alkoxy, halo, hydroxyalkyl or alkoxyalkyl.
27. A pharmaceutical composition comprising a compound of any one of Claims 1-26 and a pharmaceutically acceptable carrier or diluent.
28. A method for treating a subject with cancer, comprising: administering to the subject an effective amount of a compound of any one of Claims 1-26.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2013/000859

A. CLASSIFICATION OF SUBJECT MATTER IPC: <i>C07D 451/06</i> (2006.01) , <i>A61K 31/416</i> (2006.01) , <i>A61K 31/4439</i> (2006.01) , <i>A61P 35/00</i> (2006.01) , <i>C07D 401/12</i> (2006.01) , <i>C07D 405/12</i> (2006.01) (more IPCs on the last page) 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) IPC: <i>C07D 451/06</i> (2006.01) , <i>A61K 31/416</i> (2006.01) , <i>A61K 31/4439</i> (2006.01) , <i>A61P 35/00</i> (2006.01) , <i>C07D 401/12</i> (2006.01) , <i>C07D 405/12</i> (2006.01) , <i>C07D 405/14</i> (2006.01) , <i>C07D 498/08</i> (2006.01) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) STN, Canadian Patent Database														
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>CA 2 440 842 A1 (OINUMA et al.) 24 October 2002 (24-10-2002) claims</td> <td>1-3, 5-12 and 27</td> </tr> <tr> <td>A</td> <td>CA 2 473 986 A1 (BINCH et al.) 07 August 2003 (07-08-2003) pages 7 and 8, examples and claims</td> <td>1 to 27</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	CA 2 440 842 A1 (OINUMA et al.) 24 October 2002 (24-10-2002) claims	1-3, 5-12 and 27	A	CA 2 473 986 A1 (BINCH et al.) 07 August 2003 (07-08-2003) pages 7 and 8, examples and claims	1 to 27			
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
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A	CA 2 473 986 A1 (BINCH et al.) 07 August 2003 (07-08-2003) pages 7 and 8, examples and claims	1 to 27												
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex. <table border="1"> <tbody> <tr> <td>* Special categories of cited documents :</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </tbody> </table>			* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family	"O" document referring to an oral disclosure, use, exhibition or other means		"P" document published prior to the international filing date but later than the priority date claimed	
* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention													
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone													
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art													
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family													
"O" document referring to an oral disclosure, use, exhibition or other means														
"P" document published prior to the international filing date but later than the priority date claimed														
Date of the actual completion of the international search 11 December 2013 (11-12-2013)		Date of mailing of the international search report 27 December 2013 (27-12-2013)												
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476		Authorized officer Edith Éthier (819) 934-2325												

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim Nos. : 28

because they relate to subject matter not required to be searched by this Authority, namely :

The subject matter of claim 28 relates to a method of medical treatment which the International Search Authority is not required to search. Nevertheless, the Authority has carried out a search based on the alleged therapeutic effects of the product defined in claim 28.

2. ☐ Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. ☐ Claim Nos. :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

The claims are directed to a plurality of inventive concepts as follows:

Group A - Claims 1 to 12, 20 to 24, 26 and 27 to 28 (in part) are directed to Compounds of formula (I) wherein the phenyl ring is substituted by NR^1R^2 and their use.

Group B - Claims 13 to 19, 25 and 27 to 28 (in part) are directed to Compounds of formula (I) wherein the phenyl ring is substituted by a bridged bicyclic group not comprising a N atom.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2013/000859

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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		EP1380576A1	14 January 2004 (14-01-2004)
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		AU2003202011A1	24 July 2003 (24-07-2003)
		AU2003202011B2	29 November 2007 (29-11-2007)
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		EP1467697B1	03 December 2008 (03-12-2008)
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		GB2383950A	16 July 2003 (16-07-2003)
		GB2383950B	18 January 2006 (18-01-2006)
		JP2005516026A	02 June 2005 (02-06-2005)
		JP4166699B2	15 October 2008 (15-10-2008)
		US2006188460A1	24 August 2006 (24-08-2006)
		US7670998B2	02 March 2010 (02-03-2010)
		WO03057182A1	17 July 2003 (17-07-2003)

C07D 405/14 (2006.01) , *C07D 498/08* (2006.01)