KINASE INHIBITORS AND METHOD OF TREATING CANCER WITH SAME

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Application Nos. 61/321,332, filed April 6, 2010 and 61/321,329, field April 6, 2010. This application also claims the benefit of International Application No. PCT/CA2010/000518, filed April 6, 2010. The entire teachings of these three applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[002] 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.

[003] The polo-like kinase (PLK) family of serine/threonine kinases comprises at least four known members: PLK1, PLK2 (also known as Snk), PLK3 (also known as Fnk or Prk) and PLK4 (also known as Sak). PLK4 is the least understood and most divergent member of the PLK family. The N-terminal catalytic domain of PLK4 has a different substrate specificity from that of PLK1-3. PLK4 also has a divergent C-terminus comprising only a single polo-box sequence, not the tandem PB sequences in PLK1-3, that appears to act as a homodimerization domain rather than a localization domain (Lowery *et al.*, (2005) Oncogene 24: 248-259).

[004] PLK4 is known to be involved in the control of mitotic entry and exit, and a regulator of centrosome duplication (Habedanck *et al.* Nature Cell Biology 7: 1140-1146, 2005). PLK4 transcripts increase from S through M phase, and the protein is ubiquitylated and destroyed by the anaphase promoting complex (APC) (Hudson *et al.* Curr. Biol. 11: 441– 446, 2001; Fode *et al.* Mol. Cell. Biol. 16: 4665–4672, 1996). PLK4 is required for late mitotic progression (Fode *et al.* PNAS. 91: 6388-6392, 1994; Hudson *et al.* Curr. Biol. 11: 441–446, 2001), cell survival and postgastrulation embryonic development (Hudson *et al* . Curr. Biol. 11: 441-446, 2001). PLK4 knockout mice are embryonic lethal (E7.5), with a marked increase in mitotic and apoptotic cells (Hudson *et al.* Curr. Biol. 11: 441–446, 2001). PLK4 is transcriptionally repressed by p53 (Li *et al.* Neoplasia 7: 312-323, 2005). This repression is likely mediated through the recruitment of histone deacetylase (HDAC)

repressors and repression appears to contribute to p53-induced apoptosis (Li *et al.* Neoplasia 7: 312-323, 2005).

[005] PLK4 has been reported to be overexpressed in colorectal tumors with expression reported as low in adjacent normal intestinal mucosa (Macmillian *et al.* Ann. Surg. Oncol. 8: 729-740, 2001). In addition, PLK4 mRNA has been reported to be overexpressed in some tumor cell lines (Hitoshi, *et al.*, U.S. Patent Application No. US 2003/0027756). In addition, Applicants described overexpression of PLK4 in basal-like tumors in a co-pending U.S. Provisional Application No. 61,003,825, filed on November 20, 2007 (the entire teachings of which are incorporated herein by reference).

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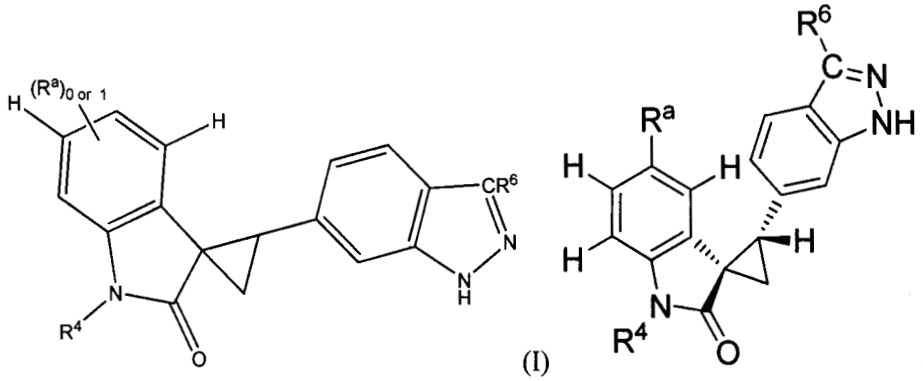
[007] The human papillomavirus (HPV-16) E7 oncoproteins are overexpressed in HPV-associated anogenital and oropharyngeal cancers. The E7 oncoprotein triggers centrosome overduplication through a pathway that involves the concurrent formation of multiple daughters at single maternal centrioles. The HPV-16 E7 oncoprotein has been used as a tool to dissect abnormal centriole biogenesis and several lines of evidence identify PLK4 as a crucial player in this process (Duensing et al Environ. Mol. Mutagen. 50: 741-747, 2009). In addition, an increased level of PLK4 transcription is found in keratinocytes stably expressing HPV-16 E7. The ability of HPV-16 E7 to upregulate PLK4 mRNA was found to depend on its ability to degrade the retinoblastoma (pRb) protein, suggesting a role of E2F-mediated gene transcription in deregulation of PLK4 (Korzeniewski et al, AACR Meeting, Washington, 2010, Abstr. 5354). These results identify PLK4 as a target for small molecule inhibition to prevent centriole abnormalities, mitotic infidelity and malignant progression in HPV-associated cancers.

[008] Therefore, agents which inhibit a protein kinase, in particular PLK4, have the potential to treat cancer. There is a need for additional agents which can act as protein kinase inhibitors, in particular PLK4 inhibitors.

SUMMARY OF THE INVENTION

[009] Applicants have now discovered that certain spiro cyclopropyl indolinone compounds are potent kinase inhibitors, such as polo-like kinases 4 (PLK4) and Aurora Kinases (*see* Example B and F). Applicants have also now discovered that these spiro cyclopropyl indolinone compounds have potent anticancer activity (*see* Example J) and exhibit anti-angiogenic activity (example K). Based on these discoveries, spiro cyclopropyl indolinone compounds, pharmaceutical compositions thereof, and methods of treating cancer with the spiro cyclopropyl indolinone compounds are disclosed herein.

[0010] One embodiment of the invention is a compound represented by Structural Formula (I) or (II):



(I) (II).

Pharmaceutically acceptable salts of the compound of Structural Formula (I) and (II) are also included in the invention. The variables in these structural formulas are defined below:

R^a is -F, methoxy, methyl or ethyl;

R_4 is –H, methyl, ethyl, 2-methoxyethyl or $-CH_2CONH_2$; and

R^6 is -C=C-(optionally substituted phenyl).

Alternative values for the variables in Structural Formulas (I) and (II) are provided below:

R^a is -F, methoxy, methyl or ethyl;

R_4 is –H or methyl; and

R^6 is –C=C-(phenyl), wherein the phenyl in –CH=CH-(phenyl) is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} aminoalkyl), (C_{1-6} alkylamino)C_{1-6} alkyl, (C_{1-6} dialkylamino)C_{1-6} alkyl, (phenyl)C_{1-6} alkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, $-(CH_2)_{0-3}$-*N*-piperidinyl, $-(CH_2)_{0-}$

$_3$-*N*-morpholinyl, -$(CH_2)_{0-3}$-*N*-pyrrolidinyl, -$(CH_2)_{0-3}$-*N*-piperazinyl and –$(CH_2)_{0-3}$-N-oxazepanyl, wherein the *N*-piperazinyl is optionally N'-substituted with C_{1-6} alkyl or C_{1-6} acyl.

[0011] In another embodiment, the invention is any one the compounds disclosed in the Exemplification section as a neutral compound or a pharmaceutically acceptable salt thereof.

[0012] In another embodiment, the present invention is a pharmaceutical composition comprising: i) a compound represented by Structural Formula (I), a compound represented by Structural Formula (II), a compound depicted in the Exemplification or a pharmaceutically acceptable salt of any of the foregoing; and ii) a pharmaceutically acceptable carrier or diluent.

[0013] Another embodiment of the invention is a method of treating a subject having cancer comprising administering to the subject a therapeutically effective amount of a compound represented by Structural Formula (I), a compound represented by Structural Formula (II), a compound depicted in the Exemplification or a pharmaceutically acceptable salt of any of the foregoing.

[0014] Another embodiment of the invention is a method of inhibiting Aurora B and/or PLK-4 in a subject in need of inhibition of Aurora B and/or PLK-4, comprising administering to the subject a therapeutically effective amount of a compound represented by Structural Formula (I), a compound represented by Structural Formula (II), a compound depicted in the Exemplification or a pharmaceutically acceptable salt of any of the foregoing.

[0015] Another embodiment of the invention is the use of a compound represented by Structural Formula (I), a compound represented by Structural Formula (II), a compound depicted in the Exemplification or a pharmaceutically acceptable salt of any of the foregoing. Alternatively, the therapy is for inhibiting Aurora B and/or PLK-4 in a subject in need of inhibition of Aurora B and/or PLK-4.

[0016] Another embodiment of the invention is the use of a compound represented by Structural Formula (I), a compound represented by Structural Formula (II), a compound depicted in the Exemplification or a pharmaceutically acceptable salt of any of the foregoing.

[0017] Another embodiment of the invention is the use of a compound represented by Structural Formula (I), a compound represented by Structural Formula (II), a compound depicted in the Exemplification or a pharmaceutically acceptable salt of any of the

foregoing for the manufacture of a medicament for inhibiting Aurora B and/or PLK-4 in a subject in need of inhibition of Aurora B and/or PLK-4.

BRIEF DESCRIPTION OF THE DRAWINGS

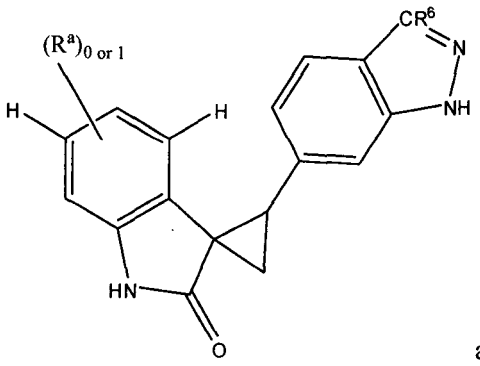
[0018] The Figure shows the anti-angiogenesis effect of compounds A23.

DETAILED DESCRIPTION OF THE INVENTION

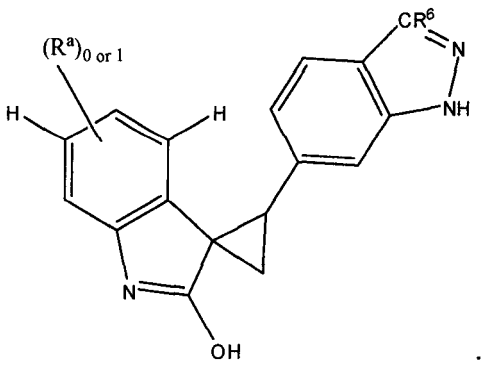
[0019] Specific examples of compounds of the invention include those exemplified in the examples below, stereoisomers thereof, and pharmaceutically acceptable salts thereof.

[0020] In Structural Formulas described herein, when a hydrogen atom(s) is depicted at a particular position(s) of the aromatic ring(s) of the structural formula(s), no substitution is permitted at that (those) particular position(s).

[0021] Tautomeric forms exist when a compound is a mixture of two or more structurally distinct compounds that are in rapid equilibrium. Certain compounds of the invention exist as tautomeric forms. For example, the following compound encompassed within Structural Formula (I) include at least the following tautomeric forms:



and

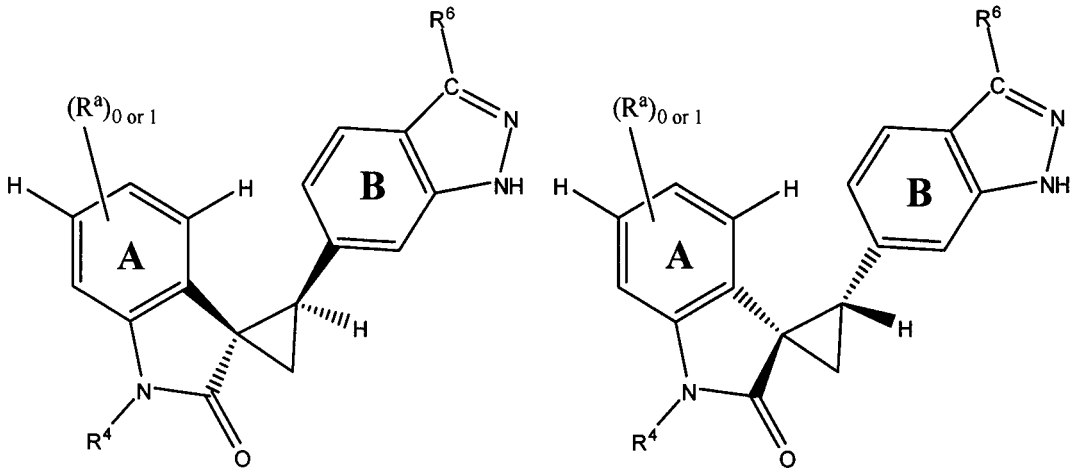


(indolinone form) (indolol form)

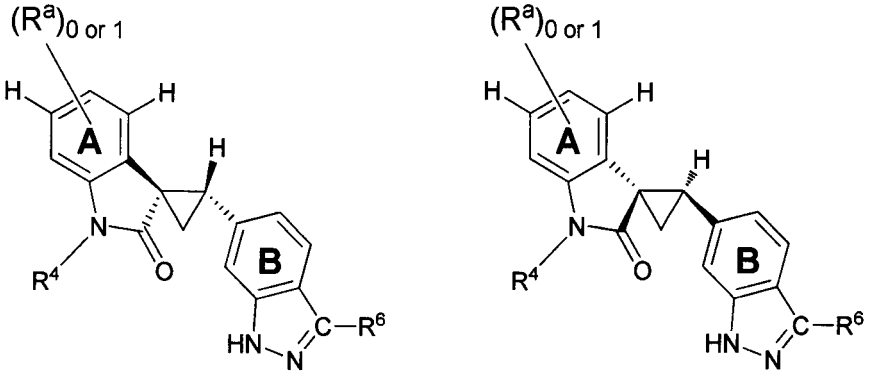
It is to be understoond that when one tautormeric form of a compound is depicted by name or structure, all tautomeric forms of the compound are included.

[0022] The compounds of the invention contain at least two chiral centers and a cyclopropane and, therefore, exist as stereoisomers, such as isomers about the cyclopropane (*i.e.*, cis/trans isomers), enantiomers, and/or diastereomers. When compounds of the

invention are depicted or named without indicating the stereochemistry, it is to be understood that both stereomerically pure forms (*e.g.*, pure cis or pure trans, enantiomerically pure, or diastereomerically pure) and stereoisomeric mixtures are encompassed. For example, compounds represented by Structural Formula (I) have "*cis*" and "*trans*" isomers shown below:



Ring **A** and Ring **B** are cis; and



Ring **A** and Ring **B** are trans.

[0023] The language "Ring **A** and Ring **B** are *cis*" means Ring **A** and Ring **B** are both on the same side of the cyclopropane whereas the language "Ring **A** and Ring **B** are *trans*" means Ring **A** and Ring **B** are on different sides of the cyclopropane. Stereoisomers of the cis/trans variety are also referred to as geometric isomers. Accordingly, the compounds of the invention depicted by Structural Formula (I) include the pure *cis* isomer, the pure *trans* isomer, and mixtures thereof, including *cis/trans* mixtures enriched in the cis geometric isomer and cis/trans mixtures enriched in the *trans* geometric

isomer. For example, Structural Formula (II) depicts a cis relationship between Ring **A** and **B**. It is to be understood that both *cis* and *trans* forms of Structural Formulas (I) with respect to Rings **A** and **B** are encompassed within the invention.

[0024] 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 both geomeric isomers in the mixture.

[0025] Racemic mixture means 50% of one enantiomer and 50% of is corresponding enantiomer. The invention encompasses all enantiomerically-pure, enantiomerically-enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures, and diastereomeric mixtures of the compounds of the invention.

[0026] 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.

[0027] 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.

[0028] 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.

[0029] Included in the invention 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 of the invention 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 invention 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.

[0030] The term "halo" as used herein means halogen and includes chloro, fluoro, bromo and iodo.

[0031] An "aliphatic group" is acyclic, non-aromatic, consists solely of carbon and hydrogen and may optionally contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight chained or branched. An aliphatic group typically contains between about one and about twenty carbon atoms, typically between about one and about ten carbon atoms, more typically between about one and about six carbon atoms. A "substituted aliphatic group" is substituted at any one or more "substitutable carbon atoms". A "substitutable carbon atom" in an aliphatic group is a carbon in the aliphatic group that is bonded to one or more hydrogen atoms. One or more hydrogen atoms can be optionally replaced with a suitable substituent group. A "haloaliphatic group" is an aliphatic group, as defined above, substituted with one or more halogen atoms.

[0032] The term "alkyl" used alone or as part of a larger moiety, such as "alkoxy", "haloalkyl", "arylalkyl", "alkylamine", "dialkyamine", "alkylamino", "dialkyamino" "alkylcarbonyl", "alkoxycarbonyl" and the like, means saturated straight-chain or branched

aliphatic group. As used herein, a C1-C6 alkyl group is referred to "lower alkyl." Similarly, the terms "lower alkoxy", "lower haloalkyl", "lower arylalkyl", "lower alkylamine", lower dialkyamine", "lower alkylamino", "lower dialkyamino" "lower alkylcarbonyl", "lower alkoxycarbonyl" include straight and branched, saturated chains containing one to six carbon atoms.

[0033] The term "alkenyl" means straight-chain or branched aliphatic group having at least one double bond.

[0034] The term "alkynyl" menas straight-chain or branched aliphatic group having at least one triple bond.

[0035] The term "alkoxy" means –O-alkyl; "hydroxyalkyl" means alkyl substituted with hydroxy; "aralkyl" means alkyl substituted with an aryl group; "alkoxyalkyl" mean alkyl substituted with an alkoxy group; "alkylamine" means amine substituted with an alkyl group; "cycloalkylalkyl" means alkyl substituted with cycloalkyl; "dialkylamine" means amine substituted with two alkyl groups; "alkylcarbonyl" means –C(O)-R, wherein R is alkyl; "alkoxycarbonyl" means -C(O)-OR, wherein R is alkyl; and where alkyl is as defined above.

[0036] 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.

[0037] The term "acyl group" means –C(O)R, wherein R is an optionally substituted alkyl group or aryl group (e.g., optionally substituted phenyl). R is preferably an unsubstituted alkyl group or phenyl.

[0038] An "alkylene group" is represented by $-[CH_2]_z-$, wherein z is a positive integer, preferably from one to eight, more preferably from one to four.

[0039] An "alkenylene" is an alkylene group in which one methylene has been replaced with a double bond.

[0040] The term "aryl group" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", means a carbocyclic aromatic ring. The term "aryl" may be used interchangeably with the terms "aryl ring" "carbocyclic aromatic ring", "aryl group" and "carbocyclic aromatic group". An aryl group typically has six to fourteen ring atoms. Examples includes phenyl, naphthyl, anthracenyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl, indenyl and the like. A "substituted aryl group" is

substituted at any one or more substitutable ring atom, which is a ring carbon atom bonded to a hydrogen.

[0041] The term "cycloalkyl" refers to a monocyclic or polycyclic saturated hydrocarbon ring system. For example, a C_{5-7} cycloalkyl includes, but is not limited to cyclopentyl, cyclohexyl or cyclopentyl, each of which is optionally substituted.

[0042] The term "heteroaryl", "heteroaromatic", "heteroaryl ring", "heteroaryl group", "heteroaromatic ring", and "heteroaromatic group", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to aromatic ring groups having five to fourteen 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). "Heteroaryl" includes monocyclic rings and polycyclic rings in which a monocyclic heteroaromatic ring is fused to one or more other carbocyclic aromatic or heteroaromatic rings. As such, "5-14 membered heteroaryl" includes monocyclic, bicyclic or tricyclic ring systems.

[0043] 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), triazolyl (e.g., 2-triazolyl, 5-triazolyl), tetrazolyl (e.g., tetrazolyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyrimidinyl, pyridinyl and pyridazinyl. Examples of polycyclic aromatic heteroaryl groups include carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, or benzisoxazolyl. A "substituted heteroaryl group" is substituted at any one or more substitutable ring atom, which is a ring carbon or ring nitrogen atom bonded to a hydrogen.

[0044] The term "heterocyclyl group" or "heterocyclic group" means a monocyclic, non-aromatic ring with 3 to 10-members containing from 1-3 ring heteroatoms or a polycyclic ring with ring with 7 to 20-members and from 1 to 4 ring heteroatoms, wherein the polycyclic ring having one or more monocyclic non-aromatic heterocyclic ring fused with one or more aromatic or heteroaromatic ring. In one embodiment, the heterocyclyl group is a bicyclic ring having a monocyclic non-aromatic heterocyclic ring fused with a phenyl group. Exmplary polycyclic heterocyclic group includes

tetrahydroisoquinolinyl (such as 1,2,3,4-tetrahydroisoquinolin-7-yl, 2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl, 1,2,3,4-tetrahydroisoquinolin-6-yl and 2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl), isoindolinyl (such as 2-ethylisoindolin-5-yl, 2-methylisoindolin-5-yl), indolinyl, tetrahydrobenzo[f]oxazepinyl (such as 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl).

[0045] The term "non-aromatic heterocyclic group" means a monocyclic, non-aromatic ring with 3 to 10-members containing from 1-3 ring heteroatoms or a polycyclic non-aromatic ring with 7 to 20-members and from 1 to 4 ring heteroatoms. Each heteroatom is independently selected from nitrogen, quaternary nitrogen, oxidized nitrogen (e.g., NO); oxygen; and sulfur, including sulfoxide and sulfone. The substituted non-aromatic heterocylic group may be attached via a suitable heteroatom or carbon atom. Representative non-aromatic heterocyclic groups include morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. A "substituted non-aromatic heterocylic group" is substituted at any one or more substitutable ring atom, which is a ring carbon or ring nitrogen atom bonded to a hydrogen.

[0046] Unless otherwise indicated, suitable substituents for a substituted aliphatic group, aryl group, heteroaryl group and non-aromatic heteroaryl groups include:

i) halogen, $-C(O)OR^1$, $-C(O)R^1$, $-C(S)R^1$, $-OC(O)R^1$-, $-C(O)NR^1R^2$, $-C(S)NR^1R^2$, $-OC(O)NR^1R^2$, $-S(O)R^1$, $-S(O)_2R^1$, $-SO_3R^1$, $-SO_2NR^1R^2$, $-OR^1$, $-SR^1$, $-NR^1R^2$, $-NR^2C(O)R^1$, $-NR^2S(O)R^1$, $-NR^2C(O)OR^1$, $-NR^2C(O)ONR^1R^2$, $-N(R^2)C(O)NR^1R^2$, $-NR^2SO_2NR^1R^2$, $-NR^2SO_2R^1$; $-NO_2$, -CN, -NCS; or two *ortho* substituents taken together form $-O-[CH_2]_p-O-$, $-S-[CH_2]_p-S-$ or $-[CH_2]_q-$; or

ii) C_{1-10} aliphatic group optionally substituted with one or more substituents selected from the group consisting halogen, nitro, cyano, $-N(R^{21})_2$, $-C(O)N(R^{21})_2$, $-C(O)N(R^{21})_2$, $-NR^{21}C(O)R^{21}$, $-SO_2R^{22}$, $-SO_2N(R^{21})_2$, $-NR^{21}SO_2R^{22}$, $-NR^{21}C(O)OR^{21}$, $-OC(O)N(R^{21})_2$, $-NR^{21}C(O)N(R^{21})_2$, $-NRC(O)ON(R)_2$, $-NR^{21}SO_2N(R^{21})_2$, $-OR^{21}$, $-SR^{21}$, C_{1-10} haloalkoxy, $-C(O)R^{21}$, $-C(O)OR^{21}$ and $-OC(O)R^{21}$; or

iii) (C_{0-10} alkylene)-Ar^1, (C_{2-10} alkenylene)-Ar^1, wherein Ar^1 is a C_{6-14} aryl group or a 5-14 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, C_{1-10} alkyl, C_{1-10} haloalkyl, (C_{1-10} haloalkoxy)C_{1-10} alkyl, (C_{1-10} alkoxy)C_{1-10}

alkyl, C_{1-10} hydroxyalkyl, C_{1-10} aminoalkyl, (C_{1-10} alkylamino)C_{1-10} alkyl, (C_{1-10} dialkylamino)C_{1-10} alkyl, -$N(R^{21})_2$, -$C(O)N(R^{21})_2$, -$C(O)N(R^{21})_2$, -$NR^{21}C(O)R^{21}$, -SO_2R^{22}, -$SO_2N(R^{21})_2$, -$NR^{21}SO_2R^{22}$, -$NR^{21}C(O)N(R^{21})_2$, -$NRC(O)ON(R)_2$, -$NR^{21}SO_2N(R^{21})_2$, -OR^{21}, -SR^{21}, C_{1-10} haloalkoxy, -$C(O)R^{21}$, -$C(O)OR^{21}$, -$OC(O)R^{21}$, phenyl and 5-6 membered heteroaryl, wherein said phenyl and said 5-6 membered heteroaryl are each independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy;

[0047] each R^1 independently is:

i) hydrogen;

ii) a C_{6-14} aryl group or a 5-14 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, -NO_2, -CN, -NCS, C_1-C_{10} aliphatic, (C_{1-10} alkylene)-Ar^{10}, (C_{2-10} alkenylene)-Ar^{10}, -$C(O)OR^{10}$, -$C(O)R^{10}$, -$C(S)R^{10}$, -$OC(O)R^{10}$, -$C(O)N(R^{11})_2$, -$C(S)N(R^{11})_2$, -$OC(O)N(R^{11})_2$, -$S(O)R^{12}$, -$S(O)_2R^{12}$, -SO_3R^{12}, -$SO_2N(R^{11})_2$, -OR^{10}, -SR^{10}, -$N(R^{11})_2$, -$NR^{11}C(O)R^{10}$, -$NR^{11}S(O)R^{12}$, -$NR^{11}C(O)OR^{12}$, -$N(R^{11})C(O)N(R^{11})_2$, -$NR^{11}SO_2N(R^{11})_2$ and -$NR^{11}SO_2R^{12}$; or

iii) a C_{1-10} aliphatic group optionally substituted with one or more substituents selected from the group consisting of halogen, -NO_2, -CN, -NCS, Ar^{10}, -$C(O)OR^{10}$, -$C(O)R^{10}$, -$C(S)R^{10}$, -$OC(O)R^{10}$, -$C(O)N(R^{11})_2$, -$C(S)N(R^{11})_2$, -$OC(O)N(R^{11})_2$, -$S(O)R^{12}$, -$S(O)_2R^{12}$, -SO_3R^{12}, -$SO_2N(R^{11})_2$, -OR^{10}, -SR^{10}, -$N(R^{11})_2$, -$NR^{11}C(O)R^{10}$, -$NR^{11}S(O)R^{12}$, -$NR^{11}C(O)OR^{12}$, -$N(R^{11})C(O)N(R^{11})_2$, -$NR^{11}SO_2N(R^{11})_2$ and

-$NR^{11}SO_2R^{12}$,

provided that R^1 is other than hydrogen when the substituent is -$S(O)R^1$, -$S(O)_2R^1$, -SO_3R^1, -$NR^2S(O)R^1$ or -$NR^2SO_2R^1$; and

[0048] each R^2 independently is –H or C_1-C_6 alkyl, or, taken together with NR^1, forms a non-aromatic heterocyclic group optionally substituted with one or more substituents selected from the group consisting of =O, =S, halogen, nitro, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} aminoalkyl, (C_{1-6} alkylamino)C_{1-6} alkyl, (C_{1-6} dialkylamino)C_{1-6} alkyl, (phenyl)C_{1-6} alkyl, (5-6 membered heteroaryl)C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyl, phenyl and 5-6 membered heteroaryl;

i) hydrogen;

ii) a C_{6-14} aryl group or a 5-14 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C_{1-10} alkyl, C_{1-10} haloalkyl, (C_{1-10} haloalkoxy)C_{1-10} alkyl, (C_{1-10} alkoxy)C_{1-10} alkyl, C_{1-10} hydroxyalkyl, C_{1-10} aminoalkyl, (C_{1-10} alkylamino)C_{1-10} alkyl, (C_{1-10} dialkylamino)C_{1-10} alkyl, (phenyl)C_{1-10} alkyl, (5-6 membered heteroaryl)C_{1-10} alkyl, amino, C_{1-10} alkylamino, C_{1-10} dialkylamino, C_{1-10} alkoxy, C_{1-10} haloalkoxy, C_{1-10} alkylcarbonyloxy, C_{1-10} alkoxycarbonyl and C_{1-10} alkylcarbonyl; or

iii) a C_{1-10} alkyl group optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, hydroxy, C_{1-10} haloalkyl, C_{1-10} alkoxy, C_{1-10} haloalkoxy, amino, C_{1-10} alkylamino, C_{1-10} dialkylamino, C_{1-10} alkylcarbonyloxy, C_{1-10} alkoxycarbonyl, C_{1-10} alkylcarbonyl and phenyl, said phenyl being optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy;

[0049] each R^{11} independently is R^{10}, $-CO_2R^{10}$, $-SO_2R^{10}$ or $-C(O)R^{10}$, or

[0050] $-N(R^{11})_2$ taken together is a non-aromatic heterocyclic group optionally substituted with one or more substituents selected from the group consisting of =O, =S, halogen, nitro, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} aminoalkyl, (C_{1-6} alkylamino)C_{1-6} alkyl, (C_{1-6} dialkylamino)C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyl and C_{1-6} alkylcarbonyl; and

[0051] each R^{12} is independently is R^{10} provided that R^{12} is not hydrogen;

[0052] each R^{21} independently is hydrogen, C_{1-6} alkyl, phenyl or 5-6 membered heteroaryl, wherein each of the phenyl and heteroaryl groups represented by R^{21} is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy, and wherein the alkyl group represented by R^{21} is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy; or

[0053] $N(R^{21})_2$ forms a non-aromatic heterocyclic group optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, =O, C_{1-3} alky, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy and amino; and

[0054] each R^{22} independently C_{1-6} alkyl, phenyl or 5-6 membered heteroaryl, wherein each of the phenyl and heteroaryl groups represented by R^{22} is independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy, and wherein the alkyl group represented by R^{22} is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy;

[0055] each R independently is hydrogen, C_{1-10} aliphatic, phenyl or 5-6 membered heteroaryl, wherein the aliphatic group represented by R is optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, phenyl, 5-6 membered heteroaryl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and wherein each of the phenyl and heteroaryl groups represented by R, and the phenyl and heteroaryl substituents for the aliphatic group represented by R independently are optionally and independently substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or

[0056] $N(R)_2$ forms a non-aromatic heterocyclic group optionally substituted with one or more substituents selected from the group consisting of =O, =S, halogen, nitro, cyano, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} aminoalkyl, (C_{1-6} alkylamino)C_{1-6} alkyl, (C_{1-6} dialkylamino)C_{1-6} alkyl, (phenyl)C_{1-6} alkyl, (5-6 membered heteroaryl)C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyl, phenyl and 5-6 membered heteroaryl;

[0057] Ar^1 is a C_{6-14} aryl group or a 5-14 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, C_{1-10} alkyl, C_{1-10} haloalkyl, (C_{1-10} haloalkoxy)C_{1-10} alkyl, (C_{1-10} alkoxy)C_{1-10} alkyl, C_{1-10} hydroxyalkyl, C_{1-10} aminoalkyl, (C_{1-10} alkylamino)C_{1-10} alkyl, (C_{1-10} dialkylamino)C_{1-10} alkyl, $-N(R^{21})_2$, $-C(O)N(R^{21})_2$, $-C(O)N(R^{21})_2$, $-NR^{21}C(O)R^{21}$, $-SO_2R^{22}$, $-SO_2N(R^{21})_2$, $-NR^{21}SO_2R^{22}$, $-NR^{21}C(O)N(R^{21})_2$, $-NRC(O)ON(R)_2$, $-NR^{21}SO_2N(R^{21})_2$, $-OR^{21}$, $-SR^{21}$, C_{1-10} haloalkoxy, $-C(O)R^{21}$, $-C(O)OR^{21}$, $-OC(O)R^{21}$, phenyl and 5-6 membered heteroaryl, wherein said phenyl and said 5-6 membered heteroaryl are

each independently and optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, amino, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy and C_{1-3} haloalkoxy;

[0058] each Ar^{10} independently is a C_{6-14} aryl group or a 5-14 membered heteroaryl group, each optionally and independently substituted with one or more substituents selected from the group consisting of halogen, nitro, cyano, -OH, -SH, -O(C_{1-10} alkyl), -S(C_{1-10} alkyl), C_{1-10} alkyl, C_{1-10} haloalkyl, (C_{1-10} haloalkoxy)C_{1-10} alkyl, (C_{1-10} alkoxy)C_{1-10} alkyl, C_{1-10} hydroxyalkyl, (C_{1-10} aminoalkyl, (C_{1-10} alkylamino)C_{1-10} alkyl, (C_{1-10} dialkylamino)C_{1-10} alkyl, (phenyl)C_{1-10} alkyl, (5-6 membered heteroaryl)C_{1-10} alkyl, amino, C_{1-10} alkylamino, C_{1-10} dialkylamino, C_{1-10} haloalkoxy, C_{1-10} alkylcarbonyloxy, C_{1-10} alkoxycarbonyl and C_{1-10} alkylcarbonyl;

[0059] each p is 1, 2 or 3; and

[0060] each q is 2, 3, 4 or 5.

[0061] Other examples of suitable substituents for an aliphatic group, aryl group, heteroaryl group and non-aromatic heteroaryl groups include halogen, nitro, cyano, hydroxy, C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, amino, C_{1-20} alkylamino, C_{1-20} dialkylamino, C_{1-20} alkoxy, (C_{1-10} alkoxy)C_{1-20} alkyl, C_{1-20} haloalkoxy, (C_{1-10} haloalkoxy)C_{1-20} alkyl and C_{1-20} haloalkyl.

[0062] Spiro cyclopropyl indolinone compounds of the invention can inhibit various kinases, including the PLK4, PLK1, PLK2, Aurora A, Aurora B and FLT-3 (*see* Examples B-G). Thus, generally, the spiro cyclopropyl indolinone compounds of the invention are useful in the treatment of diseases or conditions associated with such kinases. For example, PLK4, PLK1, Aurora A and Aurora B are believed to be involved in cellular miotic progression. Thus, small molecule inhibitors of these enzymes can be potential anti-tumor agents.

[0063] In a specific embodiment, the compounds of the invention are PLK, Aurora A, Aurora B and/or FLT-3 inhibitors, and are useful for treating diseases, such as cancer, associated with such a kinase(s). In another specific embodiment, the compounds of the invention are PLK inhibitors and are useful for treating diseases associated with PLK, such as cancer. Typically, the PLK is PLK4, PLK2 and PLK 1. In one example, the PLK is PLK1 and PLK4. In another example, the PLK is PLK4. In another specific embodiment, the compounds of the invention 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 of the invention are FLT-3 inhibitors and are useful in inhibiting FLT-3 activity for the treatment of various conditions such as cancers.

[0064] Another aspect of the invention relates to a method of treating a subject with cancer comprising administering to the subject an effective amount of a compound of the invention. In one embodiment, the compounds of the invention inhibit the growth of a tumor. Specifically, the compounds of the invention inhibit the growth of a tumor that overexpresses at least one of PLK, Aurora A, Aurora B, and FLT-3. More specifically, the compounds of the invention inhibit the growth of a tumor that overexpresses PLK, for example, PLK1, PLK2 and/or PLK4. Even more specifically, the compounds of the invention inhibit the growth of a tumor that overexpresses PLK4. In another embodiment, the compounds of the invention inhibit the growth of the tumor by inducing apoptosis of the tumor cells or by inhibiting proliferation of the tumor cells.

[0065] Cancers that can be treated or prevented by the methods of the present invention 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 specific embodiment, the cancer is lung cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma mutiform or ovarian cancer. In another specific embodiment, the cancer is lung cancer, breast cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiform or ovarian cancer. In yet another specific embodiment, the cancer is a breast cancer. In yet another specific embodiment, the cancer is a basal sub-type breast cancer or a luminal B sub-type breast cancer. In one embodiment, the basal sub-type breast cancer is ER (estrogen receptor), HER2 and PR (progesterone receptor) negative breast cancer. In yet another specific 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.

[0066] The invention further relates to a method of treating a subject with tumor cells, comprising administering to the subject, an amount of a compound disclosed herein that is effective to reduce effectively PLK activity, such as PLK 2 or PLK4 activity, in the subject. In a specific embodiment, the PLK is PLK4.

[0067] The term a "effective amount" means an amount when administered to the subject which results in beneficial or desired results, including clinical results, e.g., reduces the likelihood of developing the cancer or 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. Specifically, "treating a subject with a cancer" includes achieving, partially or substantially, one or more of the following: arresting the growth or spread of a cancer, reducing the extent of a cancer (e.g., reducing size of a tumor or reducing the number of affected sites), 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). It also reduces the likelihood of reoccurrence of the cancer.

[0068] Generally, an effective amount of a compound of the invention 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 invention may be readily determined by one of ordinary skill by routine methods known in the art.

[0069] In an embodiment, an effective amount of a compound of the invention ranges from about 0.01 to about 1000 mg/kg body weight, alternatively about 0.05 to about 500 mg/kg body weight, alternatively about 0.1 to about 100 mg/kg body weight, alternatively

about 0.1 to about 15 mg/kg body weight, alternatively about 1 to about 5 mg/kg body weight, and in another alternative, from about 2 to about 3 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject suffering from cancer and 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.

[0070] Moreover, a "treatment" regime of a subject with an effective amount of the compound of the present invention may consist of a single administration, or alternatively comprise a series of applications. For example, the compound of the present invention 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 invention, or a combination thereof. It will also be appreciated that the effective dosage of the compound used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis 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.

[0071] As used herein, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, reducing the likelihood of the spread of the disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. "Treatment" also includes reducing the likelihood of developing the disease or reducing the likelihood of reoccurrence of the disease.

[0072] 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).

[0073] In one embodiment, the method of the present invention is a mono-therapy where the pharmaceutical compositions of the invention are administered alone.

Accordingly, in this embodiment, the compound of the invention is the only pharmaceutically active ingredient in the pharmaceutical compositions or the only pharmaceutically active ingredient administered to the subject.

[0074] In another embodiment, the method of the invention is a co-therapy with one or more of other therapeutically active drugs or therapies known in the art for treating the desired diseases or indications. In one example, one or more other anti-proliferative or anticancer therapies are combined with the compounds of the invention. In another example, the compounds disclosed herein are co-administered with one or more of other anticancer drugs known in the art. Anticancer therapies that may be used in combination with the compound of the invention include surgery, radiotherapy (including, but not limited to, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes) and endocrine therapy. Anticancer agents that may be used in combination with the the compounds of the invention include biologic response modifiers (including, but not limited to, interferons, interleukins, and tumor necrosis factor (TNF)), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs (e.g. taxol and analogs thereof).

[0075] When the compounds of the invention are combined with other anticancer drugs, they can be administered contemperaneously. As used herein, "administered contemporaneously" means that two substances are administered to a subject such that they are both biologically active in the subject at the same time. The exact details of the administration will depend on the pharmacokinetics of the two substances in the presence of each other, and can include administering one substance within a period of time of one another, *e.g.*, 24 hours of administration of the other, if the pharmacokinetics are suitable. Designs of suitable dosing regimens are routine for one skilled in the art. In particular embodiments, two substances will be administered substantially simultaneously, *i.e.* within minutes of each other, or in a single composition that comprises both substances. Alternatively, the two agents can be administered separately, such that only one is biologically active in the subject at the same time.

[0076] The compounds of the invention 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 invention 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.

[0077] The compounds of the invention can be suitably formulated into pharmaceutical compositions for administration to a subject. The pharmaceutical compositions of the invention 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 (5^{th} 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.

[0078] Typically, for oral therapeutic administration, a compound of the invention may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

[0079] Typically for parenteral administration, solutions of a compound of the invention 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.

[0080] Typically, for injectable use, sterile aqueous solutions or dispersion of, and sterile powders of, a compound of the invention for the extemporaneous preparation of sterile injectable solutions or dispersions.

[0081] For nasal administration, the compounds of the invention 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.

[0082] For buccal or sublingual administration, the compounds of the invention can be formulated with with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine, as tablets, lozenges or pastilles.

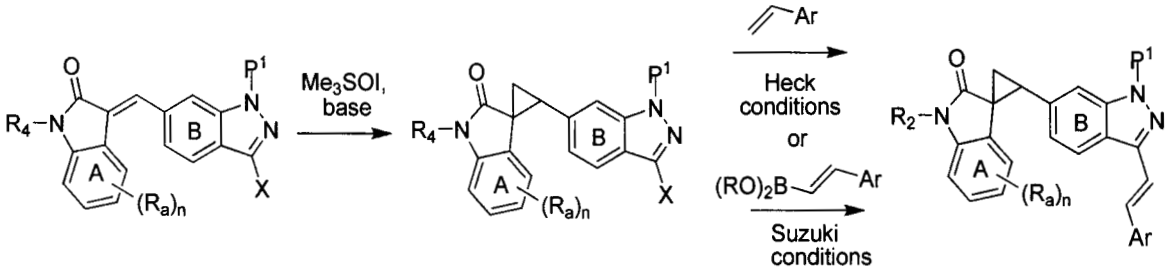
[0083] For rectal administration, the compounds of the invention can be formulated in the form of suppositories containing a conventional suppository base such as cocoa butter.

[0084] The compounds of the invention, can be formulated alone or for contemporaneous administration with other agents for treating cancer. Therefore, in another aspect, a pharmaceutical composition of the invention comprises a pharmaceutically acceptable carrier or diluent, a compound disclosed herein or a pharmacuetically acceptable salt thereof and another anti-cancer agent, for example, but not limited to a glucose metabolism inhibitor or taxol.

[0085] In accordance with another aspect of the present invention, the compounds of the invention can be prepared by processes analogous to those established in the art. By way of illustration, compounds of Formula (I), wherein Rings A and B are as defined herein may be prepared by the methods outlined in Scheme 1. Reaction of an appropriately substituted Indazolylmethyleneindolinone 1 (wherein ring A is as defined herein and ring B and C together are an indazole) is reacted with a suitable methylene source, such as trimethylsulfonium iodide, or trimethylsulfoxonium iodide in the presence of a base (such as sodium hydride, LDA or NaHMDS), in a polar solvent (such as DMF, THF or DMSO). The reaction is conveniently effected at the appropriate temperature (generally in the range of 20° to 60 °C). The vinyl linkage, wherein Ar is a phenyl and heteroaryl group as defined herein, and P^1 represents suitable indazole protecting group (such as Boc, acetyl or SEM) and X is a halide can be installed under typical Heck reaction conditions. Alternatively, wherein Ar is a phenyl and heteroaryl group as defined herein, and P^1 represents suitable

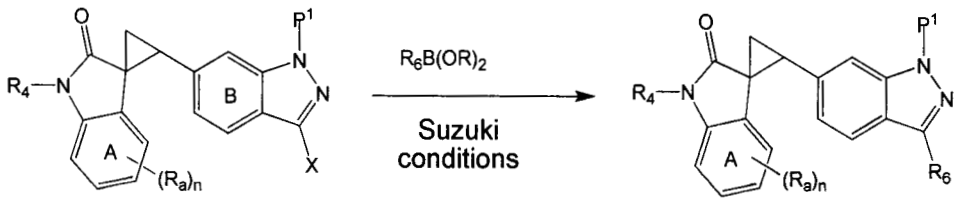
indazole protecting group (such as Boc, acetyl or SEM) and X is a halide can be installed under typical Suzuki reaction conditions, using either a boronic acid or boronate ester. The reaction is preferably effected under microwave irradiation conditions, advantageously in the range, for example of 100 to 150 °C, or generally at about 120 °C. Removal of the protecting group may be effected by any of the procedures known to effect such a transformation. For example, when the protecting group P^1 is SEM, the transformation can be effected by treatment with tetrabutylammonium fluoride in a polar solvent, such as THF, at reflux, or by stepwise treatment with boron trifluoride etherate and 2N HCl in ethanol.

Scheme 1



[0086] In another aspect of the invention (SCHEME 2), the aryl linkage wherein R_6 is as defined herein, P^1 is either H or a suitable indazole protecting group (such as Boc, acetyl or SEM) and X is a halide, can be installed under typical Suzuki reaction conditions, using either a boronic acid or boronate ester. The reaction is preferably effected under microwave irradiation conditions, advantageously in the range, for example of 100 to 150 °C, or generally at about 120 °C. Removal of the protecting group may be effected by any of the procedures known to effect such a transformation. For example, when the protecting group P^1 is SEM, the transformation can be effected by treatment with tetrabutylammonium fluoride in a polar solvent, such as THF, at reflux, or by stepwise treatment with boron trifluoride etherate and 2N HCl in ethanol.

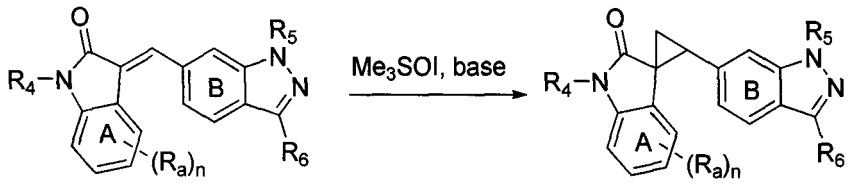
SCHEME 2



SCHEME 3 (Omitted)

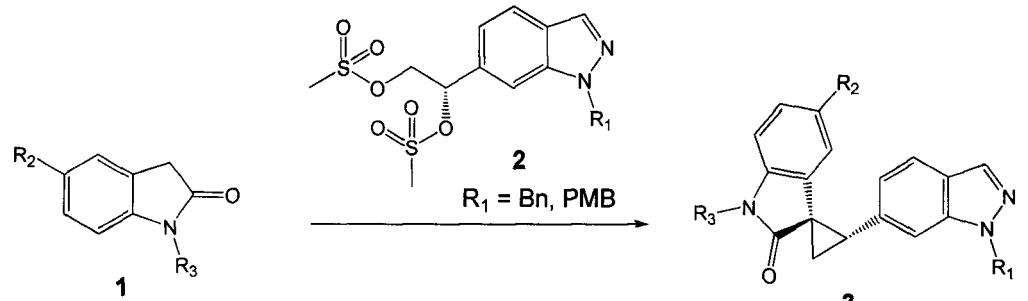
[0087] In another aspect of the invention (SCHEME 4), the cyclopropanation can be effected on compounds such as (I), wherein R_5 is as defined herein and R_6 is as defined herein, is reacted with a suitable methylene source, such as trimethylsulfonium iodide, or trimethylsulfoxonium iodide in the presence of a base (such as sodium hydride, LDA or NaHMDS), in a polar solvent (such as DMF, THF or DMSO). The reaction is conveniently effected at the appropriate temperature (generally in the range of 20° to 60 °C).

SCHEME 4



[0088] In another aspect of the invention, indazolyl-spiro-cyclopropane-indolinones **3** may be obtained from reaction of the dianions generated by treating substituted oxindoles **1** with a strong base such as sodium hydride in a suitable solvent such as THF, with bis-electrophiles **2** (Scheme 5). When the (S) dimesylate is employed, the desired (1R,2S) enantiomer form almost exclusively, with little to none of the undesired (1S,2S) diastereomer detectable.

SCHEME 5



R_2 = H, F, OMe
R_3 = Bn, CH_2CH_2OMe, Me

R_1 = Bn, PMB
R_2 = H, F, OMe
R_4 = Bn, Me, CH_2CH_2OMe

[0089] Indazolyl-spiro-cyclopropane-indolinones **3** which contain a Bn or PMB moiety may be deprotected by employment of suitable reaction conditions. Compounds **3** which contain more than one such protecting group may be deprotected at both sites in a one-pot reaction to provide compounds **4** (Scheme 6). Compounds **3** containing a PMB or Bn group

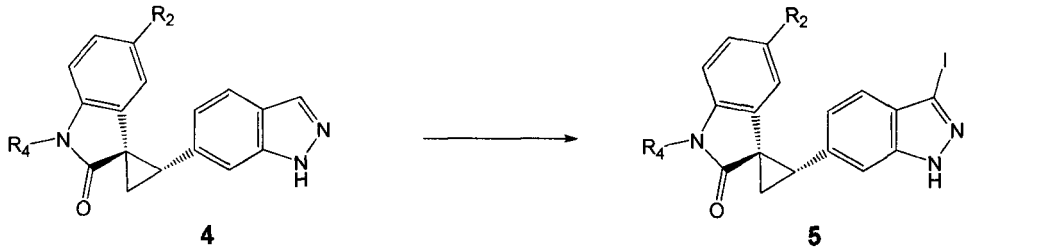
may be deprotected by treatment with a strong base, such as KO^{t}Bu or ^{t}BuLi, and oxygen donor such as O_2, MoOPH or MoOPD, in a suitable solvent such as THF, with DMSO or DMS to reduce the hydroperoxide intermediate formed in situ (A.A. Haddach, A. Kelleman, and M.V. Deaton-Rewolinski, *Tetrahedron Lett.*, **2002**, *43*, 399-402; R.M. Williams and E. Kwast, *Tetrahedron Lett.*, **1989**, *30*, 451-454). Compounds **3** containing a PMB group may alternatively be deprotected by treatment with an acid such as TFA, TfOH or a mixture of such acids, at temperatures between 50 °C – 130 °C to provide indazolyl-spiro-cyclopropane-indolinones **4**.

SCHEME 6



[0090] Indazolyl-spiro-cyclopropane-indolinones **4** may be iodinated to provide compounds of **5** (Scheme 7) by treatment with an iodinating agent such as iodine or N-iodosuccinimide, in the presence of a base such as Na_2CO_3, K_2CO_3, NaOH or KO^{t}Bu, in a suitable solvent such as acetone, ACN, DMF, DMSO, dioxane, NMP, THF, with or in the absence of water.

SCHEME 7



[0091] The relative stereochemistry of the cyclopropane ring may be assigned as (1R*,2S*) by comparison to the minor diastereomer produced in the synthesis of the racemic reference standards by use of HCOSY NMR experiment to assign the signals for each proton in the ^{1}H NMR followed by NOESY experiment to determine the through space

interaction between the cyclopropane protons and the proton at position 4 of the indolinone following (I. Moldvai, E. Gacs-Baitz, M. Balazs, M. Incze and C. Szantay; *Arch. Pharm. Pharm. Med. Chem.* **1996**, *329*, 541-549). The absolute stereochemistry of the product may be assigned as (1R,2S), based upon application of the Sharpless mnemonic to predict diol configuration as (S) and assuming an S_N2 coupling process to form the cyclopropane resulting in inversion of the (S) stereocenter of the diol with preservation of e.e.

[0092] The invention is illustrated by the following examples which are not intended to be limiting in any way. It is noted that the examples are not numbered sequentially.

EXEMPLIFICATION

EXEMPLIFICATION

A. Syntheses of Compounds of the Invention

General Experimental Methods:

[0093] Commercially available starting materials, reagents, and solvents were used as received, with the exception of *N,N*-dimethyl-1-(4-vinylphenyl)methanamine which was purified by chromatography on silica gel prior to use in Heck reactions. In general, anhydrous reactions were performed under an inert atmosphere such as nitrogen or argon. 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. Final products were sometimes purified by preparative reverse-phase HPLC. Purification was performed on a Varian PrepStar model SD-1 HPLC system with a Varian Monochrom 10u C-18 reverse-phase column using a gradient of about 5-30% acetonitrile/ 0.05% TFA water to 70-100% acetonitrile/0.05% TFA water over a 20-40-min period at a flow rate of 30-50 mL/min. Fractions containing the desired material were concentrated and lyophilized to obtain the final products. 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).

[0094] Compound names were generated using the software built into ChemBioDraw Ultra version 11.0 with the following exception. Racemic compounds with known relative

stereochemistry were named using the R*/S* system as described by North (Principles and Applications of Stereochemistry, CRC Press, 1998), wherein the lower numbered atom is arbitrarily defined as R*, and the higher numbered atoms are defined relative to that center. Thus a racemic mixture of enantiomers of a compound with two chiral centers is designated as (1*R**, 2*S**) or (1*R**, 2*R**) depending on the known relative stereochemistry. The standard R and S nomenclature or "abs" representing absolute is used to describe single enantiomers or enantiomerically enriched compounds of greater than 95% e.e.

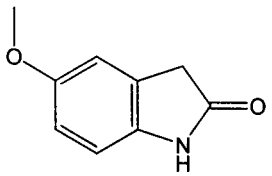
Abbreviations:

aq.	aqueous
$BF_3.OEt_2$	borontrifluoride etherate
br.	Broad
dba	dibenzylideneacetone
DCM	dichloromethane
DCM	dichloromethane
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
% e.e.	% enantiomeric excess
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
h	hours
Hex	hexane
AcOH	acetic acid
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography coupled to mass spectroscopy
MeCN	acetonitrile
MeOH	methanol
min	minutes
MsCl	methanesulfonyl chloride
MS ESI	mass spectra, electrospray ionization

NMR	nuclear magnetic resonance
O/N	overnight
$Pd(OAc)_2$	palladium acetate
PPh_3	triphenylphosphine
prepHPLC	preparative scale high pressure liquid chromatography
prepTLC	preparative scale thin layer chromatography
RBF	round bottomed flask
rt	room temperature
sat.	saturated
SEM	2-(trimethylsilyl)ethoxy)methyl
tBuOOH	tert-butyl hydroperoxide
TBAF	tetrabutylammonium fluoride
^{t}BuOK	potassium tert-butoxide
temp.	temperature
THF	tetrahydrofuran
wt%	percent by weight

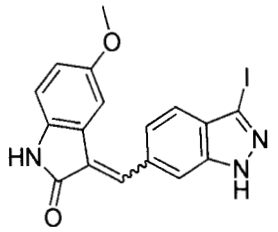
Preparation of Starting Materials

Synthesis of 5-methoxyoxindole



[0095] To a solution of 5-methoxyisatin (10.62 g, 60 mmol) in DMSO (30 mL) was added $N_2H_4 \cdot xH_2O$ (hydrazine hydrate, 6 mL, 120 mmol) dropwise over 5 min (exothermic). After addition, the resulting mixture was heated at 140 °C (oil temp.) for 2h and then cooled to rt. After diluting with H_2O (30 mL), 6 M HCl (12 mL, 72 mmol) was added and the resulting mixture was stirred for 1h at rt. Ice (30 mL) was added and the reaction mixture was stirred O/N at rt. The precipitate formed was collected by suction filtration, rinsed with H_2O, then dried to give the 5-methoxyoxindole (6.523 g) as a brown solid. (about 10% impurity being the oxime from starting material 5-methoxyisatin) ^{1}H NMR (400 MHz, d_6-DMSO) 6.78 (s, 1H), 6.85 (s, 1H), 6.72-6.79 (m, 2H), 3.39 (s, 3H); ESI 164.0 $[M + H]^+$, calcd for $[C_9H_9NO_2 + H]^+$ 164.1.

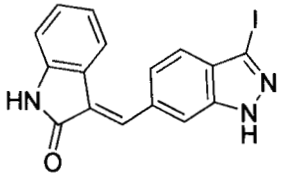
Synthesis of (E and Z)-3-((3-iodo-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one



[0096] To a mixture of 3-iodo-1H-indazole-6-carbaldehyde (1.360 g, 5 mmol) and 5-methoxyoxindole (1.06 g, 6.5 mmol) in methanol (50 mL) was added piperidine (0.1 mL, 1 mmol). The resulting mixture was refluxed (oil temp. 75 °C) for 3 h, then cooled to rt and stirred for 2h at rt. The resulting precipitates were collected by suction filtration and dried to give (E/Z)-3-((3-iodo-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one (E/Z = 2:1) as dark brick orange solid (1.966 g, 94%). The mixture was used as an intermediate without purification of the isomers.

[0097] This intermediate was also prepared using these conditions: A round bottom flask was charged with 5-methoxyoxindole (commercial reagent from Prime Organics, 300 mg, 1.84 mmol), 3-iodo-1*H*-indazole-6-carbaldehyde (500 mg, 1.84 mmol), piperidine (20 uL, 0.18 mmol) and MeOH (7 mL). The reaction was then heated to 60°C for 4h. A bright red precipitate formed which was further precipitated by cooling to room temperature. The red powder was then filtered and washed with MeOH giving 658 mg, 86% of the title compound. A mixture of (*E*)- and (*Z*)-isomers (84:16 by NMR) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) 13.78 (br. s, 1H), 10.50 (s, 1H), 9.01 (s, 1H), 8.00 (s, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 2.1 Hz, 1H), 6.81 (dd, J = 4.1, 2.2 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.77 (s, 3H); MS ESI 418.0 $[M + H]^+$, calcd for $[C_{17}H_{12}IN_3O_2 + H]^+$ 418.00.

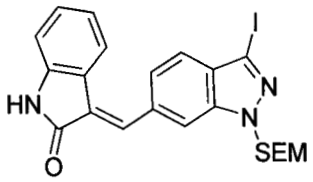
Synthesis of (E)-3-((3-iodo-1H-indazol-6-yl)methylene)indolin-2-one



[0098] To a mixture of 3-iodo-1H-indazole-6-carbaldehyde (1.360 g, 5 mmol) and 2-oxindole (732 g, 5.5 mmol) in MeOH (25 mL) was added piperidine (0.1 mL, 1 mmol). The resulting mixture was refluxed (oil temp. 75 °C) for 90 min, then cooled to rt. The resulting precipitates were collected by suction filtration and dried to give (E/Z)-3-((3-iodo-1H-indazol-6-yl)methylene)-indolin-2-one as yellow solid (E:Z = 5:1, 1.86 g). The mixture was

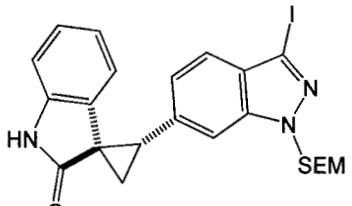
used as an intermediate without purification of the isomers, or alternatively the pure E isomer could be purified by dissolving in THF (1.57 g in 46.85 mL) at room temperature. Hexane (146.8 mL) was added to the clear solution with stirring to give a yellow precipitate. The solid suspension was heated to 70°C for 30 min & then cooled to room temperature. The yellow solid was filtered and washed with hexane (3.14 mL) to give the title compound (1.22 g, 79 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.71 (s, 1H), 10.64 (s, 1H), 7.88 (s, 1H), 7.77 (s, 1H), 7.57-7.46 (m, 3H), 7.23 (t, 1H, J = 7.6 Hz), 6.87 (d, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 7.6 Hz); MS ESI 388.0 $[M + H]^+$, calcd for $[C_{16}H_{10}IN_3O + H]^+$ 387.99.

Synthesis of (E)-3-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)-indolin-2-one



[0099] Oxindole (665 mg, 5 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (2 g, 5 mmol) were dissolved into ethanol (25 mL). Piperdine (0.1 mL) was added and the solution was heated to 70 °C for 2 h, cooled to rt and stirred overnight. The solvent was removed in vacuo to give an orange solid which was triturated with ethanol to give the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.86 (s, 1H), 7.62-7.55 (m, 3H), 7.24 (d, 1H, J = 7.8 Hz), 6.91 (d, 1H, J = 7.8 Hz), 6.86 (t, 1H, J = 7.6 Hz), 5.75 (s, 2H), 3.62-3.58 (m, 2H), 0.93-0.89 (m, 2H), -0.04 (s, 9H); MS ESI 518.0 $[M + H]^+$, calcd for $[C_{22}H_{24}IN_3O_2Sii + H]^+$ 518.4.

Synthesis of (1*R**, 2*S**)-2-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)spiro[cyclo-propane-1,3'-indolin]-2'-one

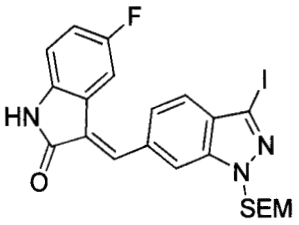


R*, S*, racemate

[00100] To a solution of trimethylsulfoxonium iodide (1.89 g, 8.6 mmol) in anhydrous DMF (40 mL) was added sodium hydride (60% dispersion in oil) (1.03 g, 25.8 mmol) at 0°C. The mixture was stirred for 15 min after which time (E)-3-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one (2.2 g, 4.3 mmol)

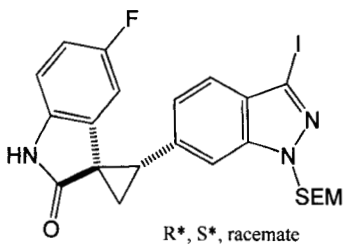
was added. The solution was stirred overnight at rt. The reaction was quenched with sat. NH_4Cl solution (50 mL), extracted with EtOAc (4 x 100 mL), dried over $MgSO_4$ and concentrated to dryness. The title compound was isolated by silica gel chromatography (CH_2Cl_2/MeOH 98:2) as a yellow solid (1.5 g, 66%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.39 (d, 1H J = 8.3 Hz), 7.09 (t, 1H, J = 7.5 Hz), 7.04 (d, 1H, J = 8.0 Hz), 6.92 (d, 1H, J = 7.8 Hz), 6.61 (t, 1H, J = 8.0 Hz), 5.90 (d, 1H, 8.0 Hz), 5.70 (s, 2H), 3.57-3.53 (m, 2H), 3.49-3.44 (m, 1H), 2.31-2.28 (m, 1H), 2.12-2.09 (m, 1H), 0.89-0.84 (m, 2H), -0.05 (s, 9H); MS ESI 532.1 $[M + H]^+$, calcd for $[C_{23}H_{26}IN_3O_2Si+ H]^+$ 532.4.

Synthesis of (E)-5-fluoro-3-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one



[00101] A round bottom flask was charged with 5-fluoroindolin-2-one (100 mg, 0.661 mmol), 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (266.18 mg, 0.661 mmol), piperidine (13 uL, 0.013 mmol) and methanol (7.5 mL). The reaction was then heated to 55°C for 4 h prior to cooling the reaction mass to room temperature. Filtration and washing with methanol (0.50 mL x 2) gave the title compound as a yellow solid (273 mg, 77%). ^1H NMR (400 MHz,$CDCl_3$) δ 8.14 (s, 1H), 8.00 (s, 1H), 7.85 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.34 (dd, J = 8.0, 2.4 Hz,1H), 6.97 (td, J = 6.4, 2.4 Hz, 1H), 6.85 (dd, J = 8.4, 4.4 Hz, 1H), 5.80 (s, 2H), 3.58 (t, J= 8.4 Hz, 2H), 0.92 (t, J= 8.4 Hz, 2H), 0.03 (s, 9H).

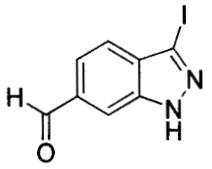
Synthesis of (1*R**,2*S**)-5'-fluoro-2-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



R*, S*, racemate

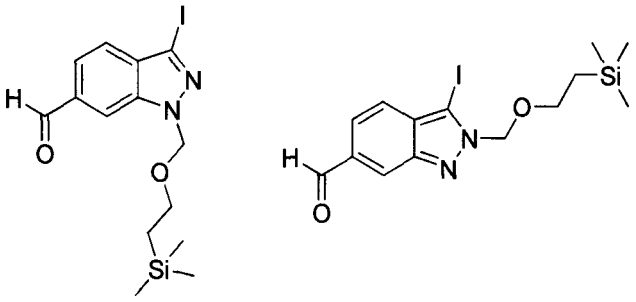
[00102] Trimethylsulfoxonium iodide (164.4 mg, 0.747 mmol) was added to a suspension of sodium hydride (89.6 mg, 2.24 mmol) (60% dispersion in oil) in DMF (2.0 mL) at room temperature. The mixture was stirred for 15 min after which time a solution of (E)-5-fluoro-3-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)indolin-2-one (200 mg, 0.373 mmol) in DMF (1.25 ml) was added. The solution was stirred at 55°C for 7.0 h prior to quenching reaction mass over 25% NH_4Cl solution (10 mL) at room temperature. The product was extracted using ethyl acetate (15 mL x 2) and the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified using silica gel column chromatography (hexane : acetone 80:20 as an eluent) to yield a creamy semi-solid, which was then triturated with hexanes (2.0 mL) to give the title compound as an off-white powder (94 mg, 46%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.46 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.86 (s, 1H), 6.78 (m, 1H), 5.72 (s, 2H), 5.68 (d, J= 8 Hz, 1H), 3.54-3.48 (m, 3H), 2.34 (br s, 1H), 2.13 (br s, 1H), 0.88 (m, 2H), 0.03 (s, 9H).

Synthesis of 3-iodo-1H-indazole-6-carbaldehyde



[00103] To a solution of 1H-indazole-6-carbaldehyde (2.00 g, 13.7 mmol), K_2CO_3 (3.79 g, 27.4 mmol) in DMF (15 mL) was added dropwise a solution of I_2 (5.91 g, 23.3 mmol) in DMF (15 mL) and the reaction allowed to stir for two h. An aqueous solution consisting of $Na_2S_2O_4$ (3.30 g) / K_2CO_3 (0.20 g) / H_2O (30 mL) was then added and the solution stirred for one h. The product was then precipitated by pouring the solution over ice-water (300 mL) and collected by vacuum filtration to give after drying 3.02 g, 81 % of a beige powder. ^1H NMR (400 MHz, CD_3OD) δ 10.11 (s, 1H), 8.11 (s, 1H), 7.74 (d, J = 8.34 Hz, 1H), 7.62 (d, J = 8.34 Hz, 1H); MS ESI 272.9 $[M + H]^+$, calcd for $[C_8H_5IN_2O + H]^+$ 272.95.

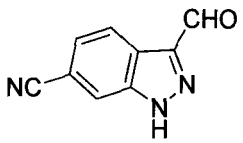
Synthesis of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde and 3-iodo-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazole-6-carbaldehyde



[00104] To a suspension of 3-iodo-1H-indazole-6-carbaldehyde (3.01 g, 11.1 mmol) in CH_2Cl_2 (70 mL) and 50 % aq. KOH (20 mL) was added tetrabutylammonium bromide (36 mg, 0.111 mmol) and the solution cooled to 0 °C. (2-(Chloromethoxy)ethyl)trimethylsilane (2.3 mL, 13.3 mmol) was then added dropwise and the reaction stirred at 0 °C for 3 hours. The solution was then transferred to a sep. funnel containing CH_2Cl_2 (200 mL) and the organic layer was washed with brine (2 x 100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography (100 % CH_2Cl_2) to give 2.88 g, 65 % of the N-1 isomer (higher eluting spot) and 757 mg, 17 % of the N-2 isomer (lower eluting spot). N-1 isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.11 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 5.82 (s, 2H), 3.60 (m, 2H), 0.91 (m, 2H), -0.042 (s, 9H); MS ESI 425.0 $[M + Na]^+$, calcd for $[C_{14}H_{19}IN_2O_2Si + Na]^+$ 425.02.

[00105] N-2 isomer : ^{1}H NMR (400 MHz, CD_3OD) 10.09 (s, 1H), 8.31 (s, 1H), 7.62 (m, 2H), 5.91 (s, 2H), 3.71 (m, 2H), 0.92 (m, 2H), -0.039 (s, 9H); MS ESI 425.0 $[M + Na]^+$, calcd for $[C_{14}H_{19}IN_2O_2Si + Na]^+$ 425.02

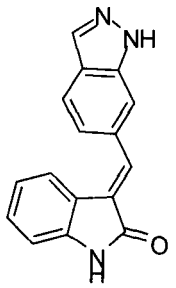
Synthesis of 3-formyl-1H-indazole-6-carbonitrile



[00106] To a solution of $NaNO_2$ (11.04g, 160 mmol) in H_2O (200 mL) was added 6-cyanoindole (5.68 g, 40 mmol) in one portion slowly. The resulting suspension was stirred for 5 min at rt. HCl (32 mL, 192 mmol 6N) was added dropwise via a dropping funnel over 30 min and the pH was about 1. The resulting suspension was stirred for 4.5 h at rt before of EtOAc (400 mL) was added. After stirring for additional 10 min to dissolve the precipitate, the two layers were separated and the aqueous layer was extracted with EtOAc (150 mL). Combined extracts were dried over Na_2SO_4. Removal of solvents afforded 6.864 g (100%) of title compound as brown (coffee color) solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.70 (s,

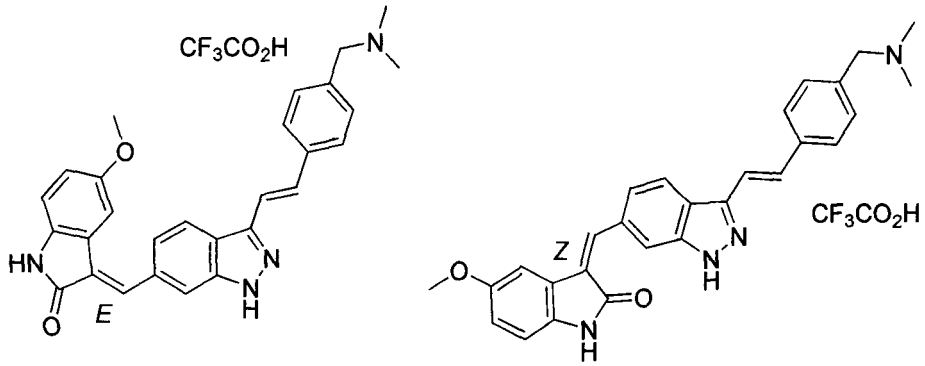
1H, NH), 10.22 (s, 1H, CHO), 8.38 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H). MS ESI 172.0 $[M + H]^+$, calcd for $[C_9H_5N_3O + H]^+$ 172.0.

Synthesis of (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one



The title compound was synthesized according to the method described for (E)-3-((1H-indazol-5-yl)methylene)indolin-2-one except reacting oxindole (67 mg, 0.216 mmol) with 1H-indazole-6-carbaldehyde (73 mg, 0.238 mmol) to obtain 32 mg, 51 %.^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.89 (s, 2H), 7.65 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.87 (t, J = 7.6 Hz, 1H); MS ESI 262.0 $[M + H]^+$, calcd for $[C_{16}H_{11}N_3O + H]^+$ 262.10.

Synthesis of (E and Z)-3-((3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-methylene)-5-methoxyindolin-2-one 2,2,2-trifluoroacetate



A. (E)-3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde

[00107] The title compound was synthesized according to the method of Example A22A in WO2010/115279, utilizing *N,N*-dimethyl-1-(4-vinylphenyl)methanamine (42 mg, 0.26 mmol) and 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (70 mg, 0.17 mmol) with heating in a sealed tube at 90°C overnight instead of with microwave irradiation. Purified by prepTLC (SiO_2 10 % MeOH/DCM) to provide the title compound to as a pale orange gum (33.4 mg, 44 %). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 10.13 (s, 1

H), 8.27 (m, 2 H), 7.81 (d, J=9.29 Hz, 1 H), 7.69 (d, J=8.28 Hz, 2 H), 7.61 (d, J=16.6 Hz, 1 H), 7.50 (d, J=16.6 Hz, 1 H), 7.43 (d, J=8.28 Hz, 2 H), 5.86 (s, 2 H), 3.82 (s, 2 H), 3.62 (t, J=8.03 Hz, 1 H), 2.50 (s, 6 H), 0.87 (t, J=8.03 Hz, 2 H), -0.09 (s, 9 H); MS ESI 436.3 [M + H]$^+$, calcd for [$C_{25}H_{33}N_3O_2Si$+ H]$^+$ 436.6.

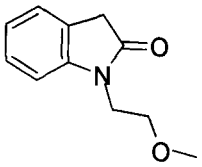
B. (E)-3-((3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one

[00108] Piperidine (0.01 mL, 0.1 mmol) was added to a solution of 5-methoxyoxindole (52 mg, 0.32 mmol) and (E)-3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1H-indazole-6-carbaldehyde (contaminated with TBAF from previous deprotection attempt, 95.5 mg, 0.22 mmol) in EtOH (5 mL). The reaction was then heated to 75°C for 25 hrs. The solvent was evaporated *in vacuo*. Chromatography (5g silica SPE tube, Silicycle, 5-10% MeOH in CH_2Cl_2) gave a brown oil (105 mg, contained product and TBAF by NMR). The residue was dissolved in EtOAc (100 mL) and washed with brine (3 x 15 mL), dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to give the title compound as a brown oil (110mg, used without further purification).

C. (E & Z)-3-((3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-methylene)-5-methoxyindolin-2-one

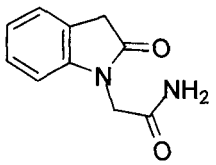
[00109] According to the method of Example A22B in WO2010/115279, 3-((3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one (19 mg, 0.033 mmol) was treated with boron trifluoride etherate, followed by 2 N HCl (water / EtOH) treatment. The solvents were removed in vacuo using additional EtOH to azeotropically remove water. The residue was dissolved in MeOH / EtOAc and filtered to remove solid, then the solvent was evaporated *in vacuo*. Purification by prep-HPLC gave the title compound (*E* isomer, first eluting fraction, 94% by HPLC) as an orange solid (11 mg, 60%,). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.26 (d, J=8.5 Hz, 1 H), 7.88 (d, J=9.3 Hz, 2 H), 7.80 (d, J=8.3 Hz, 2 H), 7.61 (s, 2 H), 7.51 - 7.58 (m, 3 H), 7.26 (s, 1 H), 6.84 (s, 2 H), 4.34 (s, 2 H), 3.63 (s, 3 H), 2.89 (s, 6 H); MS ESI 451.2 [M + H]$^+$, calcd for [$C_{28}H_{26}N_4O_2$+ H]$^+$ 451.22. The second eluting fraction was the Z-isomer (5 mg, 30%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.89 (s, 1 H), 8.15 (d, J=9.0 Hz, 1 H), 7.99 (dd, J=9.0, 1.3 Hz, 1 H), 7.90 (s, 1 H), 7.81 (d, J=8.3 Hz, 2 H), 7.57 - 7.61 (m, 2 H), 7.53 (d, J=8.3 Hz, 2 H), 7.33 (d, J=2.0 Hz, 1 H), 6.85 (dd, J=8.4, 2.4 Hz, 1 H), 6.80 (d, J=8.4 Hz, 1 H), 4.34 (s, 2 H), 3.84 (s, 3 H), 2.89 (s, 6 H); MS ESI 451.2 [M + H]$^+$, calcd for [$C_{28}H_{26}N_4O_2$+ H]$^+$ 451.22.

Synthesis of 1-(2-methoxyethyl)indolin-2-one



[00110] To a solution of isatin (2.94 g, 20 mmol) in DMF (40 mL) at 0 °C was added 60% NaH (1.00 g, 25 mmol) portionwise. After addition, the resulting mixture was stirred for 15 min at 0 °C and 1-bromo-2-methoxyethane (2.35 mL, 25 mmol) was added dropwise over 2 min. The resulting mixture was stirred for 10 min at 0 °C, warmed to rt and stirred O/N. The reaction was then cooled to 0 °C, quenched with sat. NH_4Cl, ice, H_2O, extracted with EtOAc (150 mL x 2), dried over Na_2SO_4 and concentrated to give a dark orange red liquid which was redissolved in DMSO (10 mL). N_2H_4-xH_2O (2 mL) was added dropwise over 7 min. After addition, the reaction mixture was stirred for 5 min at rt, then 2 h at 140 °C (oil temp.) before cooling to rt. Ice/H_2O (20 mL) was added, followed by 6 M HCl (7 mL, 42 mmol) and the resulting mixture was stirred for 30 min at rt. Additional ice/H_2O (40 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The crude product was purified by flash chromatography (gradient: EtOAc/hex 0 to 40%) to afford the title compound as an orange liquid (2.32 g, 61% over 2 steps). ^1H NMR (400 MHz, DMSO-d_6) δ 7.26-7.20 (m, 2H), 7.03 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 3.82 (t, J = 5.6 Hz, 2H), 3.55 (s, 2H), 3.52 (t, J = 5.8 Hz, 2H), 3.22 (s, 3H); MS ESI 191.8 $[M + H]^+$, calcd for $[C_{11}H_{13}NO_2 + H]^+$ 192.1.

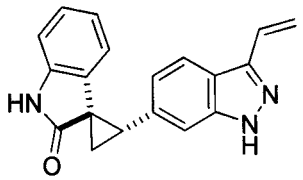
Synthesis of 2-(2-oxoindolin-1-yl)acetamide



[00111] To a mixture of isatin (5.0 g, 35 mmol), K_2CO_3 (5.5 g, 40 mmol) and chloroacetamide (3.74 g, 40 mmol) in a 100 mL of flask was added DMF (25 mL). The resulting mixture was heated at 90 °C (oil temp.) for 2 h. After cooling to rt, it was poured onto ice/H_2O (200 mL) and the resulting precipitate was collected by suction filtration to give 2-(2,3-dioxoindolin-1-yl)acetamide (4.32 g) after drying. ^1H NMR (400 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.30 (s, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 4.25 (s, 2H).

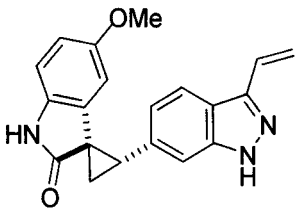
[00112] The above 2-(2,3-dioxoindolin-1-yl)acetamide (4.32 g) was redissolved in DMSO (20 mL) and N_2H_4-xH_2O (2.5 mL) was added dropwise over 10 min. After addition, the resulting mixture was stirred for 5 min at rt, then 2 h at 140 °C before cooling to rt. The reaction was quenched with ice (20 mL) and 6 M HCl (8 mL), then stirred for 30 min at rt. Suction filtration gave crude title compound (2.92 g) as a light yellow solid. The product was suspended in EtOAc (120 mL) and H_2O (60 mL) was added, followed by 2 M HCl (30 mL). The mixture was separated and suction filtration of aqueous layer affored the title compound as a light beige solid (1.78 g, 27% over 2 steps) after drying. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (s, 1H, NH), 7.28-7.08 (m, 4H), 6.99 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 4.22 (s, 2H), 3.56 (s, 2H); MS ESI 191.0 $[M + H]^+$, calcd for $[C_{10}H_{10}N_2O_2 + H]^+$ 191.1; MS ESI 174.0 $[M - NH_2]^+$, calcd for $[C_{10}H_{10}N_2O_2 - NH_2]^+$ 174.1; MS ESI 146.0 $[M - CONH_2]^+$, calcd for $[C_{10}H_{10}N_2O_2 - CONH_2]^+$ 146.1.

Synthesis of (1R*,2S*)-2-(3-vinyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



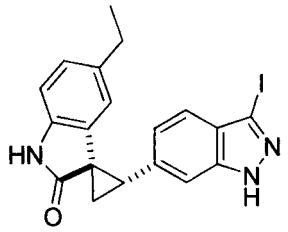
[00113] To a mixture of (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-spiro [cyclopropane-1,3'-indolin]-2'-one (802 mg, 2 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (462 mg, 3 mmol) in a 20 mL microwave vial was added $PhCH_3$/EtOH (8 mL/4 mL), followed by 1 M Na_2CO_3 (3 mL, 3 mmol) and $Ph(PPh_3)_4$ (46 mg, 0.04 mmol, 2 mol%) was added and the resulting mixture was purged with argon, then microwaved 3 h at 120 °C. After aqueous workup, the solution was extracted with EtOAc and was purified by flash chromatography (Hex/EtOAc 1:1) to give the crude title compound as a light yellow foam (512 mg) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.10-6.88 (m, 5H), 6.54 (t, J = 7.4 Hz, 1H), 6.06 (d, J = 18.0 Hz, 1H), 5.92 (d, J = 7.6 Hz, 1H), 5.49 (d, J = 7.6 Hz, 1H), 3.46 (d, J = 8.2 Hz, 1H), 2.30-2.18 (m, 2H); MS ESI 302.0 $[M + H]^+$, calcd for $[C_{19}H_{15}N_3O + H]^+$ 302.1.

Synthesis of (1R*,2S*)-5'-methoxy-2-(3-vinyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



[00114] To a mixture of (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro [cyclopropane-1,3'-indolin]-2'-one (1.00 g, 2.32 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (500 mg, 3.25 mmol) in a 20 mL microwave vial was added $PhCH_3$/EtOH (7 mL/3.5 mL), followed by 1 M Na_2CO_3 (3 mL, 3 mmol). After stirring for 1 min at rt, $Ph(PPh_3)_4$ (50 mg, 0.043 mmol, 1.9 mol%) was added and the resulting mixture was purged with argon, and microwaved 3 h at 120 °C. This reaction was repeated twice on the same scale and the resulting mixtures were combined. Aqueous workup gave the crude title compound as a dark orange solid/foam (3.10 g) which was used without further purification. A sample of pure compound can be obtained by flash chromatography (Hex/EtOAc 1:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.01 (dd, J = 18.2 Hz, J = 11.4 Hz, 1H overlapping with d, J = 6.8 Hz, 1H; total 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.61 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 6.09 (d, J = 18.0 Hz, 1H), 5.56 (d, J = 1.6 Hz, 1H), 5.52 (d, J = 11.6 Hz, 1H), 3.56 (t, J = 7.6 Hz, 1H, partially overlapping with MeOH residue), 3.26 (s, 3H), 2.24 (dd, J = 7.8 Hz, J = 5.0 Hz, 1H), 2.18 (dd, J = 9.2 Hz, J = 4.8 Hz, 1H); MS ESI 332.0 $[M + H]^+$, calcd for $[C_{20}H_{17}N_3O_2 + H]^+$ 332.1.

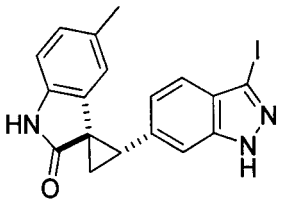
Synthesis of (1R*,2S*)-5'-ethyl-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



[00115] The title compound, as a single diastereomer, (710 g, 33% over 2 steps, triturated from hex/MeOH) was obtained as a light orange solid from 5-ethylindolin-2-one (885 mg, 5.5 mmol) and 3-iodo-1H-indazole-6-carbaldehyde (1.36 g, 5 mmol) using the method for the preparation of (1R*,2S*)-2-(3-vinyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one. ^1H NMR (400 MHz, DMSO-d_6) δ 13.44 (s, 1H), 10.51 (s, 1H), 7.44 (s, 1H), 7.30 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 7.2 Hz 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.76 (s, 1H), 3.17 (t, J = 7.8 Hz, 1H), 2.29 (dd, J = 8.0 Hz, J = 4.8 Hz, 1H), 2.18-2.04 (m,

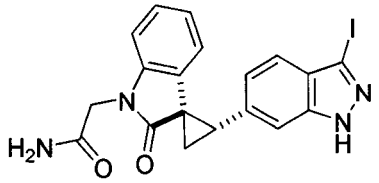
2H), 1.98 (dd, J = 8.6 Hz, J = 4.8 Hz, 1H), 0.60 (t, J = 7.4 Hz, 1H); MS ESI 430.0 $[M + H]^+$, calcd for $[C_{19}H_{16}IN_3O + H]^+$ 430.0.

Synthesis of (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-methylspiro[cyclopropane-1,3'-indolin]-2'-one



[00116] The crude title compound (2.06 g, 99% over 2 steps) was obtained as a yellow solid from 5-methylindolin-2-one (772 mg, 5.25 mmol) and 3-iodo-1H-indazole-6-carbaldehyde (1.36 g, 5 mmol) using the method for the preparation of (1R*,2S*)-2-(3-vinyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one. NMR indicated a 6:1 mixture of the title compound and the minor diasteromer. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (s, 1H), 10.51 (s, 1H), 7.47 (s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 5.86 (s, 1H), 3.18 (t, J = 8.2 Hz, 1H), 2.30-2.20 (m 1H), 2.00-1.90 (m, 1H), 1.85 (s, 3H); MS ESI 416.1 $[M + H]^+$, calcd for $[C_{18}H_{14}IN_3O + H]^+$ 416.0.

Synthesis of 2-((1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-yl)acetamide

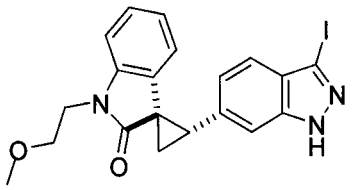


[00117] To a mixture of 2-(2-oxoindolin-1-yl)acetamide (380 mg, 2 mmol) and 3-iodo-1H-indazole-6-carbaldehyde (544 mg, 2 mmol) in MeOH (20 mL) was added piperidine (0.04 mL). The resulting mixture was heated at 75 °C (oil temp.) for 90 min. After cooling to rt, the resulting precipitate was collected by suction filtation to give a yellow solid (850 mg).

[00118] To a mixture of trimethylsulfoxonium iodide (880 mg, 4 mmol) and 60% NaH (486 mg, 12 mmol) in a 100 mL of flask was added DMF (5 mL). The resulting mixture was stirred for 5 min at rt, before a suspension of the above yellow solid (850 mg) in DMF (20 mL) was added via a pipet. After addition, the resulting pink mixture was stirred for 2 h

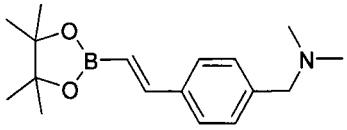
at rt and cooled to 0 °C. The reaction was quenched with ice/H_2O, sat. NH_4Cl (15 mL), followed by ice/H_2O to a total volume of 100 mL. After stirring for 2 min at rt, the resulting precipitate was collected by suction filtration to give the crude title compound as a pink solid (805 mg, 88% over 2 steps) after drying. ^1H NMR (400 MHz, DMSO-d_6) δ 13.50 (s, 1H), 7.94 (s, 1H), 7.70 (s, 1H, NH), 7.49 (s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.26 (s, 1H), 7.06 (t, J = 7.6 Hz, 1H, partially overlapping with the peak at 7.03 ppm), 7.03 (d, J = 8.8 Hz, 1H, partially overlapping with the peak at 7.06 ppm), 6.86 (d, J = 7.6 Hz, 1H), 6.60 (t, J = 7.6 Hz, 1H), 4.38 (t, J = 18.4 Hz, 2H), 3.26 (t, J = 8.8 Hz, 1H), 2.40-2.35 (m, 1H), 2.10-2.04 (m, 1H); MS ESI 459.1 $[M + H]^+$, calcd for $[C_{19}H_{15}IN_4O_2 + H]^+$ 459.0.

Synthesis of (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-1'-(2-methoxyethyl)spiro [cyclopropane-1,3'-indolin]-2'-one



[00119] The crude title compound (750 mg, 82% over 2 steps) was obtained as a light beige solid from 1-(2-methoxyethyl)indolin-2-one (382 mg, 2mmol) and 3-iodo-1H-indazole-6-carbaldehyde (544 mg, 2 mmol) using the method for the preparation of (1R*,2S*)-2-(3-vinyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one. NMR indicated a 6:1 mixture of the title compound and minor diasteromer. ^1H NMR (400 MHz, DMSO-d_6) δ 13.48 (s,1 H), 7.47 (s, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.10-7.05 (m, 2H), 6.98 (d, J = 8.3 Hz, 1H), 6.64-6.56 (m, 1H), 6.01 (d, J = 7.3 Hz, 1H), 3.98-3.92 (m, 2H), 3.63-3.57 (m, 2H), 3.25 (s, 3H and t, J = 8.6 Hz, 1H overlapping; total 4H), 2.37 (t, J = 6.1 Hz, 1H), 2.05 (dd, J = 9.0 Hz, J = 5.0 Hz, 1H); MS ESI 460.1 $[M + H]^+$, calcd for $[C_{20}H_{18}IN_3O_2 + H]^+$ 460.0.

Synthesis of (E)-N,N-dimethyl-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)methanamine

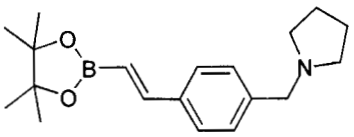


[00120] Glacial acetic acid (3 drops) was added to a mixture of 4-ethynylbenzaldehyde (250.7 mg, 1.93 mmol), dimethylamine (2M in THF, 1.5 mL, 3.0 mmol) and $NaBH(OAc)_3$ (617 mg, 2.91 mmol) in DCE (6.5 mL). The resulting mixture was stirred for 2.5 h at rt. The

reaction was quenched with saturated aqueous $NaHCO_3$ (~40 mL). The product was extracted into CH_2Cl_2 (100 mL, then 2 x 50 mL), and the combined organic layer was washed with brine (25 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification on Biotage Isolera (silica, 0-3% 2M NH_3 - methanol / CH_2Cl_2) gave 1-(4-ethynylphenyl)-N,N-dimethylmethanamine (280.1 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J= 8 Hz, 2H), 7.28 (d, J= 8 Hz, 2H), 3.42 (s, 2H), 3.07 (s, 1H), 2.24 (s, 6H).

[00121] 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (1.20 mL, 8.23 mmol) was added to an argon-purged solution of 1-(4-ethynylphenyl)-N,N-dimethylmethanamine (262 mg, 1.65 mmol) and $HRuCl(CO)(PPh_3)_3$ (104.1 mg, 0.11 mmol) in toluene (9.0 mL). The resulting mixture was heated at 50 °C for 12 h. The product was extracted into Et_2O (250 mL), and the organic layer was washed sequentially with water (3x 20 mL) and brine (20 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by column chromatography (silica gel, 50-100% CH_2Cl_2 in Et_2O) gave (E)-N,N-dimethyl-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)methanamine (402 mg, containing 20% pinacol impurity by ^1H NMR, 68% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J= 8 Hz, 2H), 7.4 (d, 1H), 7.28 (d, 2H), 6.16 (d, 1H), 3.42 (s, 2H), 2.24 (s, 6H), 1.32 (s, 12H); MS ESI 288.0 $[M + H]^+$, calcd for $[C_{17}H_{26}BNO_2 + H]^+$ 288.2.

Synthesis of ((E)-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl) pyrrolidine

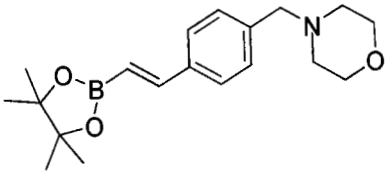


[00122] Glacial acetic acid (0.2 mL) was added to a mixture of 4-ethynylbenzaldehyde (1 g, 7.5 mmol), pyrrolidine (1.2 mL, 15 mmol) and $NaBH(OAc)_3$ (2.5 g, 11.5 mmol) in DCE (35 mL). The resulting mixture was stirred for 2 h at rt. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL). The product was extracted into CH_2Cl_2 (2 x 100 mL), and the combined organic layer was washed with brine (25 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give 1-(4-ethynylphenyl)pyrrolidine in quantitative yield. ^1H NMR ($CDCl_3$) δ: 7.45 (d, J = 7.8 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 3.62 (s, 2H), 3.06 (s, 1H), 2.51 (bs, 4H), 1.80 (bs, 4H).

[00123] To a solution of 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (1.9 g, 15 mmol) in toluene (20 mL) was added 1-(4-ethynylphenyl)pyrrolidine (1 g, 5 mmol) and $HRuCl(CO)(PPh_3)_3$ (120 mg, 0.11 mmol) under argon. The resulting mixture was heated at 50 °C for 4 h. The product was extracted into EtOAc (250 mL), and the organic layer was

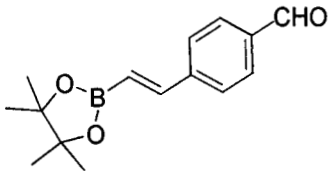
washed sequentially with water (3x 20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (silica gel, 0-20% MeOH/EtOAc) gave the title compound (1.2 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 18.6 Hz, 1H), 7.33-7.29 (m, 2H), 6.15 (d, J = 18.6 Hz, 1H), 3.61 (s, 2H), 2.51 (bs, 4H), 1.79 (bs, 4H), 1.32 (s, 12H).

Synthesis of (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl) morpholine



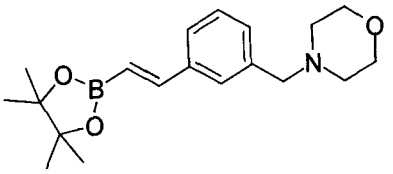
[00124] The title compound (4.35 g, 71%) was obtained as a white to yellow solid from 4-(4-bromobenzyl)morpholine (4.18 g, 16.3 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (3 mL, 17.7 mmol, 1.1 eq.) using the method for the preparation of Example A51A ($PhCH_3$ = 30 mL, 1 mol% $Pd(P^tBu_3)_2$, 80 °C, 1 h). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 18.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 6.16 (d, J = 18.0 Hz, 1H), 3.72 (t, J = 4.4 Hz, 4H), 3.50 (s, 2H), 2.47-2.42 (m, 4H), 1.32 (s, 12H); MS ESI 330.1 $[M + H]^+$, calcd for $[C_{19}H_{28}BNO_3 + H]^+$ 330.2.

Synthesis of (E)-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzaldehyde



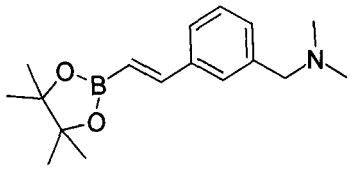
[00125] The title compound (498 mg, 71%) was obtained as a light yellow solid from 4-bromobenzaldehyde (500 mg, 2.71 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.5 mL, 2.95 mmol, 1.1 eq.) using the method for the preparation of Example A51A ($PhCH_3$ = 8 mL, 2 mol% $Pd(P^tBu_3)_2$, 80 °C, O/N). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 18.4 Hz, 1H), 6.34 (d, J = 18.4 Hz, 1H), 1.34 (s, 12H); MS ESI 258.9 $[M + H]^+$, calcd for $[C_{15}H_{19}BO_3 + H]^+$ 259.1.

Synthesis of (E)-4-(3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl) morpholine



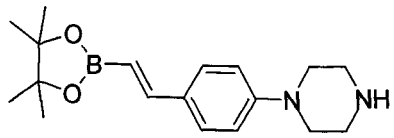
[00126] 7To a mixture of 3-ethynylbenzaldehyde (650 mg, 5 mmol) and morpholine (0.87 mL, 10 mmol) in DCE (15 mL) was added $NaBH(OAc)_3$ (1.325 g, 6.25 mmol), followed by AcOH (0.2 mL). The resulting mixture was stirred for 2 h at rt. Aqueous workup followed by extraction with EtOAc gave crude 4-(3-ethynylbenzyl)morpholine (0.98 g) as a light brown oil. The title compound (1.75 g, quantitative yield over 2 steps) was obtained as a light brown oil using the method ($PhCH_3$ = 12 mL, 1 mol% $HRuCl(CO)(PPh_3)_3$, 50 °C, 2 h) for the preparation of Example A42A. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.46-7.37 (m, 2H), 7.35-7.27 (m, 2H), 6.19 (d, J = 18.4 Hz, 1H), 3.78-3.68 (m, 4H), 3.52 (s, 2H), 2.52-2.42 (m, 4H), 1.32 (s, 12H); MS ESI 330.1 $[M + H]^+$, calcd for $[C_{19}H_{28}BNO_3 + H]^+$ 330.2.

Synthesis of (E)-N,N-dimethyl-1-(3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) vinyl)phenyl)methanamine



[00127] The title compound (1.36 g, quantitative yield over 2 steps) was obtained as a yellow oil from 3-ethynylbenzaldehyde (520 mg, 4 mmol) and Me_2NH (2 M in THF, 3 mL, 6 mol) using the method ($PhCH_3$ = 12 mL, 2 mol% $HRuCl(CO)(PPh_3)_3$, 50 °C, 2 h) for the preparation of (E)-4-(3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl) morpholine. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.45-7.38 (m, 2H), 7.35-7.27 (m, 2H), 6.19 (d, J = 18.4 Hz, 1H), 3.68-3.58 (m, 4H), 3.52 (s, 2H), 2.53-2.43 (m, 4H), 1.32 (s, 12H); MS ESI 288.1 $[M + H]^+$, calcd for $[C_{17}H_{26}BNO_2 + H]^+$ 288.2.

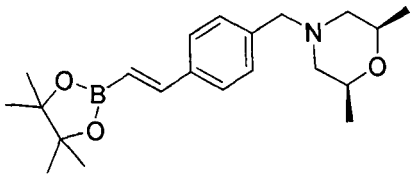
Synthesis of (E)-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl) piperazine



[00128] The title compound (267 mg, 68%) was obtained as yellow solid from 1-(4-bromophenyl)piperazine (653 mg, 2.71 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-

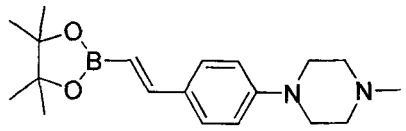
dioxaborolane (0.5 mL, 2.95 mmol, 1.1 eq.) using the method for the preparation of Example A51A ($PhCH_3$ = 12 mL, 2 mol% $Pd(P^tBu_3)_2$, 80 °C, 2 h). ^1H NMR (400 MHz, DMSO-d_6) δ 7.41 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 18.4 Hz, 1H), 6.89 (d, J = 8.0 Hz, 2H), 5.86 (d, J = 18.8 Hz, 1H), 3.17-3.11 (m, 4H), 2.90-2.84 (m, 4H), 1.22 (s, 12H); MS ESI 315.0 $[M + H]^+$, calcd for $[C_{18}H_{27}BN_2O_2 + H]^+$ 315.2.

Synthesis of Cis-2,6-dimethyl-4-(4-((E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine



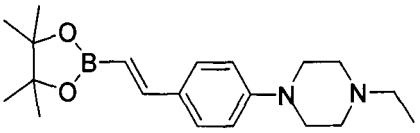
[00129] The title compound (2.52 g, 71%) was obtained as white solid from 4-(4-bromobenzyl)-cis-2,6-dimethylmorpholine (2.82 g, 10 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.85 mL, 11 mmol, 1.1 eq.) using the method for the preparation of Example A51A ($PhCH_3$ = 25 mL, 1 mol% $Pd(P^tBu_3)_2$, 80 °C, 2 h). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 18.4 Hz, 1H), 7.30 (d, J = 7.6 Hz, 2H), 6.16 (d, J = 18.4 Hz, 1H), 3.75-3.65 (m, 2H), 3.47 (s, 2H), 2.70 (d, J = 10.8 Hz, 2H), 1.75 (t, J = 10.2 Hz, 2H), 1.32 (s, 12H), 1.14 (d, J = 6.4 Hz, 6H); MS ESI 358.2 $[M + H]^+$, calcd for $[C_{21}H_{32}BNO_3 + H]^+$ 358.2.

Synthesis of (E)-1-methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine



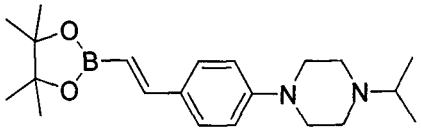
[00130] The title compound (674 mg, 76%) was obtained as a light yellow solid from 1-(4-bromophenyl)-4-methylpiperazine (691 mg, 2.71 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.5 mL, 2.95 mmol, 1.1 eq.) using the method for the preparation of Example A51A ($PhCH_3$ = 10 mL, 2 mol% $Pd(P^tBu_3)_2$, 80 °C, 2 h). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 18.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 5.99 (d, J = 18.4 Hz, 1H), 3.26-3.33 (m, 4H), 2.65-2.59 (m, 4H), 2.40 (s, 3H), 1.31 (s, 12H); MS ESI 329.1 $[M + H]^+$, calcd for $[C_{19}H_{29}BN_2O_2 + H]^+$ 329.2.

Synthesis of (E)-1-ethyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine



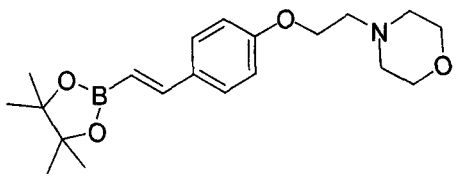
[00131] The title compound (601 mg, 65%) was obtained as a light yellow solid from 1-(4-bromophenyl)-4-ethylpiperazine (729 mg, 2.71 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.5 mL, 2.95 mmol, 1.1 eq.) using the method for the preparation of Example A51A ($PhCH_3$ = 12 mL, 2 mol% $Pd(P^tBu_3)_2$, 80 °C, 2 h). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 18.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 18.0 Hz, 1H), 3.28 (t, J = 4.8 Hz, 4H), 2.61 (t, J = 4.8 Hz, 4H), 2.48 (q, J = 7.2 Hz, 2H), 1.32 (s, 12H), 1.14 (t, J = 7.2 Hz, 3H); MS ESI 343.1 $[M + H]^+$, calcd for $[C_{20}H_{31}BN_2O_2 + H]^+$ 343.2.

Synthesis of (E)-1-isopropyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl) phenyl)piperazine



[00132] The title compound (504 mg, 52%) was obtained as a light orange solid from 1-(4-iodophenyl)-4-isopropylpiperazine (894 mg, 2.71 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.5 mL, 2.95 mmol, 1.1 eq.) using the method for the preparation of Example A51A ($PhCH_3$ = 10 mL, 2 mol% $Pd(P^tBu_3)_2$, 80 °C, O/N). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 18.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 5.98 (d, J = 18.4 Hz, 1H), 3.26 (t, J = 4.8 Hz, 4H), 2.76-2.66 (m, 5H), 1.32 (s, 12 H), 1.10 (d, J = 6.4 Hz, 6H); MS ESI 357.2 $[M + H]^+$, calcd for $[C_{21}H_{33}BN_2O_2 + H]^+$ 357.3.

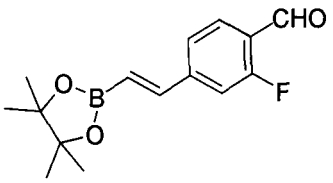
Synthesis of (E)-4-(2-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenoxy) ethyl)morpholine



[00133] The title compound (902 g, 72%) was obtained as a white solid from 4-(2-(4-bromophenoxy)ethyl)morpholine (1 g, 3.50 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.6 mL, 3.58 mmol, 1.02 eq.) using the method for the preparation of Example A51A ($PhCH_3$ = 12 mL, 2 mol% $Pd(P^tBu_3)_2$, 80 °C, O/N). ^1H NMR (400 MHz,

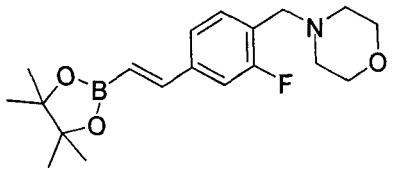
$CDCl_3$) δ 7.28 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 18.4 Hz, 1H), 6.70 (d, J = 8.0 Hz, 2H), 5.88 (d, J = 18.4 Hz, 1H), 3.90 (t, J = 4.8 Hz, 2H), 3.60-3.50 (m, 4H), 2.59 (t, J = 4.8 Hz, 2H), 2.42-2.32 (m, 4H), 1.15 (s, 12 H); MS ESI 360.2 $[M + H]^+$, calcd for $[C_{20}H_{30}BNO_4 + H]^+$ 360.2.

Synthesis of (E)-2-fluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl) benzaldehyde



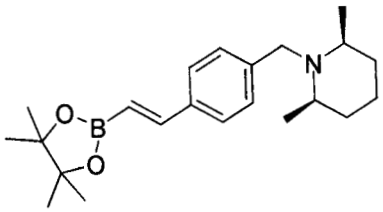
[00134] The title compound (610 mg, 55%) was obtained as yellow solid from 4-bromo-2-fluorobenzaldehyde (812 mg, 4 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.8 mL, 4.8 mmol) using the method for the preparation of Example A51A ($PhCH_3$ = 10 mL, 1 mol% $Pd(P^tBu_3)_2$, 80 °C, 1.5 h). ^1H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H, partially overlapping with the peak at 7.35 ppm), 7.35 (d, J = 17.2 Hz, 1H, partially overlapping with the peak at 7.36 ppm), 7.26 (d, J = 11.2 Hz,1H, partially overlapping with $CDCl_3$ residue), 6.32 (d, J = 18.4 Hz, 1H), 1.33 (s, 12H).

Synthesis of (E)-4-(2-fluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl) benzyl)morpholine



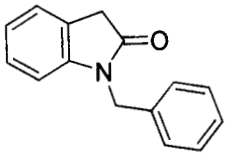
[00135] To a mixture of (E)-2-fluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzaldehyde (0.61 g, 2.2 mmol) and morpholine (0.3 mL) in DCE (20 mL) was added $NaBH(OAc)_3$ (636 mg, 3 mmol), followed by AcOH (0.5 mL). The resulting mixture was stirred for 2 h at rt. The reaction was quenched with sat. $NaHCO_3$ (10 mL), H_2O (10 mL), and extracted with EtOAc (2 x 30 mL). The solvents were removed in vacuo to afford the title compound as a white solid (0.72 g, 94%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.12 (m, 2H), 7.04 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 10.8 Hz, 1H), 5.98 (d, J = 18.4 Hz, 1H), 3.55-3.45 (m, 4H), 3.36 (s, 2H), 2.33-2.23 (m, 4H), 1.14 (s, 12H); MS ESI 348.2 $[M + H]^+$, calcd for $[C_{19}H_{27}BFNO_3 + H]^+$ 348.2.

Synthesis of Cis-2,6-dimethyl-1-(4-((E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) vinyl)benzyl)piperidine



[00136] The title compound (0.45 g, 55%) was obtained as light yellow oil from 4-(4-bromobenzyl)-cis-2,6-dimethylpiperidine (0.60 g, 2.13 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.44 mL, 2.6 mmol) using the method for the preparation of Example A51A ($PhCH_3$ = 10 mL, 2.5 mol% $Pd(P^tBu_3)_2$, 80 °C, 75 min). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.0 Hz, 2H, partially overlapping with the peak at 7.40 ppm), 7.40 (d, J = 18.8 Hz, 1H, partially overlapping with the peaks at 7.43 ppm and 7.36 ppm), 7.36 (d, J = 8.4 Hz, 2H, partially overlapping with the peak at 7.40 ppm), 6.14 (d, J = 18.4 Hz, 1H), 3.78 (s, 2H), 2.53-2.44 (m, 2H), 1.68-1.55 (m, 3H), 1.40-1.28 (m, 3H), 1.05 (d, J = 6.4 Hz, 6H); MS ESI 356.2 $[M + H]^+$, calcd for $[C_{22}H_{34}BNO_2 + H]^+$ 356.3.

Synthesis of N-Benzyl-oxindole

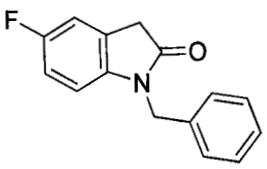


[00137] Prepared according to literature procedure (C. Martin and E. M. Carreira, *J. Am. Chem. Soc.*, **2005**, *127*, 11505-11515). A stirred solution of isatin (10.0 g, 68 mmol) in dry DMF (125 mL) was cooled in an ice bath before addition of sodium hydride (60 wt% in mineral oil, 2.86 g, 71.5 mmol) in 10 portions, the orange solution turning quickly purple. When no further evolution of gas was observed, benzyl bromide (13.4 g, 78.0 mmol) was added by syringe. A colour change back to orange was observed within 20 min. Water (300 mL) was added with stirring, and the resulting orange-red precipitate collected by filtration and washed with water and a little cold ethanol. The solid was then recrystallized from boiling ethanol (300 mL) to afford N-benzylisatin (13.7 g, 85%) as long, red needles.

[00138] N-benzylisatin (13.0 g, 55 mmol) was mixed with hydrazine hydrate (60 mL) and placed in an oil bath. The mixture was heated in stages to 125 °C, becoming first a green sludge, then yellow with clumps of a sticky solid. After a total of 5 h at 125 °C, the mixture was cooled and extracted with EtOAc (2 x 100 mL). The combined organic

portions were washed twice with 1.0 M aq. H_2SO_4, and once each with half-saturated brine then brine, dried over $MgSO_4$, filtered and concentrated to afford a pale yellow solid. Re-precipitation from ether/pentane gave the title compound as an off-white solid (9.6 g, 75%). Spectral data matches literature values (C. Martin and E. M. Carreira, *J. Am. Chem. Soc.*, **2005**, *127*, 11505-11515).

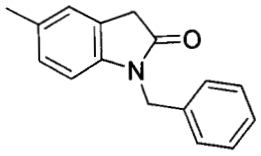
Synthesis of 1-Benzyl-5-fluoroindolin-2-one



[00139] In a manner similar to the method of N-benzylisatin, 5-fluoroisatin (10.0 g, 60.5 mmol) yielded 5-fluoro-N-benzylisatin as an orange red powder (14.5g, 93%). The crude product was used for the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 6.95 (d, J= 7.6 Hz, 1H), 6.84 (t, 1H), 6.60 (m, 1H), 4.89 (s, 2H); MS ESI 255.9 $[M + H]^+$, calcd for $[C_{15}H_{10}FNO_2 + H]^+$ 255.07.

[00140] The title compound was prepared in a manner similar to the method of N-Benzyl-oxindole using 5-fluoro-N-benzylisatin (14.5 g, 56.8 mmol). Trituration using Et_2O : hexane yielded the title compound as a pale yellow solid (10.3 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 5H), 7.00 (d, J= 7.6 Hz, 1H), 6.87 (t, 1H), 6.63 (m, 1H), 4.91 (s, 2H), 3.63 (s, 2H); MS ESI 241.9 $[M + H]^+$, calcd for $[C_{15}H_{10}FNO_2 + H]^+$ 241.09.

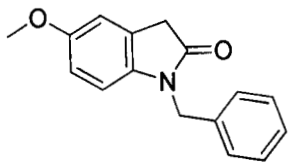
Synthesis of 1-Benzyl-5-methylindolin-2-one



[00141] To a mixture of 5-methylisatin (8.05 g, 50 mmol) and K_2CO_3 (8.16 g, 60 mmol) in DMF (100 mL) was added BnBr (6.5 mL, 55 mmol) dropwise over 2 min. After addition, the resulting mixture was heated in an oil bath at 75 °C for 1.5 h. After cooling to rt, the reaction mixture was poured onto ice/cold water (250 mL), rinsed with H_2O (50 mL) and stirred for 5 min. The resulting precipitates were collected by suction filtration and air dried to give 1-benzyl-5-methylisatin as dark red solid. MS ESI 252.0 $[M + H]^+$, calcd for $[C_{16}H_{13}NO_2 + H]^+$ 252.1.

[00142] 1-Benzyl-5-methylisatin was suspended in DMSO (100 mL) and cooled to 0 °C. Hydrazine hydrate (5 mL) was added dropwise over 5 min. After addition, the resulting clear red solution was heated at 120 °C for 2 h then 140 °C for 5 h. After cooling to rt, it was poured into a 1L Erlenmeyer flask, rinsed with H_2O (50 mL) and ice was added until a total volume about 300 mL. 2 M HCl (50 mL) was added and the mixture was extracted with EtOAc (200 mL x 2, then 100 mL), and the organic layer was dried (Na_2SO_4). Removal of solvents followed by drying under high vacuum for 2 days gave the title compound as a dark red solid (12.53 g, quantitative yield over 2 steps, contained some DMSO residue). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5H), 7.09 (s, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 4.91 (s, 2H), 3.60 (s, 2H), 2.31 (s, 3H); MS ESI 238.0 $[M + H]^+$, calcd for $[C_{16}H_{15}NO + H]^+$ 238.1.

Synthesis of 1-Benzyl-5-methoxyindolin-2-one

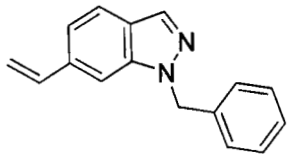


[00143] A stirred solution of 5-methoxyisatin (5.0 g, 28 mmol) in dry DMF (40 mL) was cooled in an ice bath before addition of sodium hydride (60 wt% in mineral oil, 1.7 g, 42 mmol) slowly, the dark red solution turning quickly black. After stirring for 20 min, BnBr (3.7 mL, 31 mmol) was added to the reaction mixture by syringe and the resulting mixture was stirred for 1 h. Water (150 mL) was added with stirring, and the resulting dark red precipitate collected by filtration and washed with water to give 1-benzyl-5-methoxyindoline-2,3-dione as a dark red solid (6.1 g, 81%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H), 7.17 (s, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 8.6 Hz, 1H), 4.92 (s, 2H), 3.79 (s, 3H). MS ESI 268.1 $[M + H]^+$, calcd for $[C_{16}H_{13}NO_3 + H]^+$ 268.09.

[00144] A solution of 1-benzyl-5-methoxyindoline-2,3-dione (6.1 g, 23 mmol) and hydrazine hydrate (50-60% grade, 2.9 mL, *ca.* 2 eq) in DMSO (15 mL) is heated to 140 °C in an oil bath. After 3 h, the mixture was cooled, diluted with water and EtOAc, the layers separated and the aqueous extracted with EtOAc three times (30 mL). The combined organic portions were washed with 2M H_2SO_4, brine, and dried over $MgSO_4$, filtered and concentrated to afford the crude product as a viscous brown oil. The crude product was purified by silica gel chromatography (20-50% EtOAc in hexane) to yield the title compound as a brown oil (5.0 g, 85%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H),

6.89 (s, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 4.91 (s, 2H), 3.76 (s, 3H), 3.62 (s, 2H). MS ESI 254.0 $[M + H]^+$, calcd for $[C_{16}H_{15}NO_2+ H]^+$ 254.1.

Synthesis of N1-Benzyl-6-vinyl-1H-indazole



[00145] Method 1: A mixture of N1-Benzyl-6-bromo-1H-indazole (10.2 g, 35.5 mmol) and NaOH (4.3 g, 107 mmol) in THF/water (9:1, 350 mL) was purged with nitrogen. In a separate flask, $Pd(OAc)_2$ (0.16 g, 0.7 mmol, 2 mol%) and PPh_3 (0.37 g, 1.4 mmol, 4 mol%) were stirred together in nitrogen-purged dry THF (35 mL) for 10 min, forming a red solution with some suspended solids. Vinylboronic acid pinacol ester (7.5 mL, 44.4 mmol) and the catalyst solution were added to the reaction mixture, and the resulting solution purged once more with nitrogen. The mixture was warmed in an oil bath set to 65 °C; TLC indicated consumption of starting material within 7 h. The mixture was concentrated under reduced pressure to remove most of the THF, then diluted with water (50 mL), brine (50 mL) and EtOAc (250 mL). The layers were separated and the aqueous phase extracted with further EtOAc (4 x 50 mL). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered and concentrated (at 70 °C/20 mbar) to afford the crude product. This was chromatographed on silica using 10-20% EtOAc in cyclohexane to afford the title compound (7.5 g, 90%) as a yellow oil that solidified on standing. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.29 – 7.19 (m, 5H), 7.18 – 7.13 (m, J = 7.0 Hz, , 2H), 6.75 (dd, J = 17.6, 10.9 Hz, 1H), 5.76 (d, J = 17.5 Hz, 1H), 5.53 (s, 2H), 5.26 (d, J = 10.9 Hz, 1H). MS (ES+): 235 ([M+H]+); calcd for $[C_{16}H_{14}N_2+ H]^+$ 235.1.

[00146] Method 2: using 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane: A mixture of N1-Benzyl-6-bromo-1H-indazole (1.44 g, 5.0 mmol) and NaOH (0.4 g, 10.0 mmol) in THF/water (5:1, 15 mL) was purged with nitrogen. In a separate flask, $Pd(OAc)_2$ (11 mg, 0.05 mmol, 1 mol%) and PPh_3 (26 mg, 0.1 mmol, 2 mol%) were stirred together in nitrogen-purged THF (2.5 mL) for 10 min, forming a red solution with some suspended solids. The THF used was of HPLC grade and inhibitor free; the effect of lower grade or stabilized THF is not known. 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (1.12 mL, 6.5 mmol) and the catalyst solution were added to the reaction mixture, and the resulting solution purged once more with nitrogen. The mixture was warmed in an oil bath set to 65 °C; heating was continued for 24 h but the reaction is probably complete in fewer than 8 h.

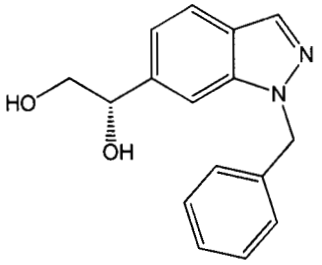
The crude mixture was then combined with a second, parallel reaction of the same scale where higher dilution had been used. The mixture was concentrated under reduced pressure to remove most of the THF, then diluted with water, brine and cyclohexane. The layers were separated and the aqueous phase extracted with further cyclohexane until TLC indicated all the desired product had been extracted (3-4 extracts). The combined organic portions were washed with brine, dried over $MgSO_4$, and then passed through a 1 cm pad of silica to remove baseline material. Any product remaining on the silica was eluted using 10% EtOAc in cyclohexane (Rf. 0.15 in this eluent). The combined eluate was concentrated to afford the title compound (2.05 g, 88%) as a yellow oil that solidified on standing and was of sufficient purity to use in subsequent reactions.

[00147] Method 3: N1-Benzyl-6-bromo-1H-indazole (half of the crude material obtained in method 3 above) was processed in two batches as follows: a mixture of crude N1-Benzyl-6-bromo-1H-indazole (153 g, containing a maximum of 0.5 mol assuming 100% yield in benzylation/equilibration) and NaOH (40 g, 1.0 mol) in THF/water (5:1, 1.5 L; HPLC grade inhibitor-free THF) was purged with nitrogen. In a separate flask, $Pd(OAc)_2$ (1.13 g, 5.0 mmol, 1 mol%) and PPh_3 (2.6 g, 10.0 mmol, 2 mol%) were stirred together in nitrogen-purged THF (250 mL) for 10 min, forming a red solution with some suspended solids. 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (112 mL, 0.65 mol) and the catalyst solution were added to the reaction mixture, and the resulting solution purged once more with nitrogen. The mixture was heated overnight in an oil bath set to 60 °C. ^1H NMR of a sample indicated that some starting material remained, and so additional vinyl donor (30 mL) was added to push to completion. Both batches of mixture were combined and the mixture was concentrated under reduced pressure to remove most of the THF, then diluted with water, brine and cyclohexane. The layers were separated and the aqueous phase extracted with further cyclohexane until TLC indicated all of the desired product had been extracted (total 3.5 L cyclohexane). The combined organic portions were washed with brine, dried over $MgSO_4$, and then passed through a 2 cm pad of silica to remove baseline material. Any product remaining on the silica was eluted using 10% EtOAc in cyclohexane (Rf. 0.15 in this eluent). The combined eluate was concentrated to afford 309 g of a crude oil comprising the title compound, a little of the diol derived from the vinyl donor, and a number of benzyl-containing impurities.

[00148] Method 4: A further reaction carried out using distilled N1-Benzyl-6-bromo-1H-indazole (64.3 g, 0.144 moles) afforded full conversion without the need for additional

portion of vinyl donor, and gave semi-crude N1-Benzyl-6-vinyl-1H-indazole (55.5 g, quantitative) which was used without further purification below.

Synthesis of (S)-1-(N1-Benzyl-1H-indazol-6-yl)-ethane-1,2-diol



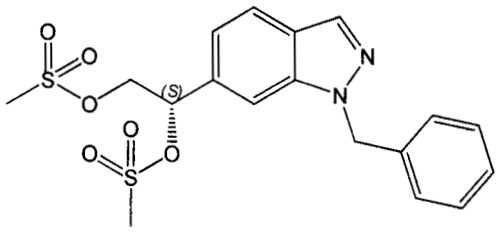
[00149] Method 1: $K_3Fe(CN)_6$ (16.7 g, 51.0 mmol), K_2CO_3 (7.05 g, 51.0 mmol), $(DHQ)_2PHAL$ (0.13 g, 0.17 mmol, 1 mol%) and $K_2OsO_4.2H_2O$ (12.8 mg, 0.034 mmol, 0.2 mol%) were placed in a roundbottomed flask. A mixture of ^{t}BuOH and water (1:1, 160 mL) was added, forming a clear, biphasic mixture on stirring. The mixture was cooled in an ice bath, resulting in partial precipitation, before addition of powdered N1-benzyl-6-vinyl-1H-indazole (4.0 g, 17.1 mmol). The resulting mixture was vigorously stirred in the ice bath for 5 h, at which point no further solid was visible and TLC indicated consumption of starting material. The reaction was quenched by addition of sodium metabisulfite (40 g), with the resulting effervescence causing the reaction mixture to overspill into the ice bath. The remaining material was added to the ice bath and the resulting mixture (containing approximately 1 L of water and ice) was stirred overnight, warming slowly. Celite and CH_2Cl_2 (200 mL) were added, the mixture thoroughly stirred and then filtered. The solids were washed thoroughly with further CH_2Cl_2 (2 x 50 mL). The biphasic filtrate was separated, and the aqueous layer extracted with $CHCl_3$ (4 x 50 mL). The combined organic portions were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was taken up in EtOAc and filtered through a pad of silica (1 cm depth x 8 cm diameter), eluting with further EtOAc, to remove baseline material. The eluate was concentrated and stripped with toluene to remove traces of ^{t}BuOH. Finally, the residue was recrystallized from hot toluene (10 mL/g) to afford the title compound as white needles (3.87 g, 84%, 98.8%ee) with the major (S) enantiomer eluting at 16.8 min (Daicel Chiralpak IB (250 x 4.6 mm); isocratic 10% EtOH in n-heptane; 1 mL/min; ambient temperature (ca. 22 °C); Detection: 254, 230, 210 nm); From the racemic reference standard, the retention time of the (R) enantiomer was 14.8 min using this method and N1-benzyl-6-vinyl-1H-indazole eluted at 5.4 min. ^{1}H NMR and mass spectral data were identical to racemic 1-(1-Benzyl-

1H-indazol-6-yl)-ethane-1,2-diol obtained above. Optical Rotation: $[\alpha]^{22}_D = 13°$ (c 1.018, MeOH).

[00150] Method 2: Semi-crude N1-Benzyl-6-vinyl-1H-indazole (Method 4 above, 55.5 g) was dihydroxylated in a similar manner to afford, after recrystallization to obtain 2 crops of solid, pure (S)-1-(N1-Benzyl-1H-indazol-6-yl)-ethane-1,2-diol (38 g, quantitative).

[00151] Method 3: $K_3Fe(CN)_6$ (0.98 kg, 3 mol), K_2CO_3 (0.55 kg, 3 mol), $(DHQ)_2PHAL$ (3.9 g, 5.0 mmol) and $K_2OsO_4.2H_2O$ (0.37 g, 1 mmol) were placed in a 10 L clamp-top reaction vessel equipped with overhead stirrer. A mixture of ^{t}BuOH and water (1:1, 7.5 L) was added, forming a clear, biphasic mixture on stirring. The mixture was cooled using a Haake EK90 chiller, resulting in partial precipitation, before addition of crude N1-benzyl-6-vinyl-1*H*-indazole (*ca.* 0.7-0.8 mol). The resulting mixture was vigorously stirred, but set solid as insufficient space was available for proper circulation in the cooling bath and the actual temperature dropped to around –20 °C when left over the weekend. Little conversion was evident. To speed up the reaction, further $(DHQ)_2PHAL$ (2.5 mmol) and $K_2OsO_4.2H_2O$ (0.5 mmol) were added, and the mixture let warm to approx. 10 °C; the reaction then proceeded satisfactorily. The reaction was quenched by portion-wise addition of sodium metabisulfite (1.5 kg). The mixture was stirred for 1 h at rt, becoming almost clear, then filtered through a pad of celite to remove precipitated OsO_2. The filtrate was extracted with CH_2Cl_2 (4 extracts, final volume 7 L), and the combined organic portions dried over $MgSO_4$, filtered and concentrated. The crude product was recrystallized from hot toluene (10 mL/g); two crops of the title compound were collected, of 98.7% and 98.0% e.e., totalling 163.7 g (55% from 6-bromo-1H-indazole).

Synthesis of (S)-Methanesulfonic acid 2-(N1-benzyl-1H-indazol-6-yl)-2-methanesulfonyloxy-ethyl ester

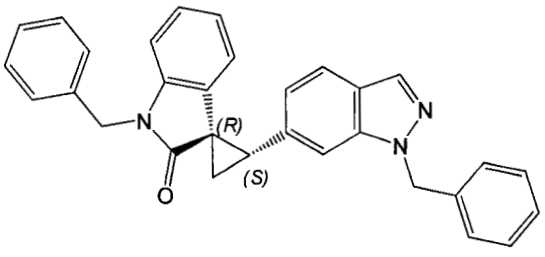


[00152] Method 1: A solution of (S)-1-(N1-Benzyl-1H-indazol-6-yl)-ethane-1,2-diol (3.75 g, 14.0 mmol, 98.8%ee) and Et_3N (4.9 mL, 35.0 mmol) in dry CH_2Cl_2 (350 mL) was cooled in an ice bath before dropwise addition of MsCl (2.17 mL, 28.0 mmol) over 10 min. The resulting mixture was left to stir for 30 min. After dilution with further CH_2Cl_2 (250

mL), the solution was washed with cold 1.0 M aq. HCl (2 x 50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), then dried over Na_2SO_4. The solution was poured onto a short silica pad (1 cm depth x 8 cm diameter) under suction. The initial filtrate did not contain any of the product; this was subsequently eluted with 1:1 Et_2O/CH_2Cl_2. The eluate was concentrated under reduced pressure to afford the title compound (5.98 g, ~quant.) as a white solid. ^1H NMR and mass spectral data were identical to racemic methanesulfonic acid 2-(1-benzyl-1H-indazol-6-yl)-2-methanesulfonyloxy-ethyl ester obtained above. The e.e. of this batch of material was not determined at this stage but was carried forward to the next step. Optical Rotation: $[\alpha]^{22}_D = 58°$ (c 0.73, $CHCl_3$).

[00153] Method 2: A solution of (S)-1-(N1-benzyl-1H-indazol-6-yl)-ethane-1,2-diol (134 g, 0.5 mol, ~98% e.e.) and Et_3N (174 mL, 1.25 mol) in CH_2Cl_2 (2.5 L) was cooled in an ice bath before slow addition of MsCl (81.3 mL, 1.05 mol) over approx. 1 h. The internal temperature increased to a maximum of 11 °C. The resulting mixture was left to stir for 30 min. The reaction was quenched with cold 1.0 M aq. HCl (400 mL), the phases separated, and the organic phase washes with further cold 1.0 M aq. HCl, aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. The solution was poured onto a short silica pad under suction. Some of the product eluted from the silica during this filtration, and the remainder was eluted using 1:1 Et_2O/CH_2Cl_2 (2 L). The eluate was concentrated under reduced pressure to afford a hard white solid. This was triturated with Et_2O (800 mL) overnight. The fine white powder was collected by filtration and washed with further Et_2O (2 x 100 mL) to yield the title compound (184.2 g, 87%, 99% e.e.) with the major (S) enantiomer eluting at 13.4 min (Daicel Chiralpak IB (250 x 4.6 mm); isocratic 30% EtOH in n-heptane; 1 mL/min; ambient temperature (ca. 22 °C); Detection: 254, 230, 210 nm); From the racemic reference standard, the retention time of the (R) enantiomer was 14.4 min using this method. The filtrate contained only a small quantity of product of low e.e. and was discarded.

Synthesis of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one

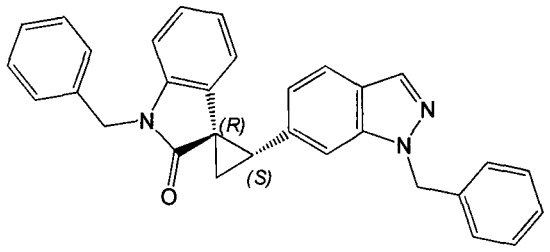


[00154] Method 1: A solution of N-benzyl-oxindole (3.57 g) in dry THF (120 mL) was cooled in an ice bath before addition of NaH (60 wt% in mineral oil, 1.92 g, 48.0 mmol) in four portions; the solution quickly became a deep purple. After 30 min, a solution of (S)-methanesulfonic acid 2-(N1-benzyl-1H-indazol-6-yl)-2-methanesulfonyloxy-ethyl ester (6.79 g, 16.0 mmol, ~98.5%ee, previously stripped twice with dry THF) in dry THF (80 mL) was added by syringe pump over a period of 1 h. TLC indicated rapid conversion to a single compound with Rf 0.45 (25% EtOAc in cyclohexane, eluted twice; starting materials Rf 0.5 & Rf 0.2). After stirring for 2 h, the mixture was poured into sat. aq. NH_4Cl (50 mL), diluted with water (50 mL), and EtOAc (100 mL). The phases were separated and the aqueous layer extracted with further portions of EtOAc (4 x 50 mL). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford a crude product that, by ^1H NMR, appeared to consist almost exclusively of the title compound. The crude product was passed through a short silica pad (1 cm depth x 5 cm diameter), eluting with 1:1 EtOAc in cyclohexane. The residue was triturated with n-heptane (3 x 50 mL) to remove mineral oil, and stripped with toluene to afford the title compound (7.0 g, up to 90% yield) as a glassy solid that contained some solvent. HPLC indicated an optical purity of 98% e.e. with the major (1R,2S) enantiomer eluting at 13.3 min (Daicel Chiralpak IA, 250 x 4.6 mm; isocratic 10% EtOH in n-heptane; 1 mL/min; ambient temperature (ca. 22 °C); Detection: 254, 230, 210 nm); From the racemic reference standard, the retention time of the (1S,2R) enantiomer was 12.1 min using this method. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.36 – 7.20 (m, 8H), 7.19 (s, 1H), 7.15 – 7.10 (m, J = 6.4 Hz, 2H), 6.99 (td, J = 7.8, 0.9 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.50 (t, J = 7.4 Hz, 1H), 5.76 (d, J = 7.3 Hz, 1H), 5.61 (d, J = 15.8 Hz, 1H), 5.53 (d, J = 15.8 Hz, 1H), 5.08 (d, J = 15.6 Hz, 1H), 4.97 (d, J = 15.7 Hz, 1H), 3.48 (t, J = 8.5 Hz, 1H), 2.28 (dd, J = 9.0, 4.5 Hz, 1H), 2.02 (dd, J = 8.0, 4.6 Hz, 1H). MS (ES+): 456 ($[M+H]^+$), calcd for $[C_{31}H_{25}N_3O + H]^+$ 456.2.

[00155] Method 2: In a separate set of individual experiments carried out in a similar manner as Method 1 but not performing any column chromatography, using between on 20-45g of (S)-methanesulfonic acid 2-(N1-benzyl-1H-indazol-6-yl)-2-methanesulfonyloxy-ethyl ester per batch, a total of 133.8g, 315 mmol was carried forward. Some batches were combined and passed through a silica plug to remove traces of baseline material before use, but this didn't seem to make any difference in subsequent reactions. The crude product was isolated as a foamy solid (174.1g, containing mineral oil from the sodium hydride accounting for approximately 10% of each crude product, as well as varying amounts of

EtOAc, estimated average yield >80% based on estimated individual batch purities). The material was carried forward without further purification.

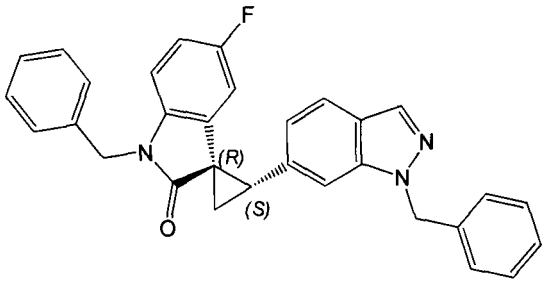
Synethsis of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



[00156] Method 1: A solution of N-benzyl-oxindole (3.57 g) in dry THF (120 mL) was cooled in an ice bath before addition of NaH (60 wt% in mineral oil, 1.92 g, 48.0 mmol) in four portions; the solution quickly became a deep purple. After 30 min, a solution of (S)-methanesulfonic acid 2-(N1-benzyl-1H-indazol-6-yl)-2-methanesulfonyloxy-ethyl ester (6.79 g, 16.0 mmol, ~98.5%ee, previously stripped twice with dry THF) in dry THF (80 mL) was added by syringe pump over a period of 1 h. TLC indicated rapid conversion to a single compound with Rf 0.45 (25% EtOAc in cyclohexane, eluted twice; starting materials Rf 0.5 & Rf 0.2). After stirring for 2 h, the mixture was poured into sat. aq. NH_4Cl (50 mL), diluted with water (50 mL), and EtOAc (100 mL). The phases were separated and the aqueous layer extracted with further portions of EtOAc (4 x 50 mL). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford a crude product that, by ^1H NMR, appeared to consist almost exclusively of the title compound. The crude product was passed through a short silica pad (1 cm depth x 5 cm diameter), eluting with 1:1 EtOAc in cyclohexane. The residue was triturated with n-heptane (3 x 50 mL) to remove mineral oil, and stripped with toluene to afford the title compound (7.0 g, up to 90% yield) as a glassy solid that contained some solvent. HPLC indicated an optical purity of 98% e.e. with the major (1R,2S) enantiomer eluting at 13.3 min (Daicel Chiralpak IA, 250 x 4.6 mm; isocratic 10% EtOH in n-heptane; 1 mL/min; ambient temperature (ca. 22 °C); Detection: 254, 230, 210 nm); From the racemic reference standard, the retention time of the (1S,2R) enantiomer was 12.1 min using this method. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.36 – 7.20 (m, 8H), 7.19 (s, 1H), 7.15 – 7.10 (m, J = 6.4 Hz, 2H), 6.99 (td, J = 7.8, 0.9 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.50 (t, J = 7.4 Hz, 1H), 5.76 (d, J = 7.3 Hz, 1H), 5.61 (d, J = 15.8 Hz, 1H), 5.53 (d, J = 15.8 Hz, 1H), 5.08 (d, J = 15.6 Hz, 1H), 4.97 (d, J = 15.7 Hz, 1H),

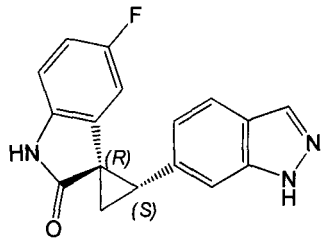
3.48 (t, J = 8.5 Hz, 1H), 2.28 (dd, J = 9.0, 4.5 Hz, 1H), 2.02 (dd, J = 8.0, 4.6 Hz, 1H). MS (ES+): 456 ([M+H]$^+$), calcd for [$C_{31}H_{25}N_3O$ + H]$^+$ 456.2.

Synthesis of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)-5'-fluorospiro[cyclopropane-1,3'-indolin]-2'-one



[00157] The title compound was prepared in a manner similar to the method of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one using (S)-1-(1-benzyl-1H-indazol-6-yl)ethane-1,2-diyl dimethanesulfonate (501.4 mg, 1.181 mmol) and 1-benzyl-5-fluoroindolin-2-one (285.0 mg, 1.181 mmol). Purification using Biotage Isolera (SNAP 25g column, 25-100% EtOAc in hexane) yielded the title compound as a cream solid (352 mg, 63%; 97%ee) with the major (1R,2S) enantiomer eluting at 7.03 min (Phenomenex Lux 5μ Cellulose-1 (150 x 4.6 mm), 1.0 mL/min isocratic at 80% EtOH in hexane for 1.0 min, then gradient 80-90% EtOH in hexane over 10 min). From the racemic reference standard, the retention time of the (1S,2R) enantiomer was 5.95 min using this method. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.40-7.27 (m, 8H), 7.17 (s, 1H), 7.11 (d, J = 7.2 Hz, 2H), 6.92 (d, J = 8.4 Hz, 1H), 6.67-6.62 (m, 2H), 5.62 (d, J = 15.6 Hz, 1H), 5.55 (d, J = 15.6 Hz, 1H), 5.51 (t, J = 6.0 Hz, 1H), 5.10 (d, J = 15.6 Hz, 1H), 4.94 (d, J = 16.0 Hz, 1H), 3.53 (t, J = 8.4 Hz, 1H), 2.32 (dd, J = 9.2, 4.4 Hz, 1H), 2.02 (dd, J = 8.0, 3.2 Hz, 1H), MS ESI 474.3 [M + H]$^+$, calcd for [$C_{31}H_{24}FN_3O$+ H]$^+$ 474.2.

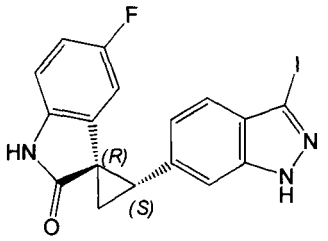
Synthesis of (1R,2S)-5'-fluoro-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



[00158] The title compound was prepared in a manner similar to the chiral synthetic method of Example A4 using (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)-5'-fluorospiro [cyclopropane-1,3'-indolin]-2'-one (560 mg, 1.18 mmol). Purification by using

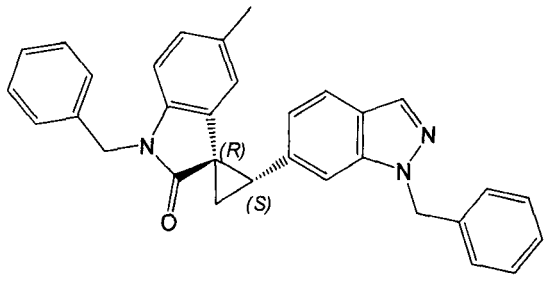
silica gel column chromatography with 5-95% EtOAc in hexane to give the title compound as a creamy solid (179 mg, 52%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.62-7.46 (m, 2H), 6.94 (d, J = 8.4 Hz, 1H), 6.88 (t, J = 4.8 Hz, 1H), 5.69 (d, J = 9.2 Hz, 1H), 3.39 (t, J = 8.0 Hz ,1H), 2.30-2.71 (m, 1H), 2.23-2.18 (m, 1H); MS ESI 294.1 $[M + H]^+$, calcd for $[C_{17}H_{12}FN_3O+ H]^+$ 294.10.

Synthesis of (1R,2S)-5'-fluoro-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



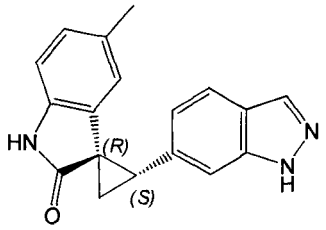
[00159] The title compound was prepared in a manner similar to the chiral synthetic method of Example A10 using (1R,2S)-5'-fluoro-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (240 mg, 0.818 mmol). Purification using Biotage Isolera with SNAP 25g column with 5-90% EtOAc in hexane yielded the title compound as a cream solid (195 mg, 57%; 97%ee) with the major (1R,2S) enantiomer eluting at 3.7 min (Phenomenex Lux 5μ Cellulose-2 (150 x 4.6 mm); isocratic 25% EtOH in n-hexane; 1.5 mL/min; 24 °C; Detection: 254 nm). From the racemic reference standard, the retention time of the (1S,2R) enantiomer was 3.2 min using this method. ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.88 (dd, J = 8.8, 4.4 Hz, 1H), 6.79 (t, J = 8.8 Hz, 1H), 5.69 (d, J = 8.4 Hz, 1H), 3.38 (t, J = 8.8 Hz ,1H), 2.28 (dd, J = 8.8, 4.2 Hz, 1H), 2.21 (dd, J = 9.2, 4.4 Hz, 1H); MS ESI 420.0 $[M + H]^+$, calcd for $[C_{17}H_{11}FIN_3O+ H]^+$ 420.0.

Synthesis of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)-5'-methylspiro [cyclopropane-1,3'-indolin]-2'-one



[00160] To a 250 mL round bottom flask charged with 60% NaH (1.20 g, 30 mmol) was added anhydr. THF (20 mL) and the resulting mixture was cooled to 0 °C. A solution of 1-benzyl-5-methylindolin-2-one (2.37 g, 10 mmol) in dry THF (25 mL) was added over 2 min, followed by rinsing with THF (5 mL). After stirring for 20 min at 0 °C, a solution of (S)-1-(1-benzyl-1H-indazol-6-yl)ethane-1,2-diyl dimethanesulfonate (4.24 g, 10 mmol) in dry THF (45 mL) was added dropwise through dropping funnel over 40 min, followed by rinsing with THF (5 mL). After addition, the resulting mixture was stirred for 30 min at 0 °C (TLC showed completion) then left O/N at rt. After cooling to 0 °C, the reaction mixture was poured into an Erlenmeyer flask containing ice (100 mL) and sat. NH_4Cl (30 mL) and extracted with EtOAc (150 mL x 2), dried (Na_2SO_4). After removal of solvents, the residue was transferred to a 100 mL RBF using 30 mL of EtOAc and cyrstals formed. Suction filtration gave the title compound as a beige solid (1.537 g). The filtrate was concentrated and purified by Biotage Isolera (20-30% EtOAc in hexane) and triturated with EtOAc/hexane to give 2nd crop as off white solid (1.560 g). The filtrate was purified using the above procedure to give 3rd crop as a beige solid (115 mg). Total 3.212 g (68%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.36-7.20 (m, 9H), 7.14 (d, J = 6.0 Hz, 2H), 6.94 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 7.2 Hz, 1H), 5.62 (d, J = 16.8 Hz, 1H, partially overlapping with s at 5.59), 5.59 (s, 1H, partially overlapping with d at 5.62), 5.55 (d, J = 16.8 Hz, 1H), 5.08 (d, J = 16.0 Hz, 1H), 4.97 (d, J = 15.6 Hz, 1H), 3.48 (t, J =8.4 Hz, 1H), 2.30-2.25 (m, 1H), 2.02-1.96 (m, 1H), 1.85 (s, 3H) ; MS ESI 470.3 $[M + H]^+$, calcd for $[C_{32}H_{27}N_3O + H]^+$ 470.2.

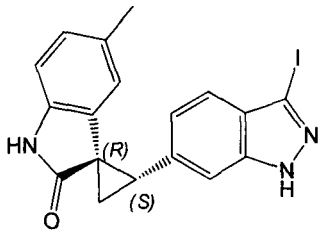
Synthesis of (1R,2S)-2-(1H-indazol-6-yl)-5'-methylspiro[cyclopropane-1,3'-indolin]-2'-one



[00161] To a 100 mL flask charged with (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)-5'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (469 mg, 1 mmol) was added dry THF (2 mL) and the resulting mixture was stirred at 0 °C before KO^tBu (1 M in THF, 18 mL, 18 mmol) was added over 2 min. After addition, the resulting mixture was stirred for 15 min at 0 °C and DMSO (1.85 mL) was added. Oxygen was bubbled through for 1 h and reaction turned from homogeneous to heterogeneous. LC-MS showed good conversion at 50 min. It was quenched with sat. NH_4Cl.

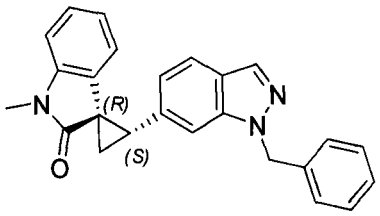
[00162] The above reaction was repeated on a larger scale using (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)-5'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (1.41 g, 3 mmol). After quenching with saturated NH_4Cl, two reactions were combined, diluted with H_2O and extracted with EtOAc (100 mL x 2). Purifcation by Biotage Isolera (10-95% EtOAc in hexane) gave the title compound as a light solid (680 mg, 53%). ^1H NMR (400 MHz, CD_3OD) δ 8.02 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.46 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 5.78 (s, 1H), 3.32 (t, overlapping with MeOH residue), 2.20-2.12 (m, 2H), 1.87 (s, 3H); MS ESI 290.1 $[M + H]^+$, calcd for $[C_{18}H_{15}N_3O + H]^+$ 290.1.

Synthesis of (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methylspiro[cyclopropane-1,3'-indolin]-2'-one



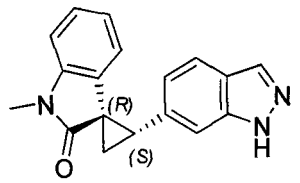
[00163] To a solution of (1R,2S)-2-(1H-indazol-6-yl)-5'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (680 mg, 2.35 mmol) in DMF (16 mL) was added K_2CO_3 (544 mg, 4 mmol), followed by iodine (851 mg, 3.2 mmol). The resulting mixture was stirred for 3 h at rt, cooled to 0 °C, quenched with sat. $Na_2S_2O_3$, diluted with H_2O, extracted with EtOAc (50 mL x 3) and dried (Na_2SO_4). Evaporation of solvents and purification by Biotage Isolera (EtOAc/hexane gradient: 10-90%) gave the title compound as a light yellow solid (794 mg, 81%; >98 % e.e.). The major (1R,2S)-enantiomer eluted at 9.6 min (Phenomenex Lux 5u Cellulose-2 (150 x 4.6 mm); isocratic 10% EtOH in n-hexane 1.75 L/min; ambient temperature; Detection: 254, 214 nm). From the racemic reference standard, the retention time of the (1S,2R)-enantiomer was 7.7 min using this method. ^1H NMR (400 MHz, DMSO-d6) δ 13.46 (s, 1H), 10.51 (s, 1H), 7.47 (s, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 5.86 (s, 1H), 3.16 (t, overlapping with trace MeOH residue), 2.32-2.25 (m, 1H), 2.00-1.93 (m, 1H), 1.85 (s, 3H); MS ESI 416.0 $[M + H]^+$, calcd for $[C_{18}H_{14}IN_3O + H]^+$ 416.0.

Synthesis of (1R,2S)-2-(1-benzyl-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one



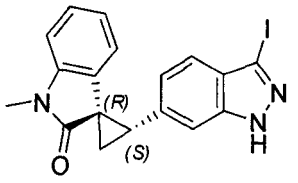
[00164] The title compound was prepared in a manner similar to the method of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one using (S)-1-(1-benzyl-1H-indazol-6-yl)ethane-1,2-diyl dimethanesulfonate (6.70 g, 15.8 mmol) and 1-methylindolin-2-one (2.33 g, 15.8 mmol). Purification via column chromatography (silica gel, 25-50% EtOAc in hexane) yielded the title compound as a pale-orange crystalline solid (5.01 g, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.30-7.25 (m, 3H), 7.18 (s, 1H), 7.13-7.10 (m, 3H), 6.92 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.55 (t, J = 7.0 Hz, 1H), 5.76 (d, J = 7.2 Hz, 1H), 5.63-5.49 (m, 2H), 3.41 (t, J = 8.8 Hz, 1H), 3.33 (s, 3H), 2.22-2.18 (m, 1H), 2.00-1.96 (m, 1H); MS ESI 380.2 $[M + H]^+$, calcd for $[C_{25}H_{21}N_3O + H]^+$ 380.18.

Synthesis of (1R,2S)-2-(1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one



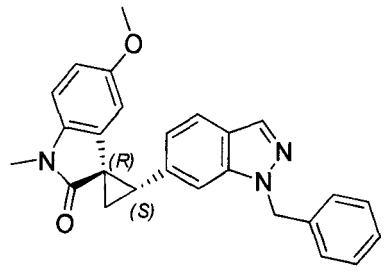
[00165] The title compound was prepared in a manner similar to the chiral synthetic method of Example A4 using (1R,2S)-2-(1-benzyl-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (1.16 g, 3.06 mmol). Purification via column chromatography (silica gel, 3-6% MeOH in CH_2Cl_2) yielded the title compound as a pale-yellow solid (656 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (br. s, 1H), 8.05 (s, 1H), 7.64 (d, 1H, J = 7.6 Hz), 7.36 (s, 1H), 7.14 (t, J = 8.7 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 6.62 (t, J = 7.6 Hz, 1H), 5.91 (d, J = 7.9 Hz, 1H), 3.46 (t, J = 7.8 Hz, 1H), 3.34 (s, 3H), 2.26-2.23 (m, 1H), 2.08-2.04 (m, 1H); MS ESI 290.1 $[M + H]^+$, calcd for $[C_{18}H_{15}N_3O+ H]^+$ 290.13.

Synthesis of (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one



[00166] The title compound was prepared in a manner similar to the chiral synthetic method of Example A10 using (1R,2S)-2-(1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (930 mg, 3.21 mmol). Precipitation with EtOAc followed by filtration and rinsing with EtOAc gave the title compound (970 mg, 73 %; >98 %ee) with the major enantiomer eluting at 2.4 min (Phenomenex Lux 5μ Amylose-2 150 x 4.6 mm, 2.5 mL/min with isocratic at 20% EtOH in hexane for 0.5 min, then gradient 20-50% EtOH in hexane over 2.5 min, then isocratic at 50% for 1 min). From the racemic reference standard, the retention time of the (1S,2R) enantiomer was 3.0 min using this method. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (br. s, 1H), 7.43-7.39 (m, 2H), 7.16 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.66 (t, J = 7.2 Hz, 1H), 5.91 (d, J = 8.0 Hz, 1H), 3.47 (t, J = 8.4 Hz, 1H), 3.35 (s, 3H), 2.30-2.26 (m, 1H), 2.08-2.04 (m, 1H); MS ESI 416.0 [M + H]$^+$, calcd for $[C_{18}H_{14}IN_3O+ H]^+$ 416.03. Optical Rotation: $[\alpha]^{23}_D$ = -210 ° (c 0.4, MeOH).

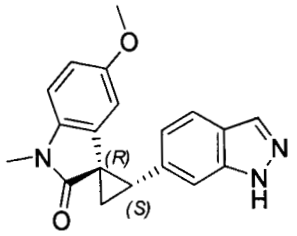
Synthesis of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)-5'-methoxy-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one



[00167] The title compound was prepared in a manner similar to the method of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one using (S)-1-(1-benzyl-1H-indazol-6-yl)ethane-1,2-diyl dimethanesulfonate (1.44 g, 3.39 mmol) and 5-methoxy-1-methylindolin-2-one (0.601 g, 3.39 mmol). Purification using Biotage Isolera (1-50% EtOAc in hexane, SNAP 25g column) yielded the title compound (light brown solid, 1.05 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H) , 7.67 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.26-7.23 (m, 3H), 7.11 (d, J = 7.6 Hz, 2H), 6.95 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.63 (d, J = 16.4 Hz, 1H), 5.58 (d, J = 16.0 Hz, 1H), 5.41 (s, 1H), 3.37 (t, J = 8.8 Hz, 1H), 3.15 (s, 3H), 2.23-2.19 (m, 1H), 2.18-2.14 (m, 1H), -OCH_3

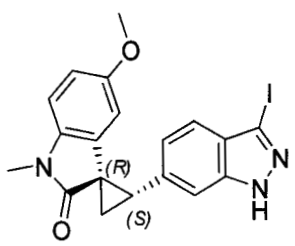
proton is obscured by methanol peak. MS ESI 410.2 $[M + H]^+$, calcd for $[C_{26}H_{23}N_3O_2 + H]^+$ 410.2.

Synthesis of (1R,2S)-2-(1H-indazol-6-yl)-5'-methoxy-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one



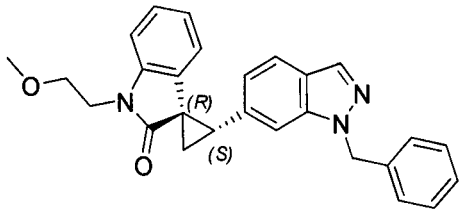
[00168] A solution of potassium-t-butoxide (1M, 19.23 mL, 0.19 mol) was added to a solution of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)-5'-methoxy-1'-methylspiro [cyclopropane-1,3'-indolin]-2'-one (0.875 g, 2.1 mmol) in anhydrous THF (2.62 mL) at 0°C and the mixture was stirred for 15 min at the same temperature. Then anhydrous DMSO (1.97 mL, 27 mmol) was added via syringe to the mixture at 0°C and stirring was continued for 5 min. The reaction mixture was purged O_2 gas for 1.5 hr at 0°C. After stirring at 0°C for a further 15 min, the reaction mixture was quenched with 25% aq. NH_4Cl (20 mL). The product was extracted using EtOAc (40 mL x 2), and the combined EtOAc layer was washed with water (10 mL) and dried (Na_2SO_4) and concentrated under vacuum at 40°C/125 mbar. The resultant pale yellow residue was purified by silica gel column chromatography using 5-10% EtOAc in hexane to give the title compound as an off-white solid (445 mg, 65%). ^1H NMR (400 MHz, CD_3OD) δ 8.02 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.47 (s, 1H), 6.95-6.90 (m, 2H), 6.68 (d, J = 8.8 Hz, 1H), 5.58 (s, 1H), 3.38 (t, J = 8.4 Hz, 1H), 3.20 (s, 3H), 2.28 (dd, J = 9.2, 4.4 Hz, 1H), 2.06 (dd, J = 8.4, 4.8 Hz, 1H), $-OCH_3$ proton is merged with Methanol peak. MS ESI 320.1 $[M + H]^+$, calcd for $[C_{19}H_{17}N_3O_2 + H]^+$ 320.2.

Synthesis of (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxy-1'-methylspiro [cyclopropane-1,3'-indolin]-2'-one



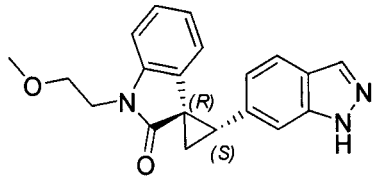
[00169] In a manner similar to the chiral synthetic method of Example A10 using (1R,2S)-2-(1H-indazol-6-yl)-5'-methoxy-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (1.34 g, 4.19 mmol), the title compound was obtained as a cream color solid (1.71 g, 91%; 98 %ee) with the major (1R,2S) enantiomer eluting at 2.6 min (Phenomenex Lux 5μ Amylose-2 150 x 4.6 mm, 2.5 mL/min with isocratic at 20% EtOH in hexane for 0.5 min, then gradient 20-50% EtOH in hexane over 2.5 min, then isocratic at 50% for 1 min). From the racemic reference standard, the retention time of the (1S,2R) enantiomer was 3.25 min using this method. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 5.53 (s, 1H), 3.46 (t, J = 8.0 Hz, 1H), 3.38 (s, 3H), 3.32 (s, 3H), 2.24 (dd, J = 8.4, 4.8 Hz, 1H), 2.04 (dd, J = 12.4, 4.8 Hz, 1H); MS ESI 446.1 $[M + H]^+$, calcd for $[C_{19}H_{16}IN_3O_2 + H]^+$ 446.0. Optical Rotation: $[\alpha]^{22}_D$ = -134° (c 0.238, MeOH).

Synthesis of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)-1'-(2-methoxyethyl)spiro[cyclopropane-1,3'-indolin]-2'-one



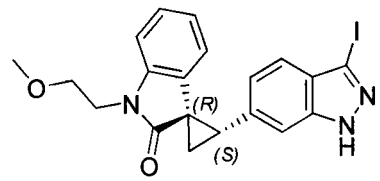
[00170] The title compound was prepared in a manner similar to the method of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one using (S)-1-(1-benzyl-1H-indazol-6-yl)ethane-1,2-diyl dimethanesulfonate (1.22 g, 2.87 mmol) and 1-(2-methoxyethyl)indolin-2-one (550.0 mg, 2.87 mmol). Purification on Biotage Isolera (0-60% EtOAc in hexane, SNAP 25g column) yielded the title compound as a pale brown solid (774 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.29-7.27 (m, 3H), 7.19 (s, 1H), 7.14-7.09 (m, 3H), 6.98 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.54 (t, J = 7.2 Hz, 1H), 5.75 (d, J = 7.6 Hz, 1H), 5.60 (t, J = 16.0 Hz, 1H), 5.51 (d, J = 16.0 Hz, 1H), 4.08-4.03 (m, 1H), 4.00-3.95 (m, 1H), 3.69 (t, J = 5.6 Hz, 2H), 3.43 (t, J = 8.0 Hz, 1H), 3.38 (s, 3H), 2.24 (dd, J = 9.2, 4.8 Hz, 1H), 2.00 (dd, J = 8.4, 5.6 Hz, 1H); MS ESI 424.2 $[M + H]^+$, calcd for $[C_{27}H_{25}N_3O_2 + H]^+$ 424.2.

Synthesis of (1R,2S)-2-(1H-indazol-6-yl)-1'-(2-methoxyethyl)spiro[cyclopropane-1,3'-indolin]-2'-one



[00171] A solution of KO^{t}Bu (1M, 11.97 mL, 11.9 mmol) was added to a solution of (1R,2S)-2-(1H-indazol-6-yl)-1'-(2-methoxyethyl)spiro[cyclopropane-1,3'-indolin]-2'-one (390 mg, 0.92 mmol) in anhydrous THF (1.95 mL) at 0°C and the mixture was stirred for 15 min at the same temperature. Then anhydrous DMSO (1.18 mL, 16.6 mmol) was added via syringe to the mixture in single lot at 0°C and stirring was continued for 5 min. Then, reaction mixture was purged with O_2 gas for 1.5 h at 0°C. After stirring at 0°C for a further 15 min, reaction mixture was quenched with 25% aq. NH_4Cl (10 mL). The product was extracted using EtOAc (20 mL x 2), and the combined EtOAc layer was washed with water (10 mL) and dried over an. sodium sulfate and concentrated under vacuum at 40°C/125 mbar. The resultant pale yellowish residue was purified by flash chromatography on Biotage Isolera (using 5-10% EtOAc in hexane, SNAP 25g column) to give the title compound as a white solid (205 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 8.0 Hz, 2H), 6.60 (t, J = 7.6 Hz, 1H), 5.90 (d, J = 7.2 Hz, 1H), 4.10-3.97 (m, 2H), 3.70 (t, J = 5.6 Hz, 2H), 3.47 (t, J = 8.4 Hz, 1H), 3.38 (s, 3H), 2.29 (dd, J = 8.8, 4.4 Hz, 1H), 2.08 (dd, J = 6.8, 4.4 Hz, 1H); MS ESI 334.2 $[M + H]^+$, calcd for $[C_{20}H_{19}N_3O_2 + H]^+$ 334.2.

Synthesis of (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-1'-(2-methoxyethyl)spiro [cyclopropane-1,3'-indolin]-2'-one

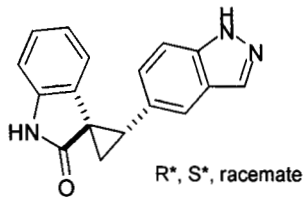


[00172] The title compound was prepared in a manner similar to the chiral synthetic method of Example A10 using (1R,2S)-2-(1H-indazol-6-yl)-1'-(2-methoxyethyl)spiro [cyclopropane-1,3'-indolin]-2'-one (260 mg, 0.779 mmol). Purification using 0-30% EtOAc in hexane on Biotage Isolera with SNAP 25g column yielded the title compound as a white solid (235 mg, 66%; 98%ee) with the major (1R,2S) enantiomer eluting at 2.6 min (Phenomenex Lux 5μ Amylose-2 150 x 4.6 mm, 2.5 mL/min with isocratic at 20% EtOH in hexane for 0.5 min, then gradient 20-50% EtOH in hexane over 2.5 min, then isocratic at 50% for 1 min). From the racemic reference standard, the retention time of the (1S,2R)

enantiomer was 3.2 min using this method. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 7.14 (t , J = 7.6 Hz, 1H), 7.06-7.01 (m, 2H), 6.63 (t, J = 7.2 Hz, 1H), 5.87 (d, J = 7.6 Hz, 1H), 4.14-3.97 (bm, 2H), 3.70 (t, J = 5.6 Hz, 2H), 3.46 (t, J = 7.6 Hz, 1H), 3.39 (s, 3H), 2.28-2.26 (m, 1H), 2.05-2.01 (m, 1H); MS ESI 460.1 [M + H]$^+$, calcd for $[C_{20}H_{18}IN_3O_2$+ H]$^+$ 460.0. Optical Rotation: $[\alpha]^{22}_D$ = -239° (c 0.243, MeOH).

Preparation of Compounds of the Invention

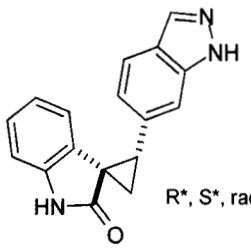
Example A1. (1*R**, 2*S**)-2-(1H-indazol-5-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



R*, S*, racemate

[00173] To a solution of trimethylsulfoxonium iodide (33 mg, 0.15 mmol) in anhydrous DMF (1 mL) was added sodium hydride (60% dispersion in oil) (16 mg, 0.4 mmol) at 0°C. The mixture was stirred for 15 min after which time (E)-3-((1H-indazol-5-yl)methylene)indolin-2-one (26 mg, 0.1 mmol) was added. The solution was stirred overnight at rt. The reaction was quenched with sat. NH_4Cl solution (2 mL), extracted with EtOAc (50 mL), dried over $MgSO_4$ and concentrated to dryness. The title was compound isolated by preparative HPLC) as a white solid (5 mg, 18%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.03 (s, 1H), 10.58 (d, 1H, J = 8.3 Hz), 8.02 (s, 1H), 7.74 (s, 1H), 7.40 (d, 1H, J = 8.9 Hz), 7.11 (d, 1H, J = 8.6 Hz), 6.98 (t, 1H, J = 7.7 Hz), 6.83 (d, 1H, J = 7.6 Hz), 6.50 (t, 1H, J = 7.3 Hz), 5.94 (d, 1H, 7.5 Hz), 3.17-3.13 (m, 1H), 2.27-2.23 (m, 1H), 1.98-1.95 (m, 1H); MS ESI 276.1 [M + H]$^+$, calcd for $[C_{17}H_{13}N_3O$+ H]$^+$ 276.3.

Example A2. (1*R**, 2*S**)-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one

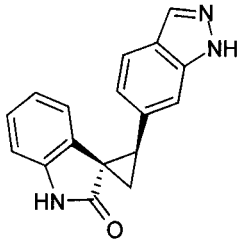


R*, S*, racemate

[00174] To a solution of trimethylsulfoxonium iodide (264 mg, 1.2 mmol) in anhydrous DMF (40 mL) was added sodium hydride (60% dispersion in oil) (140 mg, 3.48 mmol) at

0°C. The mixture was stirred for 15 min after which time (E)-3-((1H-indazol-6-yl)methylene)indolin-2-one (151 mg, 0.58 mmol) was added. The solution was stirred overnight at rt. The reaction was quenched with sat. NH_4Cl solution (10 mL), extracted with EtOAc (4 x 50 mL), dried over $MgSO_4$ and concentrated to dryness. The major diastereomer was isolated by silica gel chromatography (EtOAc/Hex 1:1) as a beige solid (44 mg, 28%). ^1H NMR (400 MHz, d_6-DMSO) δ 13.01 (s, 1H), 10.61 (d, 1H J = 8.3 Hz), 8.01 (s, 1H), 7.63 (d, 1H, J = 8.3 Hz), 7.44 (s, 1H), 6.99 (t, 1H, J = 7.5 Hz), 6.92 (d, 1H, J = 8.0 Hz), 6.84 (d, 1H, J = 8.0 Hz), 6.51 (t, 1H, J = 7.0 Hz), 5.98 (d, 1H, 8.0 Hz), 3.20-3.17 (m, 1H), 2.30-2.26 (m, 1H), 2.00-1.95 (m, 1H); MS ESI 276.1 $[M + H]^+$, calcd for $[C_{17}H_{13}N_3O+ H]^+$ 276.3.

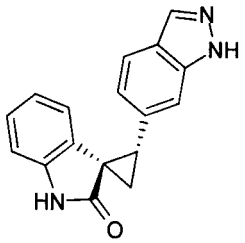
Example A3. (1*S*, 2*R*)-2-(1H-indazol-6-yl)spiro-[cyclopropane-1,3'-indolin]-2'-one



Racemic (1*R**, 2*S**)-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (25 mg, prepared in example A2) was separated using chiral HPLC: Chiralpak 1A (3 x 15 cm), (30% methanol (0.1% DEA)/CO_2, 70 mL/min) to give a white solid (11.8 mg).

Analytical HPLC: Chiralpak 1A (15 x 0.46 cm), (40% methanol (0.1% DEA)/CO_2, 3 mL/min) 98% e.e., Rt= 2.7 min.

Example A4. (1*R*, 2*S*)-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



HPLC resolution:

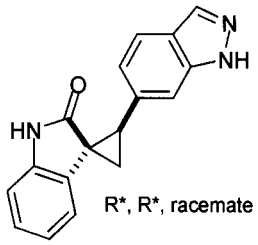
Racemic (1*R**, 2*S**)-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (25 mg, prepared in example A2) was separated using chiral HPLC: Chiralpak 1A (3 x 15 cm), (30% methanol (0.1% DEA)/CO_2, 70 mL/min) to give a white solid (11.5 mg).

Analytical HPLC: Chiralpak 1A (15 x 0.46 cm), (40% methanol (0.1% DEA)/CO_2, 3 mL/min) 97% e.e., Rt= 5.2 min).

Chiral Synthesis:

[00175] A solution of (1R,2S)-2-(N1-benzyl-1H-indazol-6-yl)spiro-[N-benzyl-cyclopropane-1,3-indolin]-2'-one (6.5 g, up to 14 mmol; contains some solvent) in a mixture of DMSO (20 mL, 286 mmol) and THF (200 mL) was cooled in ice before addition of KO^{t}Bu (10.0 g, 89 mmol). The mixture darkened immediately. The mixture was purged gently with oxygen from balloons, warming slowly to rt. NMR of a sample after 5 h showed approx. 30% conversion, and so the mixture was let stir overnight under a balloon of oxygen (no purge). No further conversion had occurred, and so further KO^{t}Bu (20.0 g, 178 mmol) was added. Uptake of oxygen was immediately evident, suggesting that this large excess of base is required for effective deprotection. After a further 5 h, the mixture was poured into sat. aq. NH_4Cl (100 mL). Most of the THF was removed under reduced pressure, and the resulting mixture was extracted with portions of EtOAc (4 x 50 mL). The combined organic portions were washed with sat. aq. sodium thiosulfate (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was slurried in CH_2Cl_2 (100 mL) and poured onto a short silica pad (2 cm depth x 5 cm diameter) under suction. The major byproduct (Rf 0.6 in 1:1 EtOAc/cyclohexane, Rf 0.15 in CH_2Cl_2) was eluted using CH_2Cl_2 (ca. 1 L). The product (Rf 0.25 in 1:1 EtOAc/cyclohexane) was eluted using 2% then 5% MeOH/EtOAc. An impurity co-eluted with the product, as the latter 'streaked' badly. Concentrating the product containing fractions afforded the title compound (2.5 g, 64%) as a pale brown solid, contaminated with a second cyclopropane-containing compound (<10%; possibly a monobenzylated compound). HPLC indicated an optical purity of 94% e.e. (although the presence of a co-eluting impurity is suspected), with the major (1R,2S) enantiomer eluting at 14.3 min (Daicel Chiralpak AS-H (250 x 4.6 mm); isocratic 40% EtOH in n-heptane; 1 mL/min; 35 °C; Detection: 254, 230, 210 nm). From the racemic reference standard, the retention time of the (1S,2R) enantiomer was 9.9 min using this method. Analytical data was identical for that obtained in Example A2.

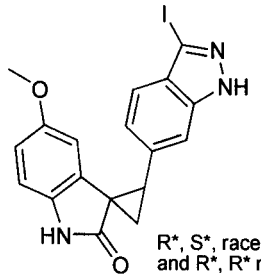
Example A5. (1*R**, 2*R**)-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



R*, R*, racemate

[00176] The minor diastereomer from the reaction of Example A2 was isolated as beige solid (3.5 mg, 2%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 10.33 (d, 1H J = 8.3 Hz), 7.99 (s, 1H), 7.59 (d, 1H, J = 8.2 Hz), 7.41 (s, 1H), 7.18-7.12 (m, 2H), 6.99-6.94 (m, 2H), 6.86 (d, 1H, J = 7.8 Hz), 3.32 (t, 1H, J = 8.3 Hz), 2.27-2.23 (m, 1H), 2.18-2.15 (m, 1H); MS ESI 276.1 $[M + H]^+$, calcd for $[C_{17}H_{13}N_3O+ H]^+$ 276.3.

Example A6. (1*R**,2*S**)- and (1*R**,2*R**)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro-[cyclopropane-1,3'-indolin]-2'-one

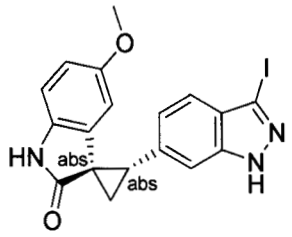


R*, S*, racemate
and R*, R* racemate

[00177] To a solution of NaH (380 mg, 9.5 mmol) in DMF (8 mL) at 0 °C was added trimethylsulfoxonium iodide (694 mg, 3.15 mmol). The resulting mixture was stirred at rt for 30 min followed by the addition of (*E/Z*)-3-((3-iodo-1*H*-indazol-6-yl)methylene)-5-methoxyindolin-2-one (658 mg, 1.6 mmol, E/Z ratio 84:16) in DMF (2 mL). The reaction mixture was stirred at rt for 18h. The reaction was cooled to 0 °C and quenched with saturated NH_4Cl. The mixture was extracted with EtOAc and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to give a yellow viscous oil. The crude product was purified by silica gel chromatography (95:5 CH_2Cl_2/MeOH) to yield a yellow solid, which was then triturated with a 1:1 mixture of hexanes and EtOAc to give the title compound as a white powder (471 mg, 69%). A mixture of diastereomers (7:1 by NMR) was obtained. In repeated runs, the ratio of diastereomers varried from 6:1 to 10:1 in favor of the 1*R**, 2*S** diastereomer. The material was used without further purification as an intermediate for subsequent reactions. Alternatively the material was recrystallized from methanol to yield the title compound as a 12:1 mixture in favour of the 1*R**, 2*S** diastereomer. Analytical data for the major isomer: ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.48

(s, 1H), 10.43 (s, 1H), 7.49 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.57 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 5.62 (d, J = 2.4 Hz, 1H), 3.29 (s, 3H), 3.18 (t, J = 8.2 Hz, 1H), 2.34 (dd, J = 7.8 Hz, J = 4.6 Hz, 1H), 1.98 (dd, J = 9.2 Hz, J = 4.8 Hz, 1H); MS ESI 432.1 $[M + H]^+$, calcd for $[C_{18}H_{14}IN_3O_2 + H]^+$ 432.0.

Example A7. (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one



HPLC Resolution:

Racemic (1*R**, 2*S**)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro spiro[cyclopropane-1,3'-indolin]-2'-one (15 g, prepared in example A6) was separated using chiral HPLC: Chiralcel OJ-H (3 x 15 cm), (30% methanol (0.1% DEA)/CO_2, 75 mL/min) to give a white solid (6.75 g).

Analytical HPLC: Chiralpak 1A (15 x 0.46 cm), (40% isopropanol (0.1% DEA)/CO_2, 3 mL/min) 99% e.e., Rt= 2.1 min).

Chiral Synthesis:

A. (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one

[00178] The title compound was prepared in a manner similar to the method of (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one using (S)-1-(1-benzyl-1H-indazol-6-yl)ethane-1,2-diyl dimethanesulfonate (3.35 g, 7.90 mmol) and 1-benzyl-5-methoxyindolin-2-one (2.00 g, 7.90 mmol). The crude product was purified by silica gel chromatography (15-40% EtOAc in hexane) followed by trituration (EtOAc) to give the title compound as a white solid (1.97 g, 52%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.36-7.23 (m, 10H), 7.14 (d, J = 7.2 Hz, 2H), 6.94 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 5.61 (d, J = 15.1 Hz, 1H), 5.54 (d, J = 15.4 Hz, 1H), 5.37 (s, 1H), 5.07 (d, J = 15.4 Hz, 1H), 4.95 (d, J = 15.7 Hz, 1H), 3.51 (t, J = 8.1 Hz, 1H), 3.18 (s, 3H), 2.32-2.29 (m, 1H), 2.09-2.00 (m, 1H). MS ESI 486.3 $[M + H]^+$, calcd for $[C_{32}H_{27}N_3O_2 + H]^+$ 486.2.

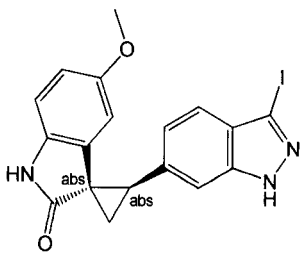
B. (1R,2S)-2-(1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one

[00179] The title compound was prepared in a manner similar to the chiral synthetic method of Example A4 using (1R,2S)-1'-benzyl-2-(1-benzyl-1H-indazol-6-yl)-5'-methoxy spiro[cyclopropane-1,3'-indolin]-2'-one (1.0 g, 2.1 mmol). Purification via column chromatography (silica gel, 30-80% EtOAc in hexane) yielded the title compound as a white solid (0.50 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (br s, 1H), 10.42 (br s, 1H), 8.02 (s, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.45 (s, 1H), 6.94 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.55 (d, J = 8.6 Hz, 1H), 5.62 (s, 1H), 3.20 (s, 3H), 3.18 (t, J = 8.7 Hz, 1H), 2.34-2.28 (m, 1H), 1.98-1.95 (m 1H). MS ESI 306.1 $[M + H]^+$, calcd for $[C_{18}H_{15}N_3O_2 + H]^+$ 306.12. Optical Rotation: $[\alpha]^{23}_D$ = -225° (c 0.441, MeOH)

C. (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one

[00180] The title compound was prepared in a manner similar to the chiral synthetic method for Example A10 using (1R,2S)-2-(1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (0.40 g, 1.3 mmol). Crude product was triturated with EtOAc (5 mL) to yield the title compound as a white solid (0.52 g, 93%, >98 % e.e.) with the major (1R,2S) enantiomer eluting at 8.5 min (Phenomenex Lux 5μ Cellulose-2 (150 x 4.6 mm); 1.0 mL/min; isocratic at 10% ^{i}PrOH in n-hexane for 1.0 min, then gradient 10-90% ^{i}PrOH in n-hexane over 10 min, then isocratic at 90% ^{i}PrOH in n-hexane for 2.0 min; 1.0 mL/min; 24 °C; Detection: 254 nm). From the racemic reference standard, the retention time of the (1S,2R) enantiomer was 6.2 min using this method. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.48 (br s, 1H), 10.43 (br s, 1H), 7.49 (s, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 5.62 (s, 1H), 3.29 (s, 3H), 3.19 (t, J = 8.4 Hz, 1H), 2.36-2.32 (m, 1H), 1.99-1.96 (m 1H). MS ESI 432.1 $[M + H]^+$, calcd for $[C_{18}H_{14}IN_3O_2 + H]^+$ 432.0. Optical Rotation: $[\alpha]^{22}_D$ = -143° (c 0.399, MeOH).

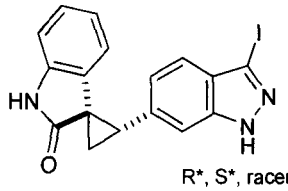
Example A8. (1S,2R)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one



Racemic (1*R**, 2*S**)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro spiro[cyclopropane-1,3'-indolin]-2'-one (15 g, prepared in example A6) was separated using chiral HPLC: Chiralcel OJ-H (3 x 15 cm), (30% methanol (0.1% DEA)/CO_2, 75 mL/min) to give a white solid (6.6 g).

Analytical HPLC: Chiralpak 1A (15 x 0.46 cm), (40% isopropanol (0.1% DEA)/CO_2, 3 mL/min) 99% e.e., Rt= 3.4 min).

Example A9. (1*R**,2*S**)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



R*, S*, racemate

A. (1R,2S*)- and (1R*,2R*)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one*

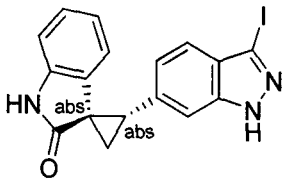
[00181] The compound was used without further purification as an intermediate, or the pure diastereomer was obtained in the following procedure. Sodium hydride (309.9 mg, 7.75 mmol) (60% dispersion in oil) added to anhydrous DMF (2.5 mL) at room temperature. Then trimethylsulfoxonium iodide (568.4 mg, 2.58 mmol) was added to the suspension at the same temperature. The mixture was stirred for 15 min after which time a solution of (E/Z)-3-((3-iodo-1H-indazol-6-yl)methylene)-indolin-2-one (500 mg, 1.29 mmol) in DMF (2.0 ml) was added. The solution was stirred at 55°C for 5h prior to quenching the reaction over methanol solution (1 mL) at room temperature for 15 min before addition of water (50 mL). The product was extracted with ethyl acetate (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness. The solid was suspended in toluene (21 mL) and collected to give the title compound (331 mg, 64 %). as a 9:1 mixture in favor of the *R**, *S** diastereomer. This white solid was used without further purification as an intermediate in subsequent reactions. ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.47 (s, 0.9H), 13.41 (s, 0.1H), 10.62 (s, 0.9H), 10.35 (s, 0.1H), 7.47 (s, 0.9H), 7.43 (s, 0.1H), 7.30 (d, J = 8.0 Hz, 0.9H), 7.26 (d, J = 8.0 Hz, 0.1H), 7.23 (m, 0.1H), 7.15 (m, 0.3H), 7.05-6.98 (m, 2H), 6.85 (m, 1H), 6.53 (t, J = 7.6 Hz, 0.9H), 5.97 (d, J = 7.6 Hz, 0.9H), 3.33 (m, 0.1H, partially obscured by water signal), 3.18 (t, J = 8.4 Hz, 0.9H), 2.31 (dd, J = 7.2, 4.8 Hz, 0.9H), 2.26 (m 0.1H), 2.16 (dd, J = 8.8, 4.0 Hz, 0.1H), 1.98 (dd, J = 8.8, 4.8 Hz, 0.9H).

B. (1R,2S*)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one*

[00182] The diastereomeric mixture (100 mg) obtained above was treated with THF (1 mL) at 55 °C for 15 min then cooled to room temperature for 30 min. The off-white solid

was collected by filtration to give the title compound (32 mg, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.47 (s, 1H), 10.62 (s, 1H), 7.47 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.02-6.98 (m, 2H), 6.84 (d, J = 7.6 Hz, 1H), 6.53 (t, J = 7.6 Hz, 1H), 5.97 (d, J = 7.6 Hz, 1H), 3.18 (t, J = 8.4 Hz, 1H), 2.31 (dd, J = 7.2 Hz, J = 4.8 Hz, 1H), 1.98 (dd, J = 8.8 Hz, J = 4.8 Hz, 1H); MS ESI 402.0 $[M + H]^+$, calcd for $[C_{17}H_{12}IN_3O + H]^+$ 402.0.

Example A10. (1R,2S)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



HPLC resolution:

Racemic (1*R**, 2*S**)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (35 mg, prepared in example A9) was separated using chiral HPLC: Lux Cellulose AXIA (150 x 21.2 mm), (Gradient 10% isopropanol/Hexane to 90% isopropanol/hexane 20 mL/min) to give a white solid (8.8 mg).

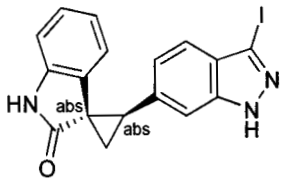
Analytical HPLC: Lux Cellulose AXIA (150 x 4.6mm), (Gradient 10% isopropanol/Hexane to 90% isopropanol/hexane 1 mL/min) 98% e.e., Rt= 7.8 min).

Chiral Synthesis:

[00183] A mixture of (1R,2S)-2-(1H-indazol-6-yl)spiro-[cyclopropane-1,3-indolin]-2'-one (2.20 g, 8.0 mmol, ca. 94%ee) and K_2CO_3 (2.21 g, 16.0 mmol) in dry DMF (20 mL) was treated with a solution of I_2 (3.45 g, 13.6 mmol) in dry DMF (15 mL), adding the latter by syringe pump over 45 min. The mixture was stirred for 1.5 h and then poured into a mixture of water (400 mL) and sat. aq. $Na_2S_2O_3$. The resulting mixture was triturated in an ultrasound bath for 30 min to break up the sticky clumps of solid, then filtered. The solids were washed with water (2 x 50 mL), partially dried under suction, then stripped twice with acetone to remove residual water. HPLC of the crude mixture indicated an optical purity of 95% e.e. with the major (1R,2S) enantiomer eluting at 14.1 min (Daicel Chiralpak AS-H (250 x 4.6 mm); isocratic 40% EtOH in n-heptane; 1 mL/min; 35 °C; Detection: 254, 230, 210 nm). From the racemic reference standard, the retention time of the (1S,2R) enantiomer was 8.4 min using this method, and both enantiomers of the minor diasteremer product were also detected at 6.0 min and 6.9 min. Baseline material was removed by passing an EtOAc solution of the product through a short silica pad (2 cm depth x 4 cm diameter), eluting with

further EtOAc. Further purification was then attempted by trituration. Et_2O and toluene removed some of the impurities, but no enhancement of optical purity was observed. Recrystallization from THF/cyclohexane and EtOAc/cyclohexane were also unsuccessful, and so the material was purified by column chromatography on silica (20 cm depth x 4 cm diameter) using 1:1 EtOAc/cyclohexane to afford the title compound (1.47 g, 46%) as an off-white powder. Analytical data was identical to that obtained in Example A9.

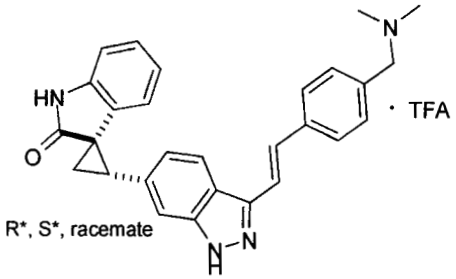
Example A11. (1S,2R)-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



Racemic (1*R**,2*S**)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (35 mg, prepared in example A9) was separated using chiral HPLC: Lux Cellulose AXIA (150 x 21.2 mm), (Gradient 10% isopropanol/Hexane to 90% isopropanol/hexane 20 mL/min) to give a white solid (7.7 mg).

Analytical HPLC: Lux Cellulose AXIA (150 x 4.6mm), (Gradient 10% isopropanol/Hexane to 90% isopropanol/hexane 1 mL/min) 98% e.e., Rt= 6.7 min).

Example A23. (1*R**,2*S**)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



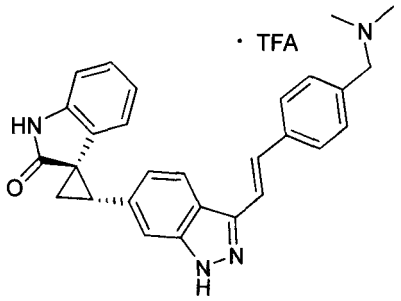
A. (E)-2-(3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one

[00184] The title compound was synthesized according to the method of Example A22 in WO2010/115279, Method 1A, using *N,N*-dimethyl-1-(4-vinylphenyl)methanamine (80 mg, 0.15 mmol). The title compound was isolated by silica gel chromatography (3:1 CH_2Cl_2/MeOH) to give the title compound as a beige solid (38 mg, 45%). MS ESI 565.4 $[M + H]^+$, calcd for $[C_{34}H_{40}N_4O_2Si+ H]^+$ 565.7.

B. (1R,2S*)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate*

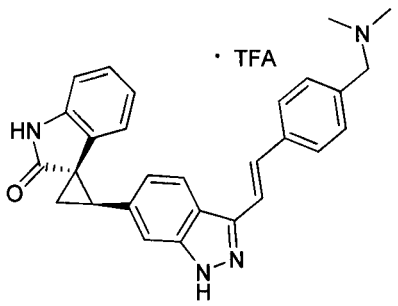
[00185] The title compound was synthesized according to the method of Example A22 in WO2010/115279, Method 1B, using (E)-2-(3-(4-((dimethylamino)methyl)styryl)-1-((2-(trimethylsilyl)-ethoxy)methyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (38 mg, 0.052 mmol). The crude reaction mixture was concentrated under reduced pressure to dryness, and purified by reverse phase preparative HPLC to give the title compound as a white solid and as the TFA salt (11 mg, 31%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.02 (d, J = 8.3 Hz, 1H), 7.78 (d, 2H, J = 8.3 Hz), 7.56-7.48 (m, 5H), 7.08-7.04 (m, 2H), 6.94 (d, 1H, J = 8.3 Hz), 6.59 (t, 1H, J = 7.8 Hz), 6.00 (d, 1H, J = 8.0 Hz), 4.38 (s, 2H) 3.39-3.33 (m, 1H), 2.90 (s, 6H), 2.28-2.22 (m, 1H), 2.22-2.17 (m, 1H); MS ESI 435.2 $[M + H]^+$, calcd for $[C_{28}H_{26}N_4O + H]^+$ 435.5.

Example A24. (1R,2S)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



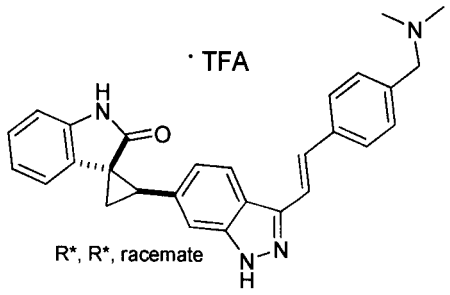
[00186] To a solution of (1R,2S)-2-(3-iodo-1H-indazol-spiro[cyclopropane-1,3'-indolin]-2'-one (20 mg, 0.05 mmol) in DMF (0.4 mL) and water (0.1 mL) was added (E)-N,N-dimethyl-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl) methanamine (25 mg, 0.08 mmol) potassium fluoride (6 mg, 0.1 mmol) and $Pd(PPh_3)_4$ (3 mg, 0.002 mmol). The mixture was heated to 120°C for 2 h under microwave irradiation. Ethyl acetate (50 mL) was added and the solution was washed with water (2 x 5 mL), brine (5 mL) and dried over $MgSO_4$. Purification by reverse phase preparatory HPLC gave the title compound as a yellow solid (12 mg, 44%).

Example A25. (1S,2R)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



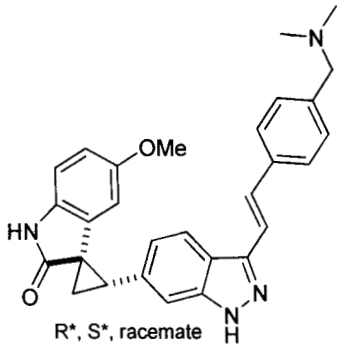
[00187] To a solution of (1S,2R)-2-(3-iodo-1H-indazol-spiro[cyclopropane-1,3'-indolin]-2'-one (20 mg, 0.05 mmol) in DMF (0.4 mL) and water (0.1 mL) was added (E)-N,N-dimethyl-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl) methanamine (25 mg, 0.08 mmol) potassium fluoride (6 mg, 0.1 mmol) and $Pd(PPh_3)_4$ (3 mg, 0.002 mmol). The mixture was heated to 120°C for 2 h under microwave irradiation. Ethyl acetate (50 mL) was added and the solution was washed with water (2 x 5 mL), brine (5 mL) and dried over $MgSO_4$. Purification by reverse phase preparatory HPLC gave the title compound as a yellow solid (4 mg, 15%).

Example A26. (1*R**,2*R**)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00188] During a larger scale preparation of Example A23 (obtained as a pale yellow solid, 63 mg), the corresponding minor diastereomer, i.e. the title compound, was obtained as a white solid by reverse phase preparative HPLC (4.6 mg). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.00 (d, 1H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.4 Hz), 7.56-7.50 (m, 5H), 7.23 (t, 1H, J = 7.6 Hz), 7.16-7.05 (m, 3H), 6.96 (d, 1H, J = 7.6 Hz), 4.33 (s, 2H) 3.44-3.38 (m, 1H), 2.88 (s, 6H), 2.43-2.40 (m, 1H), 2.25-2.23 (m, 1H); MS ESI 435.2 $[M + H]^+$, calcd for $[C_{28}H_{26}N_4O + H]^+$ 435.5.

Example A34. (1*R**,2*S**)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one

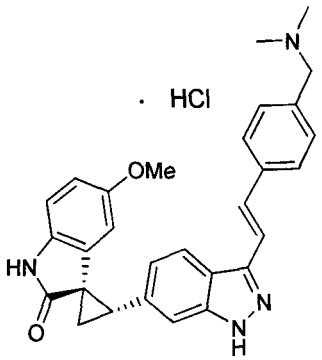


[00189] *A*, DMF (3 mL) was added to a mixture of NaH (60%, 85.2 mg, 2.1 mmol) and trimethylsulfoxonium iodide (131.5 mg, 0.60 mmol). The resulting mixture was stirred at rt for 10 min followed by the addition of (E)-3-((3-(4-((dimethylamino)methyl)-styryl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one 2,2,2-trifluoroacetate (163mg, 0.29 mmol) as a solution in DMF (6 mL, divided for transfer and vial rinse). The reaction mixture was not complete after stirring at rt for 24h. The mixture was heated at 55°C for 1h but was still not complete. After cooling to rt, NaH (60%, 44 mg, 1.1 mmol) and trimethylsulfoxonium iodide (69.5 mg, 0.31 mmol) was added and the mixture was heated at 55°C for 1h prior to quenching by addition of water (25mL) and brine (25mL). The mixture was extracted with EtOAc (300mL) and the organic layer was washed with brine (2 x 25mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5-7.5% 2M NH_3-MeOH in DCM) to yield the title compound as a yellow solid (42.8 mg, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.11 (s, 1H), 10.43 (s, 1H), 8.07 (d, J = 8.8Hz, 1H), 7.64 (d, J = 7.6Hz, 2H), 7.47 (m, 3H), 7.29 (d, J = 8.0Hz, 2H), 7.03 (d, J = 8.8Hz, 1H), 6.74 (d, J = 8.4Hz, 1H), 6.57 (dd, J = 8.4, 2.4Hz, 1H), 5.65 (d, J = 2.4Hz, 1H), 3.38 (s, 2H), 3.28 (s, 3H), 3.20 (t, J = 7.6Hz, 1H), 2.34 (m, 1H), 2.14 (s, 6H), 1.99 (m, 1H); MS ESI $[M+H]^+$ 465.2, calcd for $[C_{29}H_{28}N_4O_2+H]^+$ 465.2.

[00190] *B*. Larger scale, TFA salt: NaH (60%, 491 mg, 12.29 mmol) was added in 3 portions to an ice cooled mixture of trimethylsulfoxonium iodide (959.3 mg, 4.36 mmol) in DMF (12 mL). The resulting mixture was stirred at 0°C for 10 min followed by the addition of (E)-3-((3-(4-((dimethylamino)methyl)-styryl)-1H-indazol-6-yl)methylene)-5-methoxyindolin-2-one hydrochloride (984.4 mg, 2.02 mmol) as a suspension in DMF (12 mL, divided for transfer and vial rinse). The reaction mixture was warmed to room temperature over 10 min, then heated at 55°C for 17h prior to quenching by addition of water (25mL) and brine (25 mL). The mixture was extracted with ~1:1 Et_2O / DCM (250 mL, noted emulsion), followed by DCM (2 x 50 mL) and the organic layer was washed with brine (25mL), dried over Na_2SO_4 and concentrated *in vacuo*, and purified by silica gel

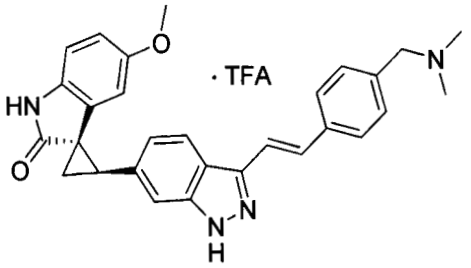
chromatography (2-8% 2M NH_3-MeOH in DCM). Further purification by preparative HPLC to yielded the major diastereomer as the TFA salt (yellow solid, 168.4 mg, 18%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.04 (d, *J*=8.8 Hz, 1 H), 7.78 (d, *J*=7.5 Hz, 2 H), 7.37 - 7.65 (m, 5 H), 7.07 (d, *J*=8.5 Hz, 1 H), 6.84 (d, *J*=8.5 Hz, 1 H), 6.62 (d, *J*=8.3 Hz, 1 H), 5.59 (br. s., 1 H), 4.33 (s, 2 H), 3.37 (m, 1 H), 3.27 (s, 3 H), 2.89 (s, 6 H), 2.26 (m, 1 H), 2.19 (m, 1 H); MS ESI $[M+H]^+$ 465.3, calcd for $[C_{29}H_{28}N_4O_2+H]^+$ 465.2.

Example A35. (1R,2S)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one hydrochloride



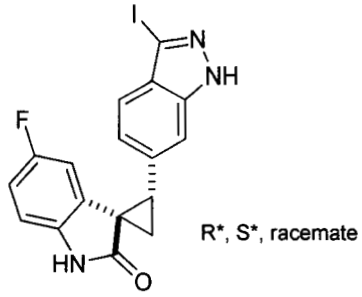
[00191] The title compound was prepared in a similar manner to Example A51B using (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (251.3 mg, 0.58 mmol) and (E)-N,N-dimethyl-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)methanamine (191.5 mg, 0.67 mmol). The product was extracted using EtOAc (40 mL) with a Varian 3mL ChemElut cartridge. After removal of the solvents in vacuo, the title compound was purified by chromatography on Biotage (silica, SNAP-25g, 5-20% MeOH in DCM). Trituration with with 1:1 Et_2O/DCM yielded the title compound (92.1 mg, 34%). HCl (1M in Et_2O, 0.25 mL, 0.25 mmol) was added in a drop-wise manner to an ice cooled solution of the free base (92 mg, 0.20 mmol) in THF (10 mL), and the resulting mixture was allowed to stir in ice for 40 minutes, then Et_2O (10 mL) was added to the mixture. Filtration under vacuum yielded the title compound as the hydrochloride salt (orange-red solid, 79 mg, 79%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.05 (d, J=8.5 Hz, 1 H), 7.77 (d, J=8.0 Hz, 2 H), 7.48 - 7.63 (m, 5 H), 7.09 (d, J=8.3 Hz, 1 H), 6.84 (d, J=8.5 Hz, 1 H), 6.61 (dd, J=8.3, 2.3 Hz, 1 H), 5.61 (d, J=2.3 Hz, 1 H), 4.36 (s, 2 H), 3.35 (m, 1 H), 3.28 (s, 3 H), 2.89 (s, 6 H), 2.26 (dd, J=7.7, 5.1 Hz, 1 H), 2.18 (dd, J=8.8, 4.8 Hz, 1 H); MS ESI $[M+H]^+$ 465.3, calcd for $[C_{29}H_{28}N_4O_2+H]^+$ 465.2. Optical Rotation: $[\alpha]^{24}_D$ = -70° (c 0.445, MeOH).

Example A36. (1S,2R)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00192] The title compound was synthesized according to the method of Example A51B, by using (1S,2R)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (40 mg, 0.092mmol) and (E)-N,N-dimethyl-1(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxa borolan-2-yl)vinyl)benzyl)methanamine (33.3 mg, 0.115 mmol). Purification by preparative HPLC gave the title compound as a cream solid (22 mg, 39%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 7.6 Hz, 2H), 7.54-7.49 (m, 5H), 7.04 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 5.58 (s, 1H), 4.33 (s, 2H), 3.37 (t, J = 8.4 Hz, 1H), 3.26 (s, 3H), 2.88 (s, 6H), 2.25-2.23 (m, 1H), 2.20-2.21 (m, 1H); MS ESI 465.3 $[M + H]^+$, calcd for $[C_{29}H_{28}N_4O_2 + H]^+$ 465.2. Optical Rotation: $[\alpha]^{23}_D = 85°$ (c 0.542, Methanol).

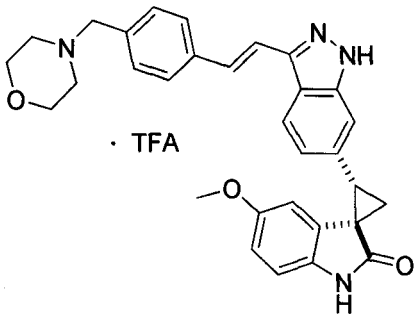
Example A40. (1*R**,2*S**)-5'-fluoro-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



[00193] Trimethylsulfoxonium iodide (173.8 mg, 0.789 mmol) was added to a suspension of sodium hydride (94.76 mg, 4.12 mmol) (60% dispersion in oil) in THF (4.0 mL) at room temperature. The mixture was stirred for 15 min after which time a solution of (Z)-5-fluoro-3-((3-iodo-1H-indazol-6-yl)methylene)indolin-2-one (160 mg, 0.394 mmol) in THF (2.4 mL) was added. The solution was stirred at 50 °C for 7 h prior to quenching the reaction mass over 10% NH_4Cl solution (15 mL) at room temperature. The product was extracted using ethyl acetate (15 mL x 2) and the organic layer was dried over Na_2SO_4 and

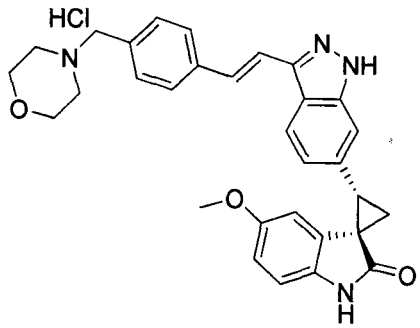
evaporated *in vacuo*. Trituration with hexane (5 mL) gave the title compound as a cream solid (89 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.50 (s, 1H), 10.65 (s, 1H), 7.50 (s, 1H), 7.31 (d, 1H, J = 8.4 Hz), 7.00 (d, 1H, J = 8.4 Hz), 6.85-6.81 (m, 2H), 5.81 (d, 1H, J = 8.4 Hz), 3.22 (m, 1H), 2.43 (m, 1H), 2.01 (m, 1H); MS ESI 420.0 $[M + H]^+$, calcd for $[C_{17}H_{11}FIN_3O + H]^+$ 420.0.

Example A41.(1R*,2S*)-(E)-5'-methoxy-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

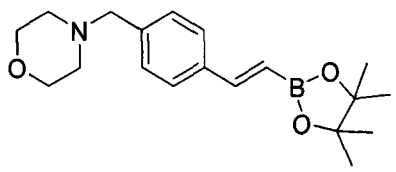


[00194] The title compound was synthesized according to the method of Example A45 in WO2010/115279, except substituting (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (30 mg, 0.070 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (30 mg, 0.091 mmol). Purification by column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5 to 94:6) gave crude material which was 85% pure by LC-MS. This material was further purified by prep-HPLC to give a white solid (18 mg, 51 %); Spectral was data identical to that obtained in Example A42B.

Example A42. (1R,2S)-(E)-5'-methoxy-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one hydrochloride

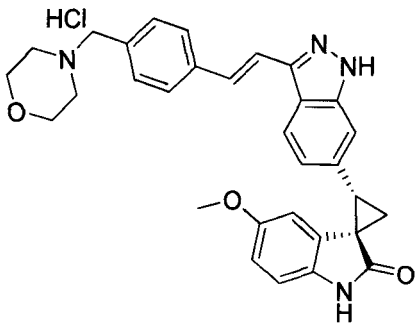


A. (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine



[00195] An oven-dried round-bottom flask was cooled under $N_{2\,(g)}$ and then charged with 4-(4-ethynylbenzyl)morpholine (120 mg, 0.596 mmol), toluene (2.5 mL), and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.43 mL, 2.98 mmol). The mixture was stirred for 15 min while purging the solution with $N_{2\,(g)}$. $HRuCl(CO)(PPh_3)_3$ (29 mg, 0.030 mmol) was then added and the reaction heated to 50 °C for 18 h. The reaction was quenched with $NaHCO_3$ (sat.) (10 mL), extracted with EtOAc, and the organic layer washed with brine (2X) and then dried over $MgSO_4$. The solvent was removed and the resulting residue purified by column chromatography (silica gel, Hexanes/EtOAc, 2:3 to 1:2) to give a white solid (155 mg, 79 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 2H, J = 8.0 Hz), 7.38 (d, 1H, J = 18.8 Hz), 7.30 (m, 2H), 6.15 (d, 1H, J = 18.5 Hz), 3.72 (bs, 4H), 3.49 (bs, 2H), 2.45 (bs, 4H), 1.31 (s, 12H); MS ESI 330.1 $[M + H]^+$, calcd for $[C_{19}H_{28}BNO_3 + H]^+$ 330.22.

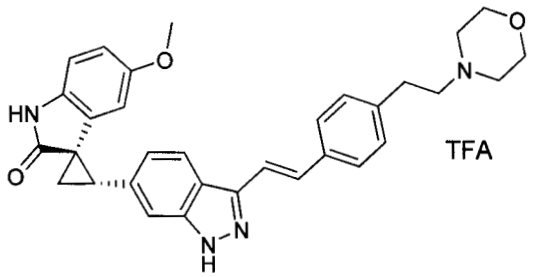
B. (1R,2S)-5'-methoxy-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one hydrochloride



[00196] A round-bottom flask was charged with (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (255 mg, 0.592 mmol), (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (260 mg, 0.710 mmol), LiCl (75 mg, 1.78 mmol), dioxane (6.0 mL), and Na_2CO_3 (3.0 mL of a 1M aqueous solution). The mixture was purged with a balloon of $Ar_{\,(g)}$ for 15 min and then $Pd(PPh_3)_4$ (21 mg, 0.0178 mmol) was added and the reaction heated to 100 °C for 18 h. The reaction was cooled, EtOAc and $NaHCO_3$ (sat.) were added, and the mixture transferred to a separatory funnel. The organic layer was washed with $NaHCO_3$ (sat.), Brine and then dried over $MgSO_4$. The solvent was removed and the residue purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 9:1) to give a solid which was sonicated with Et_2O and filtered to

give 183 mg, 61 % of a white solid. The HCl salt was prepared by dissolving the free base (183 mg, 0.361 mmol) into THF (2 mL) and then HCl (0.72 mL of a 1M solution in Et_2O) was added. A precipitate immediately formed which was further precipitated with Et_2O (10 mL). The solid was quickly filtered and washed with Et_2O to give, after drying, an off-white solid (153 mg, 78 %). ^1H NMR (400 MHz, CD_3OD) δ 8.04 (d, 1H, J = 8.4 Hz), 7.78 (d, 2H, J = 8.2 Hz), 7.57-7.50 (m, 5H), 7.07 (d, 1H, J = 8.6 Hz), 6.83 (d, 1H, J = 8.5 Hz), 6.61 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.2 Hz), 5.58 (d, 1H, J = 2.2 Hz), 4.39 (s, 2H), 4.09-4.04 (m, 2H), 3.78-3.72 (m, 2H), 3.43-3.33 (m, 3H), 3.27-3.20 (m, 5H), 2.27-2.23 (m, 1H), 2.21-2.16 (m, 1H); MS ESI 507.3 $[M + H]^+$, calcd for $[C_{31}H_{30}N_4O_3 + H]^+$ 507.24.

Example A51. Synthesis of (1R,2S)-(E)-5'-methoxy-2-(3-(4-(2-morpholinoethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



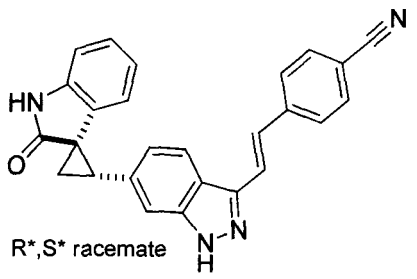
A. (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl) phenethyl)morpholine

[00197] To a mixture of 4-(4-bromophenethyl)morpholine (731 mg, 2.71 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.5 mL, 2.95 mmol, 1.1 eq.) and toluene (10 mL) in a 20 mL microwave vial was added Et_3N (0.76 mL, 5.4 mmol, 2 eq.), followed by $Pd(P^tBu_3)_2$ (14 mg, 0.027 mmol, 1 mol%). The resulting mixture was purged with argon, then capped and heated at 80 °C (oil temp.) for 2 h. After cooling to rt, it was quenched with sat. $NaHCO_3$ (10 mL), H_2O (10 mL), extracted with EtOAc (30 mL x 2) and dried (Na_2SO_4). After evaporation of the solvents, the residue was purified by Biotage column system (EtOAc/hex gradient: 0-100%) to give (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenethyl)morpholine as a white solid (714 mg, 77%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 19.0 Hz, 1H), 7.19 (d, J = 7.8 Hz, 2H), 6.13 (d, J = 18.3 Hz, 1H), 3.75 (t, J = 4.4 Hz, 4H), 2.84-2.77 (m, 2H), 2.63-2.56 (m, 2H), 2.53 (br, pseudo s, 4H), 1.32 (s, 12H).

B. Synthesis of (1R,2S)-5'-methoxy-2-(3-(4-(2-morpholinoethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one

[00198] To a mixture of (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro [cyclopropane-1,3'-indolin]-2'-one (172 mg, 0.4 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenethyl)morpholine (138 mg, 0.4 mmol) in $PhCH_3$/EtOH (8 mL/4 mL) in a 20 mL microwave vial was added 1 M Na_2CO_3 (0.8 mL, 0.8 mmol), followed by $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 5 mol%). The resulting mixture was purged with argon, then microwaved for 2 h at 125 °C. After cooling to rt, the mixture was diluted with H_2O (20 mL), extracted with EtOAc (30 mL x 2) and dried (Na_2SO_4). After removal of solvents, the residue was redissolved in DMF (4 mL) and purified by preparatory HPLC to give the title compound (TFA salt, 115 mg, 45%) as a pale yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.43 (s, 1H), 7.37 (d, J = 6.4 Hz, 2H), 7.28 (d, J = 7.2 Hz, 2H), 6.95 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 5.57 (s, 1H), 4.06 (d, J = 11.2 Hz, 2H), 3.80 (t, J = 11.2 Hz, 2H), 3.56 (d, J = 11.2 Hz, 2H), 3.38 (t, J = 7.6 Hz, 2H), 3.27-3.12 (m, 5H), 3.07 (t, 2H), 2.20-2.10 (m, 2H); MS ESI 521.4 $[M + H]^+$, calcd for $[C_{32}H_{32}N_4O_3 + H]^+$ 521.2.

Example A54. 4-((E)-2-(6-((1*R**,2*S**)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-yl)-1H-indazol-3-yl)vinyl)benzonitrile



A. 6-formyl-1H-indazole-3-carbonitrile

[00199] To a solution of 3-iodo-1H-indazole-6-carbaldehyde (3 g, 10.8 mmol) in DMF (25 mL) was added Copper cyanide (1.9 g, 21 mmol). The solution was heated by microwave irradiation at 185°C for 10 min. Water (100 mL) was added and a white precipitate was collected. The precipitate was dissolved in EtOAc (250 mL), washed with water (2 x 25 mL), dried over $MgSO_4$ and concentrated to give the title compound as a white solid (1.1g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.92 (bs, 1H), 10.17 (s, 1H), 8.39 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H).

B. (E)-6-((2-oxoindolin-3-ylidene)methyl)-1H-indazole-3-carbonitrile

[00200] To a mixture of 6-formyl-1H-indazole-3-carbonitrile (1.10 g, 6.4 mmol) and 2-oxindole (871 mg, 6.5 mmol) in EtOH (25 mL) was added piperidine (0.1 mL, 1 mmol). The resulting mixture was refluxed (oil temp. 75 °C) for 90 min, then cooled to rt. The resulting precipitate was collected by suction filtration and dried to give the title compound as an orange solid (1.5 g, 82%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.6 (s, 1H), 10.66 (s, 1H), 8.09 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H) 7.78 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.48 (d, 1H, J = 7.8 Hz), 7.24 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.83 (t, J = 7.8 Hz, 1H).

C. *6-((1R*,2S*)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-yl)-1H-indazole-3-carbonitrile*

[00201] The title compound was synthesized according to the method of Example A1, using (E)-6-((2-oxoindolin-3-ylidene)methyl)-1H-indazole-3-carbonitrile (1.5 g, 5.2 mmol) to give the title compound as a yellow solid (1.3 g, 83%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (d, J = 8.3 Hz, 1H), 7.61 (s, 1H), 7.18 (d, J = 8.5 Hz, 1H) 7.08-7.04 (m, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.58 (t, J = 7.6 Hz, 1H), 5.93 (d, J = 7.8 Hz, 1H), 3.38-3.34 (m, 1H), 2.27-2.18 (m, 1H).

D. *6-((1R*,2S*)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-yl)-1H-indazole-3-carbaldehyde*

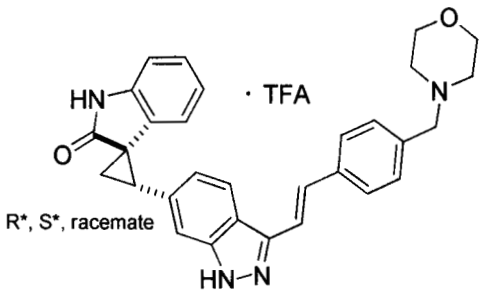
[00202] To a solution of 6-((1R*,2S*)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-yl)-1H-indazole-3-carbonitrile (1g, 3.3 mmol) in pyridine (30 mL) acetic acid (8 mL) and water (8 mL) and Raney Nickel (1 g). Sodium hypophosphite (1.8 g, 21 mmol) was dissolved in water (10 mL) and added dropwise and the reaction was stirred overnight. The product was extracted into ethyl acetate (300 mL), washed with brine (50 mL), dried over $MgSO_4$ and concentrated to dryness. The residue was purified by silica gel chromatography (95:5 CH_2Cl_2/MeOH) to give the title compound as a yellow solid (300 mg, 30%). ^{1}H NMR (400 MHz, CD_3OD) δ 10.17 (s, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.55 (s, 1H), 7.17 (d, J = 8.5 Hz, 1H) 7.08-7.04 (m, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.56 (t, J = 7.6 Hz, 1H), 5.93 (d, J = 7.5 Hz, 1H), 3.38-3.34 (m, 1H), 2.27-2.17 (m, 1H).

E. *4-((E)-2-(6-((1R*,2S*)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-yl)-1H-indazol-3-yl)vinyl)benzonitrile*

[00203] Diethyl 4-cyanobenzylphosphonate (600 mg, 2.4 mmol) was dissolved into DMF (5 mL) at 0°C. Potassium tert-butoxide (540 mg, 4.8 mmol) was added and the mixture was stirred for 5 min. Compound A54D (200 mg, 0.66 mmol) was dissolved into DMF (5 mL) and added dropwise to the solution and the mixture was stirred for 90 min. The reaction was quenched with HCl (0.1 N) and the resulting precipitate collected. The precipitate was dissolved into EtOAc (100 mL) and washed with H_2O (2 x 10 mL), brine (10 mL), dried

over $MgSO_4$ and concentrated to dryness. The residue was purified by silica gel chromatography to give the title compound as a white solid (100 mg, 38%). ^1H NMR (400 MHz, CD_3OD) δ 8.04 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.6 Hz, 2H), 7.66-7.53 (m, 2H), 7.48 (s, 1H), 7.08-7.04 (m, 2H), 6.94 (d, J = 8.3 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 5.99 (d, J = 7.5 Hz, 1H), 3.38-3.34 (m, 1H), 2.27-2.18 (m, 2H); MS ESI 403.1 $[M + H]^+$, calcd for $[C_{26}H_{18}N_4O + H]^+$ 403.1.

Example A55. (1R*,2S*)-(E)-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



A. 4-((E)-2-(6-((1R,2S*)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-yl)-1H-indazol-3-yl)vinyl)benzaldehyde*

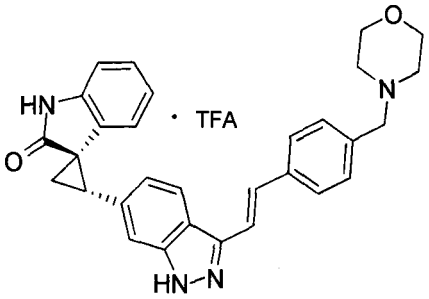
[00204] The title compound was synthesized according to the method of Example A54D, except substituting 4-((E)-2-(6-((1*R**,2*S**)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-yl)-1H-indazol-3-yl)vinyl)benzonitrile (100 mg, 0.25 mmol). Purification by silica gel chromatography (99:1 CH_2Cl_2/MeOH) gave the title compound as an orange solid (95 mg, 94%). MS ESI 406.2 $[M + H]^+$, calcd for $[C_{26}H_{19}N_3O_2 + H]^+$ 406.2.

B. (1R,2S*)-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate*

[00205] To a solution of Example A55A (40 mg, 0.1 mmol) in THF (3 mL) was added morpholine (43 mg, 0.5 mmol) and titanium isopropoxide (57 mg, 0.2 mmol) and the reaction was stirred 30 min. Sodium borohydride (13 mg, 0.2 mmol) was added and the mixture was heated to 50°C overnight. The reaction was quenched with water (2 mL) and extracted with ethyl acetate (25 mL) dried over $MgSO_4$ and concentrated to dryness. The residue was purified by reversed phase preparatory HPLC to give the title compound as the TFA salt (5 mg, 9%). ^1H NMR (400 MHz, CD_3OD) δ 8.02 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.6 Hz, 2H), 7.75-7.48 (m, 5H), 7.08-7.05 (m, 2H), 6.94 (d, J = 8.3 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 5.99 (d, J = 7.5 Hz, 1H) 4.39 (s, 2H) 4.12-4.04 (m, 2H), 3.79-3.68 (m, 2H) 3.44-

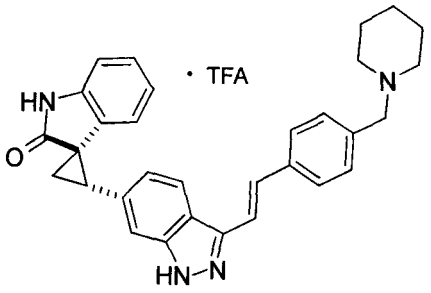
3.34 (m, 3H), 3.30-3.19 (m, 2H) 2.28-2.16 (m, 2H); MS ESI 477.3 $[M + H]^+$, calcd for $[C_{30}H_{28}N_4O_2 + H]^+$ 477.2.

Example A56. (1R,2S)-(E)-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



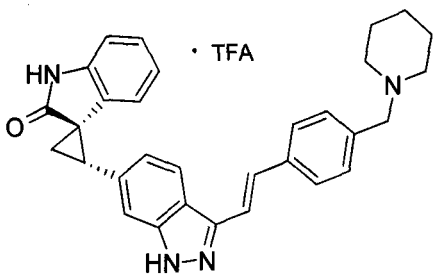
[00206] The title compound was synthesized according to the method of Example A51B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl) [cyclopropane-1,3'-indolin]-2'-one (150 mg, 0.37 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (160 mg, 0.48 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (122 mg, 58%). $[\alpha]^{23.8°}_D$ = -79° (c 0.33, Methanol). Spectral was data identical to that obtained in Example A55.

Example A57. (1R*,2S*)-(E)-2-(3-(4-(piperidin-1-ylmethyl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



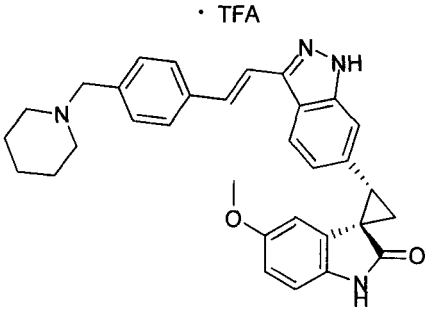
[00207] The title compound was synthesized according to the method of Example A55, method B, except substituting piperidine (43 mg, 0.5 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (8 mg, 28%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.75-7.48 (m, 5H), 7.08-7.05 (m, 2H), 6.94 (d, J = 7.5 Hz, 1H), 6.59 (t, J = 7.7 Hz, 1H), 5.99 (d, J = 7.3 Hz, 1H) 4.31 (s, 2H) 3.53-3.45 (m, 2H), 3.39-3.34 (m, 1H), 3.04-2.93 (m, 2H) 2.27-2.17 (m, 2H), 2.02-1.95 (m, 2H), 1.88-1.71 (m, 3H), 1.57-1.45 (m, 1H); MS ESI 475.3 $[M + H]^+$, calcd for $[C_{31}H_{30}N_4O + H]^+$ 475.2.

Example A58. (1R,2S)-(E)-2-(3-(4-(piperidin-1-ylmethyl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



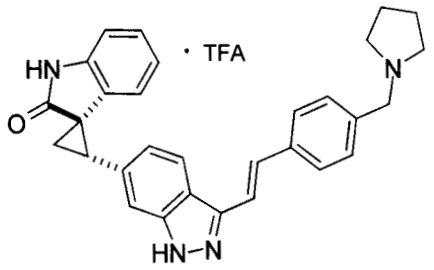
[00208] The title compound was synthesized according to the method of Example A51B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl) [cyclopropane-1,3'-indolin]-2'-one (50 mg, 0.12 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)piperidine (59 mg, 0.18 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (13 mg, 20%). $[\alpha]^{23.6°}_{D}$ = -109° (c 0.35, Methanol). Spectral was data identical to that obtained in Example A57.

Example A59. (1R,2S)-(E)-5'-methoxy-2-(3-(4-(piperidin-1-ylmethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



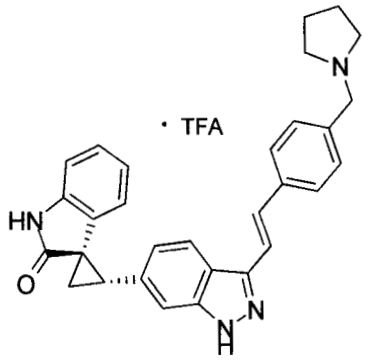
[00209] The title compound was synthesized according to the method of Example A51B, except substituting (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl) piperidine (59 mg, 0.18 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (17 mg, 23%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.6 Hz, 2H), 7.53-7.49 (m, 5H), 7.05 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.61 (dd, J = 8.4, 2.3 Hz, 1H), 5.58 (d, J = 2.3 Hz, 1H) 4.30 (s, 2H), 3.52-3.44 (m, 2H), 3.38-3.34 (m, 1H), 3.26 (s, 3H), 3.01-2.93 (m, 2H), 2.26-2.17 (m, 4H), 2.00-1.91 (m, 2H), 1.89-1.67 (m, 3H), 1.58-1.46 (m, 1H); MS ESI 505.3 $[M + H]^+$, calcd for $[C_{32}H_{32}N_4O_2 + H]^+$ 505.3. $[\alpha]^{22.6°}_{D}$ = -69° (c 0.29, Methanol).

Example A60. (1R*,2S*)-(E)-2-(3-(4-(pyrrolidin-1-ylmethyl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



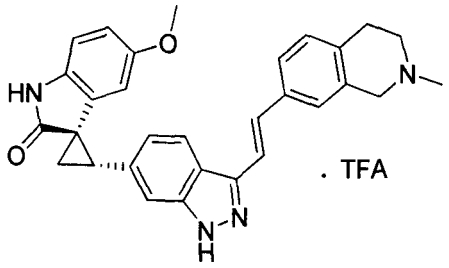
[00210] The title compound was synthesized according to the method of Example A55, except substituting pyrrolidine (71 mg, 0.86 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (34 mg, 35%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.55-7.48 (m, 5H), 7.08-7.05 (m, 2H), 6.94 (d, J = 7.8 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 5.99 (d, J = 7.5 Hz, 1H) 4.40 (s, 2H), 3.55-3.46 (m, 2H), 3.38-3.34 (m, 1H), 3.27-3.16 (m, 2H), 2.27-2.17 (m, 4H), 2.06-1.98 (m, 2H); MS ESI 461.3 $[M + H]^+$, calcd for $[C_{30}H_{28}N_4O + H]^+$ 461.2.

Example A61. (1R,2S)-(E)-2-(3-(4-(pyrolidin-1-ylmethyl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00211] The title compound was synthesized according to the method of Example A51B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl) [cyclopropane-1,3'-indolin]-2'-one (175 mg, 0.43 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)pyrrolidine (225 mg, 0.64 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (123 mg, 51%). Spectral was data identical to that obtained in Example A60.

Example A64. (1R,2S)-5'-methoxy-2-(3-((E)-2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)vinyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



A. 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline

[00212] To a solution of 7-bromo-1,2,3,4-tetrahydroisoquinoline (1g, 4.7 mmol) in formic acid (20 mL) was added formalin (1.2 mL, 15 mmol). The solution was heated to 150°C for 5 min under microwave irradiation. The solvent was removed in vacuo and the residue was dissolved into ethyl acetate (100 mL), washed with sat. sodium bicarbonate (2 x 10 mL), brine (10 mL) and dried over $MgSO_4$. Removal of the solvent gave the title compound as a white solid (800 mg, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 1H), 7.70 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.11 (s, 2H), 3.37-3.34 (m, 2H), 3.27-3.24 (m, 2H) 2.95 (s, 3H); MS ESI 225.9, 227.9 $[M + H]^+$, calcd for $[C_{10}H_{12}BrN + H]^+$ 226.0, 228.0.

B. (E)-2-methyl-7-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1,2,3,4-tetrahydroisoquinoline

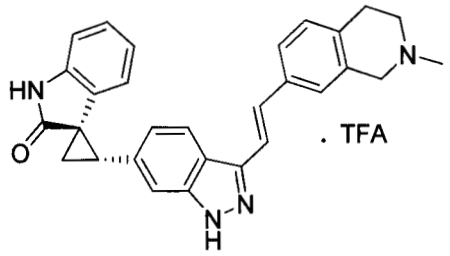
[00213] The title compound was synthesized according to the method of Example A51A, except substituting 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (720 mg, 3.2 mmol). The title compound isolated as an orange oil (700 mg, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 18.6 Hz, 1H), 7.29-7.26 (m, 1H), 7.13 (s, 1H), 7.08 (d, J = 7.3 Hz, 1H), 6.10 (d, J= 18.6 Hz, 1H), 3.57(s, 2H), 2.93-2.90 (m, 2H), 2.70-2.67 (m, 2H), 2.46 (s, 3H), 1.32 (s, 12H); MS ESI 300.2 $[M + H]^+$, calcd for $[C_{18}H_{26}BNO_2 + H]^+$ 300.2.

C. *(1R,2S)-5'-methoxy-2-(3-((E)-2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)vinyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one*

[00214] The title compound was synthesized according to the method of Example A51B, except substituting (E)-2-methyl-7-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1,2,3,4-tetrahydroisoquinoline (80 mg, 0.3 mmol) Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (32 mg, 38%). ^1H NMR (400 MHz, CD_3OD) δ 8.01 (d, J = 8.3 Hz, 1H), 7.64-7.60 (m, 1H), 7.49-7.45 (m, 4H), 7.32 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.63-6.59 (m, 1H), 5.99-5.98 (m,

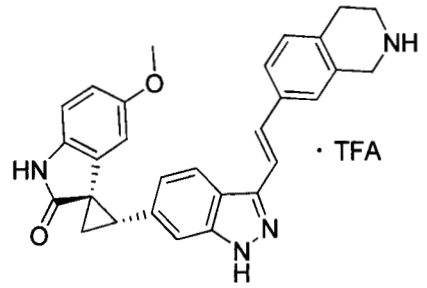
1H), 4.65-4.58 (m, 1H) 4.42-4.34 (m, 1H), 3.84-3.75 (m, 1H), 3.49-3.40 (m, 1H), 3.39-3.33 (m, 1H), 3.27 (s, 3H), 3.24-3.17 (m, 2H), 3.09 (s, 3H), 2.27-2.18 (m, 2H); MS ESI 477.3 [M + H]$^+$, calcd for [$C_{30}H_{28}N_4O_2$ + H]$^+$ 477.2. $[\alpha]^{24.2°}_D$ = -85° (c 0.40, Methanol).

Example A65. (1R,2S)-2-(3-((E)-2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)vinyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



[00215] The title compound was synthesized according to the method of Example A51B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl) [cyclopropane-1,3'-indolin]-2'-one (150 mg, 0.37 mmol) and (E)-2-methyl-7-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1,2,3,4-tetrahydroisoquinoline (150 mg, 0.55 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (35 mg, 17%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.45 (bs, 4H), 7.30 (d, J = 8.0 Hz, 1H), 7.08-6.93 (m, 2H), 6.94 (d, J = 7.8 Hz, 1H), 6.57 (t, J = 7.40 Hz, 1H), 5.98 (d, J = 7.3 Hz, 1H), 4.64-4.59 (m., 1H), 4.39-4.32 (m, 1H), 3.82-3.77 (m, 1H), 3.49-3.37 (m, 1H), 3.37-3.33 (m, 1H), 3.30-3.20 (m, 2H), 3.08 (s, 3H), 2.27-2.17 (m, 2H); MS ESI 447.3 [M + H]$^+$, calcd for [$C_{29}H_{26}N_4O$ + H]$^+$ 447.2. $[\alpha]^{23.4°}_D$ = -124° (c 0.25, Methanol).

Example A66. (1R,2S)-5'-methoxy-2-(3-((E)-2-(1,2,3,4-tetrahydroisoquinolin-7-yl)vinyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



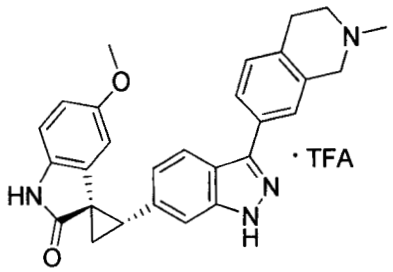
A. (E)-2,2,2-trifluoro-1-(7-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone

[00216] The title compound was synthesized according to the method of Example A51A, except substituting 1-(7-bromo-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone (415 mg, 1.32 mmol). The title compound was purified by silica gel chromatography (3:2 hexanes/EtOAC) to give the title compound as a white solid (300 mg, 58%). MS ESI 382.2 $[M + H]^+$, calcd for $[C_{19}H_{23}BF_3NO_3 + H]^+$ 382.2.

B. *(1R,2S)-5'-methoxy-2-(3-((E)-2-(1,2,3,4-tetrahydroisoquinolin-7-yl)vinyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one*

[00217] The title compound was synthesized according to the method of Example A51B, except substituting (E)-2,2,2-trifluoro-1-(7-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone (80 mg, 0.21 mmol) Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (26 mg, 31%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.48 (bs, 4H), 7.29 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 5.58 (s, 1H), 4.41 (s, 2H), 3.54 (t, J = 6.0 Hz, 2H), 3.40-3.33 (m, 1H), 3.27 (s, 3H), 3.19-3.11 (m, 2H), 2.29-2.14 (m, 2H); MS ESI 463.3 $[M + H]^+$, calcd for $[C_{29}H_{26}N_4O_2 + H]^+$ 463.2.

[00218] Example A70. (1R,2S)-5'-methoxy-2-(3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



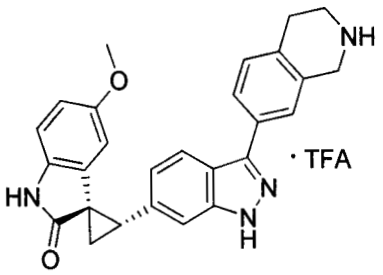
A. 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro isoquinoline

[00219] The title compound was synthesized according to the method of Example A69 in WO2010/115279 method A, except substituting 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (450 mg, 2 mmol). Trituration with hexane gave the title compound as a brown solid (300 mg, 55%). MS ESI 274.1.1 $[M + H]^+$, calcd for $[C_{16}H_{26}BNO_3 + H]^+$ 274.2.

B. (1R,2S)-5'-methoxy-2-(3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one

[00220] The title compound was synthesized according to the method of Example A42B, except substituting 2-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroisoquinoline (80 mg, 0.29 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (32 mg, 40%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (t, J = 8.9 Hz, 2H), 7.79 (s, 1H), 7.53 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 9.0 Hz, 1H), 6.84 (d, J = 9.3 Hz, 1H), 6.62 (d, J = 7.0 Hz, 1H), 5.60 (s, 1H), 4.73-4.63 (m, 1H), 4.47-4.42 (m, 1H), 3.85-3.78 (m, 1H), 3.52-3.42 (m, 1H), 3.41-3.28 (m, 3H), 3.27 (s, 3H), 3.11 (s, 3H), 2.29-2.18 (m, 2H); MS ESI 451.3 $[M + H]^+$, calcd for $[C_{28}H_{26}N_4O_2 + H]^+$ 451.2.

[00221] Example A71. (1R,2S)-5'-methoxy-2-(3-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



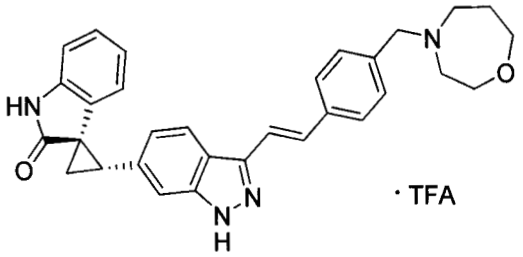
A. 2,2,2-trifluoro-1-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro isoquinolin-2(1H)-yl)ethanone

[00222] The title compound was synthesized according to the method of Example A69 in method A WO2010/115279, except substituting 1-(7-bromo-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone (450 mg, 2 mmol). Silica gel chromatography (3:2 hexane/EtOAc) gave the title compound as a white (320 mg, 90%). MS ESI 356.1 $[M + H]^+$, calcd for $[C_{17}H_{21}BF_3NO_3 + H]^+$ 356.2.

B. (1R,2S)-5'-methoxy-2-(3-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one

[00223] The title compound was synthesized according to the method of Example A42B, except substituting 2,2,2-trifluoro-1-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone (100 mg, 0.2 mmol). Purification by reverse phase

preparatory HPLC gave the title compound as a yellow TFA salt (18 mg, 17%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (t, J = 8.3 Hz, 1H), 7.90 (d, J = 6.78 Hz, 1H), 7.80 (s, 1H), 7.53 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 6.62 (d, J = 8.3 Hz, 1H), 5.60 (s, 1H), 4.48 (s, 2H), 3.60-3.53 (m, 2H), 3.41-3.33 (m, 1H), 3.27 (s, 3H), 3.20 (t, J = 6.6 Hz, 2H), 2.29-2.18 (m, 2H); MS ESI 437.1 $[M + H]^+$, calcd for $[C_{27}H_{24}N_4O_2 + H]^+$ 437.2.Example A72. (1R,2S)-(E)-2-(3-(4-((1,4-oxazepan-4-yl)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



A. 4-(4-bromobenzyl)-1,4-oxazepane

[00224] To a solution of 4-bromobenzaldehyde (616 mg, 3.3 mmol) in dichloroethane (50 mL) was added homomorpholine hydrochloride (548 mg, 4 mmol) and acetic acid (0.1 mL). Sodium triacetoxyborohydride (3.4 g, 16 mmol) was added and the reaction was stirred overnight. The reaction was quenched with sat. NH_4Cl (30 mL). Ethyl acetate (250 mL) was added and the solution was washed with sat. $NaHCO_3$ (2 x 50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated to dryness. The residue was flushed through a silica plug with (5% MeOH/CH_2Cl_2) to give a white solid (850 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 7.3 Hz, 2H), 7.10 (d, J = 7.3 Hz, 2H), 3.66-3.57 (m, 2H), 3.55-3.50 (m, 2H), 3.46-3.42 (m, 2H), 3.16-3.10 (m, 2H), 2.55-2.45 (m, 4H), 1.75-1.65 (m, 2H).

B. (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)-1,4-oxazepane

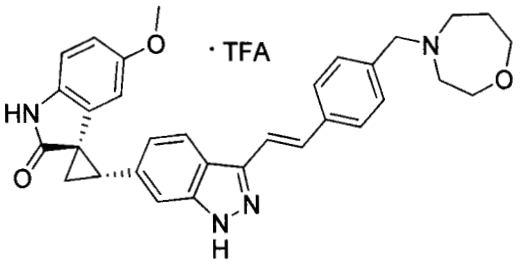
[00225] The title compound was synthesized according to the method of Example A51A, except substituting 4-(4-bromobenzyl)-1,4-oxazepane (500 mg, 1.86 mmol). The title compound isolated as an orange oil (560 mg, 88%). MS ESI 344.2 $[M + H]^+$, calcd for $[C_{20}H_{30}BNO_3 + H]^+$ 344.2.

C. (1R,2S)-2-(3-(4-((1,4-oxazepan-4-yl)methyl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one

[00226] The title compound was synthesized according to the method of Example A51B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl) [cyclopropane-1,3'-indolin]-2'-one (100 mg, 0.25 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)-1,4-oxazepane (103 mg, 0.30 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (38 mg, 26%).

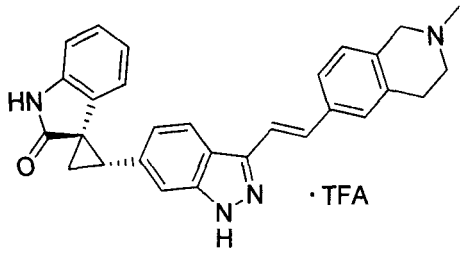
^{1}H NMR (400 MHz, MeOD) δ 8.02 (d, J = 9.0 Hz, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.61-7.53 (m, 4H), 7.48 (s, 1H), 7.08-7.04 (m, 2H), 6.94 (d, J = 7.5 Hz, 1H), 6.60-6.56 (m, 1H), 5.99 (d, J = 7.8 Hz, 1H), 4.45 (s, 2H), 4.02-3.80 (m, 4H), 3.65-3.60 (m, 1H), 3.57-3.35 (m, 4H), 2.29-2.12 (m, 4H); MS ESI 491.3 $[M + H]^+$, calcd for $[C_{31}H_{30}N_4O_2 + H]^+$ 490.2. $[\alpha]^{23.4°}_D$ = -146° (c 0.39, Methanol).

Example A73. (1R,2S)-(E)-2-(3-(4-((1,4-oxazepan-4-yl)methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



[00227] The title compound was synthesized according to the method of Example A51B, except substituting (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)-1,4-oxazepane (103 mg, 0.30 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (48 mg, 31%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.57-7.49 (m, 5H), 7.05 (d, *J* = 8.28 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 5.58 (s, 1H), 4.44 (s, 2H), 3.99-3.75 (m, 4H), 3.69-3.55 (m, 1H), 3.55-3.34 (m, 4H), 3.26 (s, 3H) 2.28-2.11 (m, 4H); MS ESI 521.3 $[M + H]^+$, calcd for $[C_{32}H_{32}N_4O_3 + H]^+$ 520.2. $[\alpha]^{22.8°}_D$ = -76° (c 0.33, Methanol).

Example A74. (1R,2S)-2-(3-((E)-2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)vinyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



A. 6-bromo-2-methylisoquinolinium trifluoromethanesulfonate

[00228] A solution of 6-bromoisoquinoline (618 mg, 3 mmol) in CH_2Cl_2 (35 mL) was cooled to 0°C under argon. Methyl triflate (0.38 mL, 3.3 mmol) was added dropwise and the mixture was warmed to rt. The precipitate was filtered, triturated with ether and dried to give the title compound as a yellow solid (1.03 g, 93%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.83 (s, 1H), 8.64-8.56 (m, 2H), 8.41 (d, J = 7.0 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.20 (d, J = 9.03 Hz, 1H), 4.53 (s, 3H).

B. 6-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline

[00229] To a solution of 6-bromo-2-methylisoquinolinium trifluoromethanesulfonate (371 mg, 1 mmol) in methanol (10 mL) was added bromocresol green indicator. Sodium borohydride (93 mg, 2.5 mmol) was added and the reaction was stirred at rt. HCl in acetic acid (1M) was added periodically to maintain a yellow color. After 1 h, water (50 mL) was added and the solution was basified with NaOH (1M), extracted into CH_2Cl_2 (100 mL), dried over $MgSO_4$ and concentrated to give the title compound as a white solid (200 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7,17 (m, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 3.51 (s, 2H), 2.93-2.82 (m, 2H), 2.65 (t, *J* = 5.8 Hz, 2H), 2.45 (s, 3H).

C. (E)-2-methyl-6-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1,2,3,4-tetrahydroisoquinoline

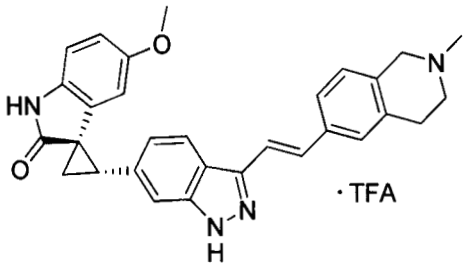
[00230] The title compound was synthesized according to the method of Example A51A, except substituting 6-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (720 mg, 3.2 mmol). The title compound isolated as a brown oil (720 mg, 75%). MS ESI 300.2 $[M + H]^+$, calcd for $[C_{18}H_{26}BNO_2 + H]^+$ 300.2.

D. (1R,2S)-2-(3-((E)-2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)vinyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one

[00231] The title compound was synthesized according to the method of Example A51B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl) [cyclopropane-1,3'-indolin]-2'-one

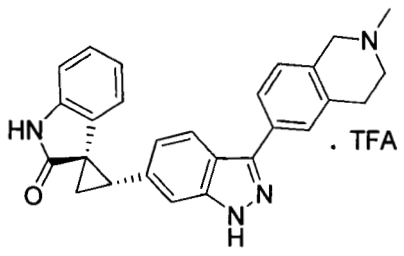
(122 mg, 0.3 mmol) and (E)-2-methyl-6-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1,2,3,4-tetrahydroisoquinoline (110 mg, 0.37 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (38 mg, 14%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.54 (s, 1H), 7.50-7.43 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 7.10-6.99 (m, 2H), 6.94 (d, J = 7.8 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 5.99 (d, J = 7.8 Hz, 1H), 4.64-4.53 (m, 1H), 4.41-4.27 (m, 1H), 3.82-3.75 (m, 1H), 3.51-3.33 (m, 2H), 3.28-3.16 (m, 2H), 3.08 (s, 3H), 2.28-2.16 (m, 2H); MS ESI 447.3 $[M + H]^+$, calcd for $[C_{29}H_{26}N_4O + H]^+$ 447.2. $[\alpha]^{23.6°}_D$ = -147° (c 0.30, Methanol).

Example A75. (1R,2S)-5'-methoxy-2-(3-((E)-2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)vinyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



[00232] The title compound was synthesized according to the method of Example A51B, except substituting (E)-2-methyl-6-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1,2,3,4-tetrahydroisoquinoline (134 mg, 0.45 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (42 mg, 25%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.54 (s, 1H), 7.48 (bs, 3H), 7.23 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.62 (d, *J* = 8. 8 Hz, 1H), 5.58 (s, 1H), 4.60-4.51 (m, 1H), 4.37-4.33 (m, 1H), 3.82-3.75 (m, 1H), 3.51-3.33 (m, 2H), 3.28-3.16 (m, 2H), 3.27 (s, 3H), 3.08 (s, 3H), 2.28-2.15 (m, 2H); MS ESI 477.3 $[M + H]^+$, calcd for $[C_{29}H_{26}N_4O + H]^+$ 477.2.

Example A76. (1R,2S)-2-(3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



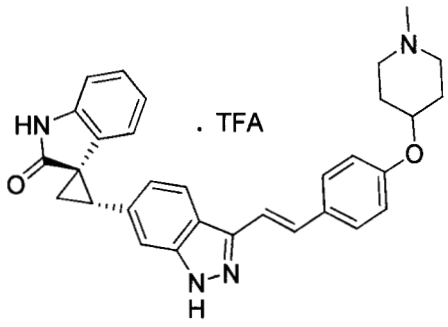
A. 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydro isoquinoline

[00233] The title compound was synthesized according to the method of Example A69 method AWO2010/115279, except substituting 6-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (450 mg, 2 mmol). Trituration with hexane gave the title compound as a brown solid (265 mg, 49%). MS ESI 274.1 $[M + H]^+$, calcd for $[C_{16}H_{26}BNO_3 + H]^+$ 274.2.

B. (1R,2S)-2-(3-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one

[00234] The title compound was synthesized according to the method of Example A42B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl) [cyclopropane-1,3'-indolin]-2'-one (64 mg, 0.15 mmol) and 2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydroisoquinoline (80 mg, 0.29 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (24 mg, 31%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.95-7.81 (m, 3H), 7.50 (s, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.08-6.99 (m, 2H), 6.94 (d, J = 7.5 Hz, 1H), 6.57 (t, J = 7.5 Hz, 1H), 6.00 (d, J = 7.5 Hz, 1H), 4.66-4.62 (m, 1H), 4.43-4.38 (m, 1H), 3.85-3.78 (m, 1H), 3.52-3.42 (m, 1H), 3.41-3.33 (m, 1H), 3.32-3.20 (m, 2H), 3.10 (s, 3H), 2.27-2.14 (m, 2H); MS ESI 421.3 $[M + H]^+$, calcd for $[C_{27}H_{24}N_4O + H]^+$ 421.2.

Example A78. (1R,2S)-(E)-2-(3-(4-(1-methylpiperidin-4-yloxy)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



A. 4-(4-bromophenoxy)-1-methylpiperidine

[00235] Prepared according to the method of Example A64 in WO2010/115279 method A, except substituting 4-(4-bromophenoxy)piperidine (256 mg, 1 mmol). The title compound was isolated as a white solid (270 mg, 99%). ^{1}H NMR ($CDCl_3$) δ: 7.36 (d, J =

8.3 Hz, 2H), 6.79 (d, J = 8.3 Hz, 2H), 4.28 (bs, 1H), 2.73-2.65 (m, 2H), 2.32 (s, 3H), 2.32-2.25 (m, 2H), 2.05-1.95 (m, 2H), 1.86-1.80 (m, 2H).

B. (E)-1-methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenoxy) piperidine

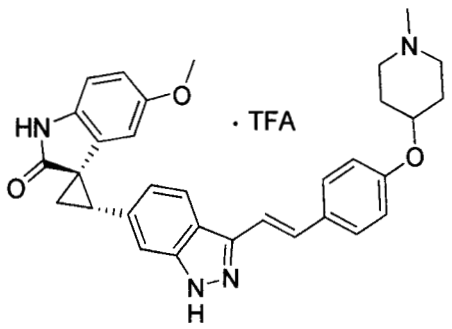
[00236] The title compound was synthesized according to the method of Example A51A, except substituting 4-(4-bromophenoxy)-1-methylpiperidine (270 mg, 1 mmol). The title compound isolated as an orange oil (340 mg, 99%). MS ESI 344.2 $[M + H]^+$, calcd for $[C_{20}H_{30}BNO_3 + H]^+$ 344.2.

C. (1R,2S)-2-(3-(4-(1-methylpiperidin-4-yloxy)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one

[00237] The title compound was synthesized according to the method of Example A51B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl) [cyclopropane-1,3'-indolin]-2'-one (100 mg, 0.25 mmol) and (E)-1-methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenoxy)piperidine (105 mg, 0.3 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (35 mg, 25%). ^1H NMR (CD_3OD) δ: 7.99-7.97 (m, 1H), 7.63-7.56 (m, 2H), 7.50-7.42 (m, 2H), 7.36-7.28 (m, 1H), 7.10-7.01 (m, 4H), 6.97-6.91 (m, 1H), 6.59 (t, J = 7.7 Hz, 1H), 5.99 (d, J = 7.8 Hz, 1H), 4.84-4.79 (m, 0.5H), 4.65-4.60 (m, 0.5H), 3.65-3.62 (m, 1H), 3.47-3.34 (m, 3H), 3.25-3.13 (m, 1H), 2.94 (s, 3H), 2.44-2.40 (m, 1H), 2.32-2.01 (m, 5H), 1.96-1.81 (m, 1H); MS ESI 491.2 $[M + H]^+$, calcd for $[C_{31}H_{30}N_4O_2 + H]^+$ 491.3.

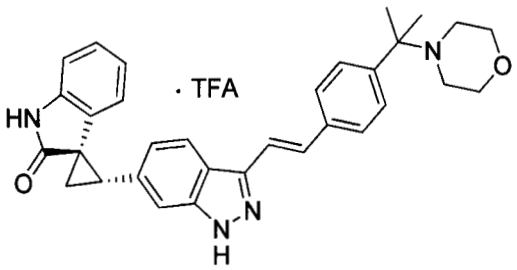
$[\alpha]^{22}_D$ = -154 ° (c 0.43, MeOH).

Example A79. (1R,2S)-(E)-5'-methoxy-2-(3-(4-(1-methylpiperidin-4-yloxy)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



[00238] The title compound was synthesized according to the method of Example A51B, except substituting (E)-1-methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl) phenoxy)piperidine (105 mg, 0.3 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (36 mg, 25%). ^{1}H NMR (CD_3OD) δ: 7.95 (d, J = 8.8 Hz, 1H), 7.56-7.53 (m, 2H), 7.45-7.40 (m, 2H), 7.30-7.26 (m, 1H), 7.04-6.98 (m, 4H), 6.83 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 5.58 (s, 1H),, 4.81-4.54 (m, 1H) 3.65-3.33 (m, 4H), 3.24 (s, 3H), 3.23-3.13 (m, 1H) 2.92 (s, 3H), 2.44-2.37 (m, 1H), 2.32-2.01 (m, 5H), 1.96-1.81 (m, 1H); MS ESI 521.3 $[M + H]^+$, calcd for $[C_{32}H_{32}N_4O_3 + H]^+$ 521.2.

Example A80. (1R,2S)-(E)-2-(3-(4-(2-morpholinopropan-2-yl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



A. 2-methyl-2-morpholinopropanenitrile

[00239] Acetone cyanohydrin (4.3 g, 50 mmol) was dissolved into acetone (5 mL). Morpholine (4.3 g, 50 mmol) was added and the solution was stirred at rt for 24 h. The volatile solvents were removed in vacuo to give the title compound as a clear liquid in quantitative yield. MS ESI 155.0 $[M + H]^+$, calcd for $[C_8H_{14}N_2O + H]^+$ 155.1.

B. 4-(2-(4-bromophenyl)propan-2-yl)morpholine

[00240] Magnesium turnings (190 mg, 7.4 mmol) was added to dry THF (15 mL) under argon. 1,4-dibromobenzene (2.43 g, 10.3 mmol) was added and the solution was heated to reflux for 30 min. 2-Methyl-2-morpholinopropanenitrile (1 g, 6.6 mmol) was dissolved into THF (30 mL) and added dropwise to the solution at reflux. The mixture was stirred for 2 h and cooled to rt. The reaction was quenched with sat. K_2CO_3 solution and extracted with CH_2Cl_2 (200 mL), dried over $MgSO_4$ and concentrated to an orange oil. The crude mixture was purified on a Biotage silica column (2-15% MeOH in CH_2Cl_2) to give the title compound as a yellow oil (204 mg, 10%). MS ESI 284.0, 286.0 $[M + H]^+$, calcd for $[C_{13}H_{18}BrNO + H]^+$ 284.1, 286.1.

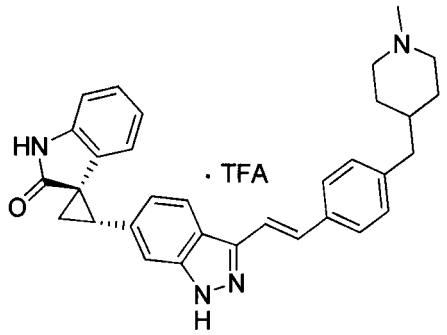
C. (E)-4-(2-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)propan-2-yl)morpholine

[00241] The title compound was synthesized according to the method of Example A51A, except substituting 4-(2-(4-bromophenyl)propan-2-yl)morpholine (200 mg, 0.7 mmol). The title compound isolated as an orange oil (140 mg, 40%). MS ESI 358.1 $[M + H]^+$, calcd for $[C_{21}H_{32}BNO_3 + H]^+$ 358.2.

D. (1R,2S)-2-(3-(4-(2-morpholinopropan-2-yl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one

[00242] The title compound was synthesized according to the method of Example A51B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl) [cyclopropane-1,3'-indolin]-2'-one (100 mg, 0.25 mmol) and (E)-1-methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenoxy)piperidine (140 mg, 0.4 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (51 mg, 34%). ^{1}H NMR (CD_3OD) δ: 7.98 (d, J = 8.5 Hz, 1H), 7.80-7.76 (m, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.52 - 7.46 (m, 3H), 7.08-6.98 (m, 2H), 6.94 (d, J = 7.8 Hz, 1H), 6.56 (t, J = 7.7 Hz, 1H), 5.98 (d, J = 7.5 Hz, 1H), 4.06-3.96 (m, 2H), 3.83-3.73 (m, 2H), 3.35-3.29 (m, 3H), 3.13-3.08 (m, 2H), 2.26-2.14 (m, 2H), 1.90 (s, 6H); MS ESI 418.2 $[M - C_4H_8NO]^+$, calcd for $[C_{32}H_{32}N_4O_2 - C_4H_8NO]^+$ 418.2. $[\alpha]^{22.8°}_D$ = -109° (c 0.32, Methanol).

Example A81. (1R,2S)-(E)-2-(3-(4-((1-methylpiperidin-4-yl)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



A. tert-butyl 4-(4-bromobenzyl)piperidine-1-carboxylate

[00243] To a solution of tert-butyl 4-methylenepiperidine-1-carboxylate (1 g, 5.1 mmol) was added 9-BBN solution (10.2 mL of 0.5 M solution, 5.1 mmol) and the mixture was heated to reflux for 1 h under argon. The solution was then cooled to rt and 1,4-

iodobromobenzene (1.3 g, 4.7 mmol) was added, followed by K_2CO_3 (843 mg, 6.1 mmol), DMF (10 mL), water (1 mL) and $Pd(dppf)Cl_2$ (114 mg, 0.15 mmol). The solution was heated to 60°C under argon for 3 h and cooled to rt. Ethyl acetate (250 mL) was added and the solution was washed with water (2 x 50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by Biotage silica gel column (50:50 Hexane/Ethyl acetate) to give the title compound as a yellow solid (1.2 g, 72%).

B. 4-(4-bromobenzyl)piperidine

[00244] To a solution of tert-butyl 4-(4-bromobenzyl)piperidine-1-carboxylate (780 mg, 2.2 mmol) in CH_2Cl_2 (15 mmol), was added TFA (0.5 mL) and the mixture was stirred at rt for 1 h. The solvent was removed in vacuo and the residue dissolved into CH_2Cl_2 (50 mL), washed with NaOH (0.1M, 10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated to dryness to give the title compound as a beige solid (520 mg, 93%).

C. 4-(4-bromobenzyl)-1-methylpiperidine

[00245] Prepared according to the method of Example A69 method A in WO2010/115279, except substituting 4-(4-bromobenzyl)piperidine (520 mg, 2 mmol). The title compound was isolated as a brown solid (490 mg, 89%). ^1H NMR ($CDCl_3$) δ 7.39 (d, J = 7.5 Hz, 2H), 7.01 (d, J = 7.8 Hz, 2H), 2.93 (d, J = 11.0 Hz, 2H), 2.50 (d, J = 6.8 Hz, 2H), 2.32 (s, 3H), 1.99-1.94 (m, 2H), 1.65-1.62 (m, 2H), 1.50-1.35 (m, 3H).

D. (E)-1-methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl) piperidine

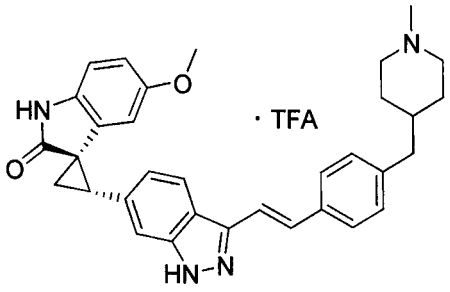
[00246] The title compound was synthesized according to the method of Example A51A, except substituting 4-(4-bromobenzyl)-1-methylpiperidine (267 mg, 1 mmol). The title compound isolated as an orange oil (340 mg, 99%). MS ESI 342.2 $[M + H]^+$, calcd for $[C_{21}H_{32}BNO_2 + H]^+$ 342.2.

E. (1R,2S)-2-(3-(4-((1-methylpiperidin-4-yl)methyl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one

[00247] The title compound was synthesized according to the method of Example A51B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl) [cyclopropane-1,3'-indolin]-2'-one (100 mg, 0.25 mmol) and (E)-1-methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)piperidine (105 mg, 0.3 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (39 mg, 27%). ^1H NMR (CD_3OD) δ:

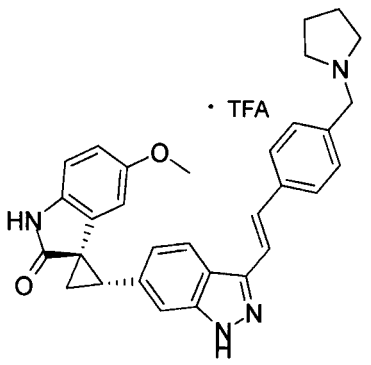
7.97 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 7.3 Hz, 2H), 7.51-7.37 (m, 3H), 7.22 (d, J = 7.5 Hz, 2H), 7.08-7.01 (m, 2H), 6.94 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 7.5 Hz, 1H), 5.99 (d, J = 7.5 Hz, 1H), 3.50-3.47 (m, 2H), 3.37 - 3.31 (m, 1H), 2.97 - 2.92 (m, 2H), 2.83 (s, 3H), 2.63 (d, J = 6.0 Hz, 2H), 2.26 - 2.14 (m, 2H), 1.96 - 1.81 (m, 3H), 1.56 - 1.41 (m, 2H); MS ESI 489.4 $[M + H]^+$, calcd for $[C_{32}H_{32}N_4O + H]^+$ 489.3. $[\alpha]^{22.8°}_D$ = -96° (c 0.26, Methanol).

Example A82. (1R,2S)-(E)-5'-methoxy-2-(3-(4-((1-methylpiperidin-4-yl)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate salt



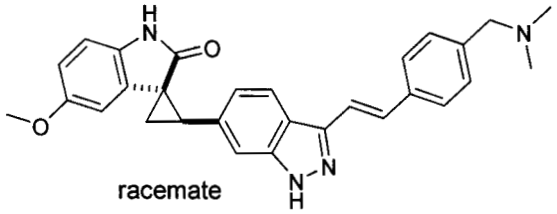
[00248] The title compound was synthesized according to the method of Example A51B, except substituting (E)-1-methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl) benzyl)piperidine (105 mg, 0.3 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (24 mg, 17%). ^{1}H NMR (CD_3OD) δ: 7.97 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.51-7.36 (m, 3H), 7.20 (d, J = 7.5 Hz, 2H), 7.01 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 5.59 (s,1H), 3.50-3.47 (m, 2H), 3.37-3.31 (m, 1H), 3.25 (s, 3H), 2.97-2.92 (m, 2H), 2.83 (s, 3H), 2.62 (d, J = 6.0 Hz, 2H), 2.26-2.14 (m, 2H), 1.96-1.81 (m, 3H), 1.53-1.44 (m, 2H); MS ESI 519.3 $[M + H]^+$, calcd for $[C_{33}H_{34}N_4O_2 + H]^+$ 519.3. $[\alpha]^{22.8°}_D$ = -100° (c 0.29, Methanol).

Example A83. (1R,2S)-(E)-5'-methoxy-2-(3-(4-(pyrrolidin-1-ylmethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



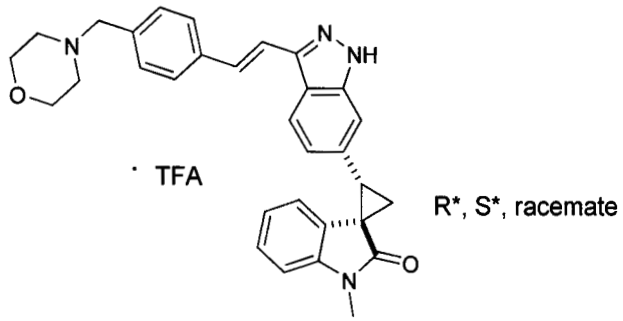
[00249] The title compound was synthesized according to the method of Example A51B, except substituting (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl) pyrrolidine (50 mg, 0.16 mmol). Purification by reverse phase preparatory HPLC gave the title compound as a yellow TFA salt (19 mg, 21%). ^{1}H NMR (CD_3OD) δ: 8.02 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.56-7.47 (m, 5H), 7.05 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 5.58 (s, 1H), 4.39 (s, 2H), 3.52 (bs., 2H), 3.37 (t, J = 8.5 Hz, 1H), 3.27 (s, 3H), 3.25-3.16 (m, 2H), 2.27-2.14 (m, 4H), 2.03 (bs., 2H); MS ESI 491.3 $[M + H]^+$, calcd for $[C_{31}H_{30}N_4O_2 + H]^+$ 491.2. $[\alpha]^{24.2°}_D$ = -117° (c 0.52, Methanol).

Example A84. (1R*,2R*)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one



[00250] The minor diastereomer from the reaction of Example A34B was isolated as yellow-orange solid film (36 mg, 3%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.99 (d, J=8.5 Hz, 1 H), 7.75 (d, J=8.0 Hz, 2 H), 7.56-7.46 (m, 5 H), 7.15 (d, J=8.5 Hz, 1 H), 6.87 (d, J=8.3 Hz, 1 H), 6.82-6.72 (m, 2 H), 4.31 (s, 2 H), 3.81 (s, 3 H), 3.39 (t, J=8.8 Hz, 1 H), 2.87 (s, 6 H), 2.41 (dd, J=8.4, 4.9 Hz, 1 H), 2.23 (dd, J=8.8, 4.8 Hz, 1 H); MS ESI $[M+ H]^+$ 465.2, calcd for $[C_{29}H_{28}N_4O_2+ H]^+$ 465.2.

Example A87. (1R*,2S*)-(E)-1'-methyl-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



A. (E)-3-((3-iodo-1H-indazol-6-yl)methylene)-1-methylindolin-2-one

[00251] The title compound was synthesized according to the method described for (E)-3-((1H-indazol-5-yl)methylene)indolin-2-one, except substituting 3-iodo-1H-indazole-6-carbaldehyde (462 mg, 1.70 mmol) and 1-methylindolin-2-one (250 mg, 1.70 mmol), the title compound was obtained as a yellow-orange solid (545 mg, 80 %); MS ESI 402.2 [M + H]$^+$, calcd for [$C_{17}H_{12}IN_3O$ + H]$^+$ 402.01.

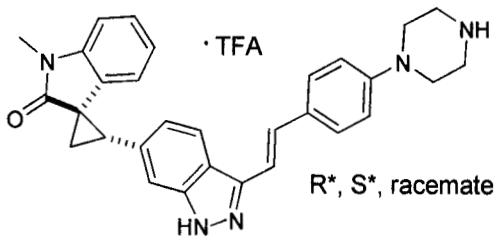
B. (1R,2S*)-2-(3-iodo-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one*

[00252] The title compound was synthesized according to the method of Example A6, except substituting (E)-3-((3-iodo-1H-indazol-6-yl)methylene)-1-methylindolin-2-one (545 mg, 1.36 mmol) to give the title compound as a 9:1 mixture of diastereomers (405 mg, 72 %); MS ESI 416.0 [M + H]$^+$, calcd for [$C_{18}H_{14}IN_3O$ + H]$^+$ 416.03.

C. (1R,2S*)-(E)-1'-methyl-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate*

[00253] The title compound was synthesized according to the method of Example A45 in WO2010/115279, except substituting (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (30 mg, 0.072 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (31 mg, 0.094 mmol). After Suzuki coupling, the solvent was removed and the residue was purified by prep-HPLC to give the title compound (16mg, 45%); ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.54-7.46 (m, 5H), 7.14 (t, J = 7.8 Hz, 1H), 7.02 (d, J = 8.1 Hz, 2H), 6.64 (t, J = 7.3 Hz, 1H), 6.02 (d, J = 7.2 Hz, 1H), 4.38 (s, 2H), 4.08-4.04 (m, 2H), 3.75-3.69 (m, 2H), 3.43-3.34 (m, 6H), 3.27-3.19 (m, 2H), 2.29–2.25 (m, 1H), 2.22-2.18 (m, 1H); MS ESI [M + H]$^+$ 491.3, calcd for [$C_{31}H_{30}N_4O_2$ + H]$^+$ 491.24.

Example A89. (1R*,2S*)-(E)-1'-methyl-2-(3-(4-(piperazin-1-yl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



A. tert-butyl 4-(4-ethynylphenyl)piperazine-1-carboxylate

[00254] A microwave vial was charged with *tert*-butyl 4-(4-iodophenyl)piperazine-1-carboxylate (300 mg, 0.773 mmol), trimethylsilylacetylene (0.22 mL, 1.54 mmol), NEt_3 (3.0 mL), DMF (1.5 mL), CuI (15 mg, 0.080 mmol), and $PdCl_2(PPh_3)_2$ (27 mg, 0.039 mmol). The vial was capped and heated in the microwave at 100 °C for 1 h. After removing the NEt_3 *in vacuo*, the residue was extracted with EtOAc (15 mL). The organic layer was then washed with $NaHCO_3$ (sat.) (5 mL), H_2O (5 mL), brine (5 mL) and then dried over $MgSO_4$. The solvent was removed and then the material was dissolved into MeOH (4 mL) and THF (2 mL). K_2CO_3 (1.0 mL of a 1M solution) was added and the reaction stirred for 3 h. The solvent was removed and the residue extracted with EtOAc (15 mL). The organic layer was washed with brine (5 mL) and then dried over $MgSO_4$. The solvent was removed and the product dried under high vacuum to give the title compound as a brown solid (212 mg, 96 %); MS ESI 287.0 $[M + H]^+$, calcd for $[C_{17}H_{22}N_2O_2 + H]^+$ 287.18.

B. (E)-tert-butyl 4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl) piperazine-1-carboxylate

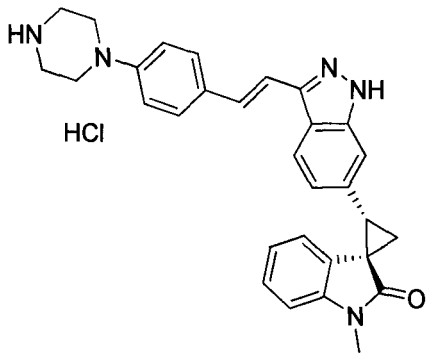
[00255] The title compound was synthesized according to the method of Example A42A, except substituting *tert*-butyl 4-(4-ethynylphenyl)piperazine-1-carboxylate (212 mg, 0.740 mmol) to give, after column chromatography (silica gel, Hexanes/EtOAc, 6:1 to 5:1), the title compound as a pale-yellow solid (137 mg, 45 %); MS ESI 415.3 $[M + H]^+$, calcd for $[C_{23}H_{35}BN_2O_4 + H]^+$ 415.28.

C. (1R,2S*)-(E)-1'-methyl-2-(3-(4-(piperazin-1-yl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate*

[00256] The title compound was synthesized according to the method of Example A45 in WO2010/115279, except substituting (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (37 mg, 0.090 mmol) and (E)-tert-butyl 4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine-1-carboxylate (45 mg, 0.109 mmol). The solvent was removed and the Boc-protected amine purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5) to give an impure product which dissolved into CH_2Cl_2 (2.0 mL) and TFA (200 uL) was added. The reaction was stirred for 2 h, the solvent removed and the residue purified by prep-HPLC to give the title compound as an off-white powder (2.0 mg, 4.0 %); ^1H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.46-7.41 (m, 2H), 7.30 (d, J = 17 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.06-6.99 (m, 4H), 6.65 (t, J = 8.0 Hz, 1H), 6.02 (d, J = 7.7 Hz, 1H), 3.49-3.44 (m,

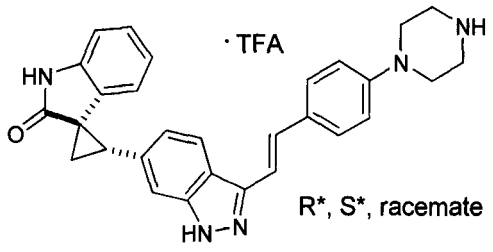
4H), 3.40-3.31 (m, 8H), 2.28-2.25 (m, 1H), 2.21-2.18 (m, 1H); MS ESI $[M + H]^+$ 476.2, calcd for $[C_{30}H_{29}N_5O + H]^+$ 476.25.

Example A90. (1R,2S)-(E)-1'-methyl-2-(3-(4-(piperazin-1-yl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one hydrochloride



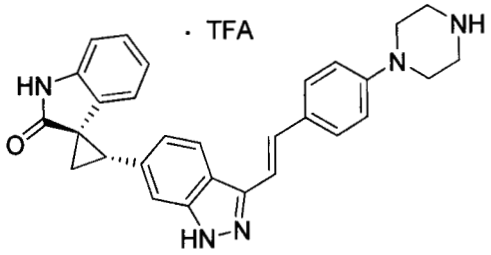
[00257] The title compound was synthesized according to the method of Example A42B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (218 mg, 0.526 mmol) and (E)-tert-butyl 4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine-1-carboxylate (261 mg, 0.631 mmol). The Boc-protected intermediate was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 97:3 to 96:4) to give 218 mg, 72 %. This material was dissolved into CH_2Cl_2 (6.0 mL) and TFA (1.0 mL) and stirred for 2 h, the solvent was removed and the residue purified by prep-HPLC which gave the TFA salt. This material was free-based by washing with $NaHCO_3$ (sat.) (10 mL) and extracting with EtOAc (2 x 50mL). The HCl salt was prepared according to the method of A42B which gave, after drying, the title product (48 mg, 15 %); Spectral data was identical to that obtained in Example A89. Optical Rotation: $[\alpha]^{22}_D = -100^\circ$ (c 0.43, MeOH).

Example A91. (1R*,2S*)-(E)-2-(3-(4-(piperazin-1-yl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



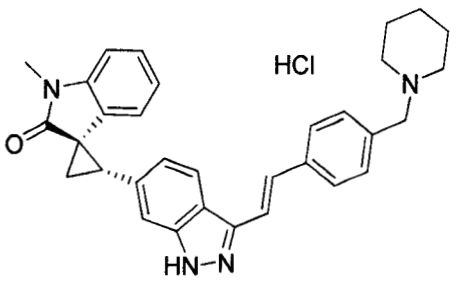
[00258] The title compound was synthesized according to the method of Example A45 in WO2010/115279, except substituting (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (72 mg, 0.180 mmol) and (E)-tert-butyl 4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine-1-carboxylate (90 mg, 0.217 mmol). The solvent was removed and the residue purified by column chromatography (silica gel, hexanes/EtOAc, 2:1) to give 38 mg of the Boc-protected amine which dissolved into CH_2Cl_2 (2.0 mL) and TFA (0.1 mL) was added. The reaction was stirred for 3 h, the solvent was removed and the residue purified by prep-HPLC to yield the title compound (6.5 mg, 6.0 %); ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 8.6 Hz, 2H), 7.47-7.42 (m, 2H), 7.30 (d, J = 17 Hz, 1H), 7.06-7.01 (m, 4H), 6.93 (d, J = 7.6 Hz, 1H), 6.58 (t, J = 7.6 Hz, 1H), 5.98 (d, J = 8.0 Hz, 1H), 3.49-3.44 (m, 4H), 3.40-3.31 (m, 5H), 2.26-2.22 (m, 1H), 2.19-2.16 (m, 1H); MS ESI $[M + H]^+$ 462.2, calcd for $[C_{29}H_{27}N_5O + H]^+$ 462.23.

Example A92. (1R,2S)-(E)-2-(3-(4-(piperazin-1-yl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



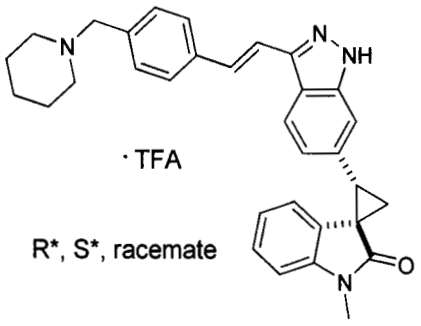
[00259] The title compound was synthesized according to the method of Example A91, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (40 mg, 0.1 mmol). The title compound was isolated as a yellow solid (23 mg, 40%). The spectral data was identical to that obtained for Example A91.

Example A94. (1R,2S)-(E)-1'-methyl-2-(3-(4-(piperidin-1-ylmethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one hydrochloride



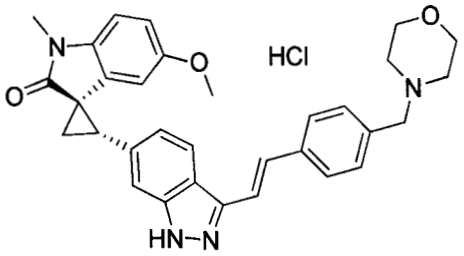
[00260] The title compound was synthesized according to the method of Example A42B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (594 mg, 1.43 mmol) and (E)-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)piperidine (563 mg, 1.72 mmol). Purification by column chromatography (silica gel, CH_2Cl_2/MeOH/7N NH_3 in MeOH, 91:8:1) gave 443 mg, 63 % of the free base as a pale orange solid. The HCl salt was prepared according to the method for A42B, which gave, after drying, the title product (378 mg, 50%); ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 7.2 Hz, 2H), 7.54-7.47 (m, 5H), 7.15 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.9 Hz, 2H), 6.64 (t, J = 7.9 Hz, 1H), 6.02 (d, J = 6.6 Hz, 1H), 4.31 (s, 2H), 3.48-3.45 (m, 2H), 3.39 (t, J = 8.2 Hz, 1H), 3.36 (s, 3H), 3.01-2.95 (m, 2H), 2.29-2.26 (m, 1H), 2.22-2.19 (m, 1H), 1.99-1.72 (m, 5H), 1.57-1.50 (m, 1H); MS ESI $[M + H]^+$ 489.3, calcd for $[C_{32}H_{32}N_4O+ H]^+$ 489.27. Optical Rotation: $[\alpha]^{22}_D$ = -122° (c 0.49, MeOH).

Example A95. (1R*,2S*)-(E)-1'-methyl-2-(3-(4-(piperidin-1-ylmethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



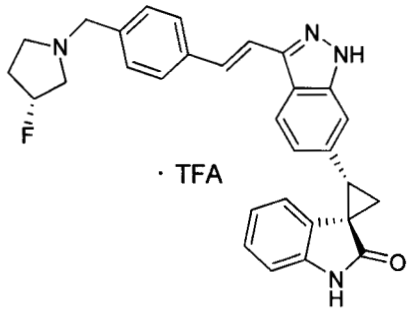
[00261] The title compound was synthesized according to the method of Example A43 in WO2010/115279, except substituting (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (44 mg, 0.106 mmol) and (E)-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)piperidine (45 mg, 0.138 mmol). Purification by prep-HPLC gave the title compound (6.5 mg, 10 %); Spectral data was identical to that in obtained in Example A94.

Example A102. (1R,2S)-(E)-5'-methoxy-1'-methyl-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one hydrochloride



[00262] The title compound was synthesized according to the method of Example A42B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxy-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (512 mg, 1.15 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (454 mg, 1.38 mmol). Purification by column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5 to 92:8) gave the free base as a yellow solid. The HCl salt was prepared according to the method of A42B, which gave after drying, the title product as a pale-yellow solid (346 mg, 54 %); ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.56-7.49 (m, 5H), 7.04 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 8.6 Hz, 1H), 5.63 (s, 1H), 4.39 (s, 2H), 4.08-4.05 (m, 2H), 3.77-3.71 (m, 2H), 3.35-3.23 (m, 11H), 2.27-2.25 (m, 1H), 2.22-2.19 (m, 1H); MS ESI $[M + H]^+$ 521.3, calcd for $[C_{32}H_{32}N_4O_3 + H]^+$ 521.26. Optical Rotation: $[\alpha]^{22}_D$ = -85° (c 0.59, MeOH).

Example A106. (1R,2S)-(E)-2-(3-(4-(((R)-3-fluoropyrrolidin-1-yl)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



A. (R)-1-(4-bromobenzyl)-3-fluoropyrrolidine

[00263] The title compound was synthesized according to the method of Example A105B in WO2010/115279, except substituting (R)-3-fluoropyrrolidine hydrochloride (576 mg, 4.59 mmol) and 4-bromobenzaldehyde (849 mg, 4.59 mmol) which gave 1.09 g, 91 % of a clear, colourless oil; MS ESI $[M + H]^+$ 258.0, calcd for $[C_{11}H_{13}BrFN + H]^+$ 258.03.

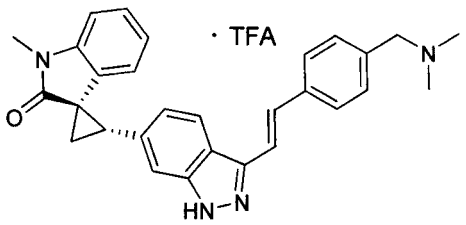
B. (3R)-3-fluoro-1-(4-((E)-2-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)vinyl)benzyl)pyrrolidine

[00264] The title compound was synthesized according to the method of Example A51A, except substituting (R)-1-(4-bromobenzyl)-3-fluoropyrrolidine (1.07 g, 4.15 mmol) and 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (0.77 mL, 4.57 mmol) which gave 1.40 g, 91 % of a pale orange solid; MS ESI $[M + H]^+$ 332.3, calcd for $[C_{19}H_{27}BFNO_2 + H]^+$ 332.22.

C. (1R,2S)-(E)-2-(3-(4-(((R)-3-fluoropyrrolidin-1-yl)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

[00265] The title compound was synthesized according to the method of Example A42B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (630 mg, 1.57 mmol) and (3R)-3-fluoro-1-(4-((E)-2-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)vinyl)benzyl)pyrrolidine (622 mg, 1.88 mmol). The title product was obtained as a pale-yellow solid after prep-HPLC purification (338 mg, 48 %); ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, 1H, J = 8.3 Hz), 7.73 (d, 2H, J = 7.80 Hz), 7.55-7.45 (m, 5H), 7.06-7.00 (m, 2H), 6.93 (d, 1H, J = 7.7 Hz), 6.56 (t, 1H, J = 7.5 Hz), 5.97 (d, 1H, J = 7.5 Hz), 5.46 (d, 1H, J = 52.4 Hz), 4.46 (s, 2H), 3.73-3.31 (m, 5H), 2.65-2.44 (m, 2H), 2.26-2.15 (m, 2H); MS ESI $[M + H]^+$ 479.3, calcd for $[C_{30}H_{27}FN_4O + H]^+$ 479.22. Optical Rotation: $[\alpha]^{22}_D$ = -125° (c 0.44, MeOH).

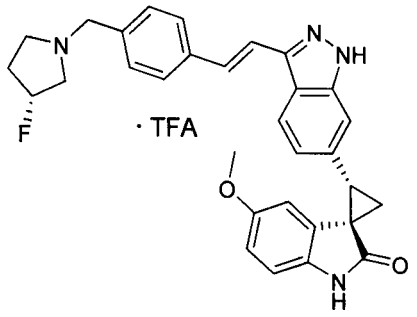
Example A109. (1R,2S)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00266] The title compound was synthesized according to the method of Example A42B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (134 mg, 0.322 mmol) and (E)-N,N-dimethyl-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)methanamine (111 mg, 0.386 mmol). Purification by prep-HPLC resulted in a pale-yellow solid which was sonicated with Et_2O and filtered to give the title product (42 mg, 23 %); ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, 1H, J = 8.0

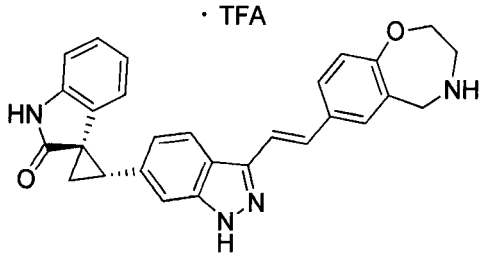
Hz), 7.76 (d, 2H, J = 7.6 Hz), 7.54-7.47 (m, 5H), 7.15 (t, 1H, J = 8.2 Hz), 7.03 (d, 2H, J = 7.8 Hz), 6.64 (t, 1H, J = 7.5 Hz), 6.02 (d, 1H, J = 7.0 Hz), 4.33 (s, 2H), 3.41-3.35 (m, 4H), 2.88 (s, 6H), 2.29-2.26 (m, 1H), 2.22-2.19 (m, 1H); MS ESI $[M + H]^+$ 449.2, calcd for $[C_{29}H_{28}N_4O+ H]^+$ 449.23. Optical Rotation: $[\alpha]^{22}_D$ = -152° (c 0.42, MeOH).

Example A112. (1R,2S)-(E)-2-(3-(4-(((R)-3-fluoropyrrolidin-1-yl)methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

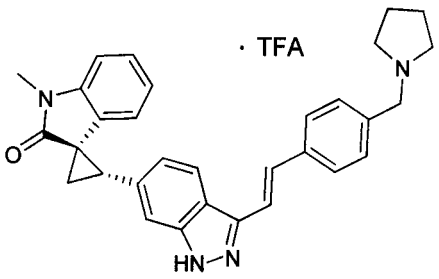


[00267] The title compound was synthesized according to the method of Example A42B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (125 mg, 0.290 mmol) and (3R)-3-fluoro-1-(4-((E)-2-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)vinyl)benzyl)pyrrolidine (115 mg, 0.348 mmol). Purification by prep-HPLC gave 64 mg, 35 % of the title compound as a beige solid; ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (d, 1H, J = 8.3 Hz), 7.75 (d, 2H, J = 7.9 Hz), 7.55-7.48 (m, 5H), 7.04 (d, 1H, J = 8.5 Hz), 6.82 (d, 1H, J = 8.2 Hz), 6.60 (d, 1H, J = 8.5 Hz), 5.58 (s, 1H), 5.46 (d, 1H, J = 53.2 Hz), 4.46 (bs, 2H), 3.80-3.48 (m, 4H), 3.36 (t, 1H, J = 8.8 Hz), 3.26 (s, 3H), 2.54-2.33 (m, 2H), 2.27-2.24 (m, 1H), 2.22-2.17 (m, 1H); MS ESI $[M + H]^+$ 509.3, calcd for $[C_{31}H_{29}FN_4O_2 + H]^+$ 509.24. Optical Rotation: $[\alpha]^{22}_D$ = -91° (c 0.58, MeOH).

Example A113. (1R,2S)-2-(3-((E)-2-(2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl) vinyl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

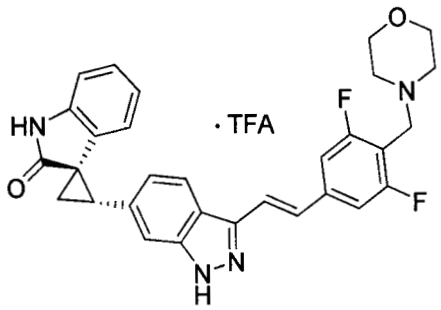


[00268] The title compound was synthesized according to the method of Example A51B, by using (1R,2S)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (105 mg, 0.27 mmol) and (E)-tert-butyl 7-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate (130 mg, 0.32 mmol). The residue from the reaction was dissolved into CH_2Cl_2 (5 mL) and TFA (0.2 mL) was added and the mixture was stirred for 1 h and concentrated to dryness. Purification by preparative HPLC gave the title compound as a cream solid (40 mg, 30%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 8.2 Hz, 1H), 7.68-7.64 (m, 2H), 7.50-7.39 (m, 3H), 7.16 (d, J = 8.2 Hz, 1H), 7.07-7.01 (m, 2H), 6.94 (d, J = 7.8 Hz, 1H), 6.57 (t, J = 7.6 Hz, 1H), 5.98 (d, J = 7.4 Hz, 1H), 4.45 (s, 2H), 4.39 (br. s, 2H), 3.68 (br. s, 2H), 3.39-3.33 (m, 1H) 2.25-2.16 (m, 2H); MS ESI 449.3 $[M + H]^+$, calcd for $[C_{28}H_{24}N_4O_2 + H]^+$ 449.2.Example A115. (1R,2S)-(E)-1'-methyl-2-(3-(4-(pyrrolidin-1-ylmethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00269] The title compound was synthesized according to the method of Example A42B, except substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (147 mg, 0.353 mmol) and (E)-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)pyrrolidine (133 mg, 0.424 mmol). Purification by prep-HPLC gave the title compound as an pale-yellow solid (46 mg, 22 %); ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, 1H, J = 8.7 Hz), 7.73 (d, 2H, J = 7.4 Hz), 7.53-7.44 (m, 5H), 7.14 (t, 1H, J = 7.2 Hz), 7.01 (d, 2H, J = 7.9 Hz), 6.63 (t, 1H, J = 7.4 Hz), 6.01 (d, 1H, J = 7.6 Hz), 4.38 (s, 2H), 3.55-3.45 (m, 2H), 3.40-3.32 (m, 1H), 3.34 (s, 3H), 3.26-3.16 (m, 2H), 2.28-2.17 (m, 4H), 2.05-1.95 (m, 2H); MS ESI $[M + H]^+$ 475.4, calcd for $[C_{31}H_{30}N_4O + H]^+$ 475.25. Optical Rotation: $[\alpha]^{22}_D$ = -148° (c 0.40, MeOH).

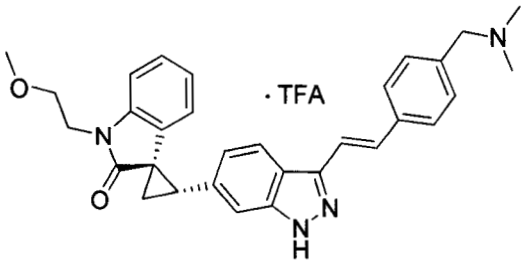
Example A116. (1R,2S)-(E)-2-(3-(3,5-difluoro-4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00270] The title compound was synthesized according to the method of Example A51B, by using (1R,2S)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (125 mg, 0.311 mmol) and (E)-4-(2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (130.9 mg, 0.358 mmol). Purification by preparative HPLC gave the title compound as a cream solid (88 mg, 45%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 16.8 Hz, 1H), 7.46-7.42 (m, 4H), 7.04-6.99 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 6.53 (t, J = 7.6 Hz, 1H), 5.95 (d, J = 7.6 Hz, 1H), 4.48 (s, 2H), 4.08-3.84 (bm, 4H), 3.49-3.35 (bm, 5H), 2.26-2.23 (m, 1H), 2.21-2.17 (m, 1H); MS ESI 513.3 $[M + H]^+$, calcd for $[C_{30}H_{26}F_2N_4O_2 + H]^+$ 513.21.

Optical Rotation $[\alpha]^{23}_D$ = -121° (c 0.34, MeOH).

Example A131. (1R,2S)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-1'-(2-methoxyethyl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

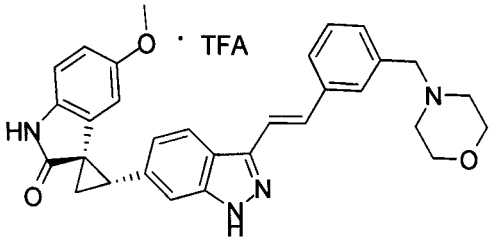


[00271] The title compound was synthesized according to the method of Example A51B, by using (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-1'-(2-methoxyethyl)spiro[cyclopropane-1,3'-indolin]-2'-one (490 mg, 1.07 mmol) and (E)-N,N-dimethyl-1(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)methanamine (321.7 mg, 1.12 mmol). Purification by preparative HPLC gave the title compound as a off-white solid (297 mg, 46%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 7.6 Hz, 2H), 7.50-7.42 (m, 5H), 7.08-7.03 (m, 2H), 6.93 (d, J = 8.4 Hz, 1H), 6.55 (t, J = 7.6 Hz, 1H), 5.96 (d, J = 7.6 Hz, 1H), 4.30 (s, 2H), 4.01 (t, J = 4.8 Hz, 2H), 3.67 (t, J = 5.2 Hz, 2H), 3.35-3.31 (m, 4H), 2.86

(s, 6H), 2.21-2.20 (m, 1H), 2.17-2.14 (m, 1H); MS ESI 493.4 $[M + H]^+$, calcd for $[C_{31}H_{32}N_4O_2 + H]^+$ 493.26.

$[\alpha]^{23}_D$ = -169 ° (c 0.36, MeOH).

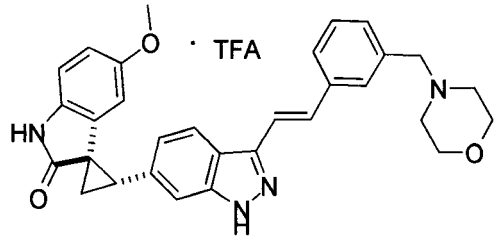
Example A132. (1R,2S)-5'-methoxy-2-(3-(3-(morpholinomethyl)styryl)-1H-indazol-6-yl) spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00272] The title compound (163 mg, 67%, TFA salt) was obtained as a white solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (172 mg, 0.4 mmol) and (E)-4-(3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (184 mg, 0.56 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 8 mL/4 mL, 5 mol% $Pd(PPh_3)_4$, 125 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.89 (d, J = 8.4 Hz, 1H), 7.72 (s, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.50-7.37 (m, 5H), 6.93 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.56 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 5.56 (d, J = 2.0 Hz, 1H), 4.37 (s, 2H), 4.10-4.08 (m, 2H), 3.82-3.71 (m, 2H), 3.45-3.35 (m, 2H), 3.32 (t, J = 8.2 Hz, 1H), 3.25-3.15 (m, 5H; s, 3H at 3.20 ppm and m, 2H overlapping), 2.20-2.10 (m, 2H); MS ESI 507.3 $[M + H]^+$, calcd for $[C_{31}H_{30}N_4O_3 + H]^+$ 507.2

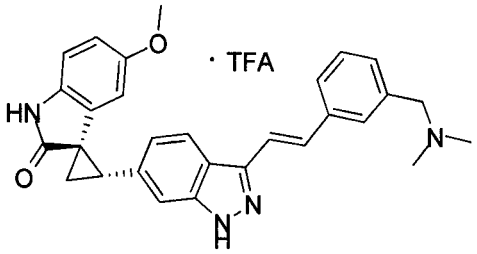
Optical Rotation $[\alpha]^{22}_D$ = -89° (c 0.34, MeOH).

Example A133. (1R*,2S*)-5'-methoxy-2-(3-(3-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00273] To a mixture of (1R*,2S*)-5'-methoxy-2-(3-vinyl-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one (66 mg, 0.2 mmol), 4-(3-bromobenzyl)morpholine (56 mg, 0.22 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $P(o\text{-}tol)_3$ (6.7 mg, 0.022 mmol) in DMF (2 mL) was added $^iPr_2NEt$ (0.07 mL, 0.4 mmol). The resulting mixture was purged with argon, then microwaved 30 min at 150 °C. The crude mixture was passed through a microfilter then purified by prep-HPLC to give the title compound (50 mg, 40%) as a light yellow foam. NMR indicated 13% branched isomer. Spectral data was identical to that in obtained in Example A132.

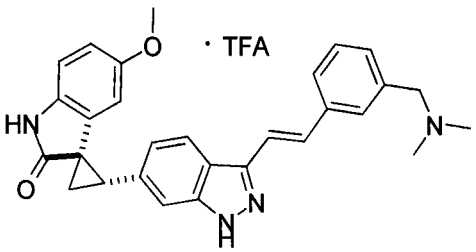
Example A134. (1R,2S)-2-(3-(3-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00274] The title compound (89 mg, 38%, TFA salt) was obtained as a pale yellow solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (172 mg, 0.4 mmol) and (E)-N,N-dimethyl-1-(3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)methanamine (161 mg, 0.56 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 8 mL/4 mL, 5 mol% $Pd(PPh_3)_4$, 125 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.93 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H, partially overlapping with the peak at 7.70 ppm), 7.70 (d, J = 8.0 Hz, 1H, partially overlapping with the peak at 7.73 ppm), 7.52-7.45 (m, 4H), 7.40 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.58 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 5.57 (d, J = 2.4 Hz, 1H), 4.34 (s, 2H), 3.33 (t, J = 8.8 Hz, partially overlapping with MeOH residue, 1H), 3.23 (s, 3H), 2.89 (s, 6H), 2.22-2.12 (m, 2H); MS ESI 465.3 $[M + H]^+$, calcd for $[C_{29}H_{28}N_4O_2 + H]^+$ 465.2.

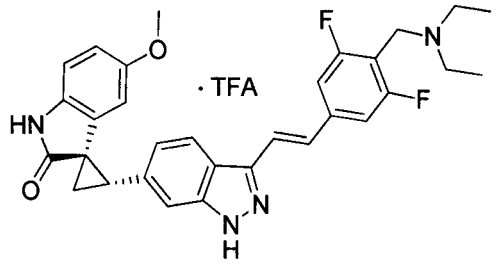
Optical Rotation $[\alpha]^{22}_D$ = -82° (c 0.38, MeOH).

Example A135. (1R*,2S*)-2-(3-(3-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00275] To a mixture of crude (1R*,2S*)-5'-methoxy-2-(3-vinyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (100 mg, 0.2 mmol), 1-(3-bromophenyl)-N,N-dimethylmethanamine (43 mg, 0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $P(o\text{-}tol)_3$ (6.7 mg, 0.022 mmol) in DMF (2 mL) was added $^iPr_2NEt$ (0.07 mL, 0.4 mmol). The resulting mixture was purged with argon, then microwaved 30 min at 125 °C. It was passed through a microfilter then purified by prep-HPLC to give the title compound as a light yellow solid. NMR indicated 7% branched isomer (43 mg, 37%). Spectral data was identical to that in obtained in Example A134.

Example A146. (1*R*,2*S*)-(E)-2-(3-(4-((diethylamino)methyl)-3,5-difluorostyryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

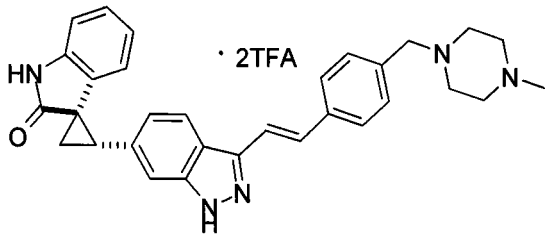


[00276] The title compound was synthesized according to the method of Example A51B, by using (1R,2S)-2-(3-iodo-1H-indazol-6-yl-)-5'-methoxyspioro[cyclopropane-1,3'-indolin]-2'-one (125 mg, 0.289 mmol) and (E)-N-(2,6-Difluoro-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)N-ethylethanamine (122.2 mg, 0.347 mmol). Purification by preparative HPLC gave the title compound as a cream solid (59 mg, 31.6%). ^1H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 16.8 Hz, 1H), 7.50-7.45 (m, 4H), 7.03 (s, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 8.8 Hz, 1H), 5.57 (s, 1H), 4.46 (s, 2H), 3.37-3.28 (m, 5H), 3.25 (s, 3H), 2.25-2.22 (m,1H), 2.19-2.17 (m,

1H), 1.26 (t, J = 11.2 Hz, 6H); MS ESI 529.3 $[M + H]^+$, calcd for $[C_{31}H_{30}F_2N_4O_2 + H]^+$ 529.2.

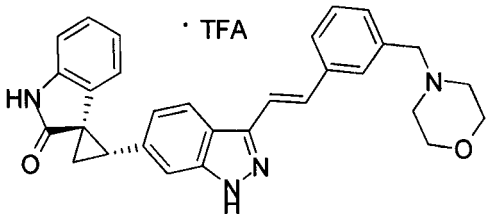
Optical Rotation: $[\alpha]^{23}_D$ = -80° (c 0.65, Methanol).

Example A147. (1R*,2S*)-(E)-2-(3-(4-((4-methylpiperazin-1-yl)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one bis-2,2,2-trifluoroacetate



[00277] To a mixture of (1R*,2S*)-2-(3-vinyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (60.2 mg, 0.2 mmol) and 1-(4-bromobenzyl)-4-methylpiperazine (53.8 mg, 0.2 mmol) in DMF (2 mL) was added $^iPr_2NEt$ (0.07 mL), followed by $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $P(o\text{-}tol)_3$ (6.7 mg, 0.022 mmol). The resulting mixture was purged with argon, and then microwaved 2 h at 100 °C. LC-MS showed low conversion. Additional $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $P(o\text{-}tol)_3$ (6.7 mg, 0.022 mmol) were added and the reaction mixture was purged with argon and microwaved 2 h at 125 °C. Purification by prep-HPLC gave the title compound as a white solid (23 mg, 16%). ^1H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.53-7.46 (m, 5H), 7.05 (t, J = 7.6 Hz, 1H, partially overlapping with the peak at 7.04 ppm), 7.04 (d, J = 8.0 Hz, 1H, partially overlapping with the peak at 7.05 ppm), 6.94 (d, J = 7.6 Hz, 1H), 6.58 (t, J = 7.4 Hz, 1H), 5.99 (d, J = 8.0 Hz, 1H), 4.19 (s, 2H), 3.60-3.30 (m, 9H), 2.95 (s, 3H), 2.24 (dd, J = 7.6 Hz, 4.8 Hz, 1H), 2.18 (dd, J = 9.0 Hz, J = 4.6 Hz, 1H); MS ESI 490.3 $[M + H]^+$, calcd for $[C_{31}H_{31}N_5O + H]^+$ 490.3.

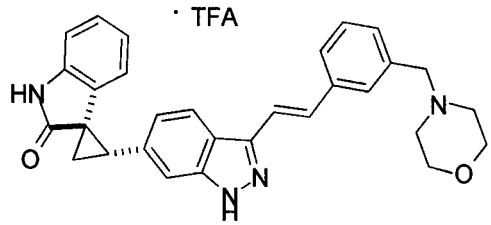
Example A151. (1R,2S)-(E)-2-(3-(3-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00278] The title compound (158 mg, 67%, TFA salt) was obtained as a white solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-spiro[cyclopropane-1,3'-indolin]-2'-one (160 mg, 0.4 mmol) and (E)-4-(3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl) morpholine (184 mg, 0.56 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 8 mL/4 mL, 5 mol% $Pd(PPh_3)_4$, 125 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.50-7.38 (m, 5H), 6.98 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 8.0 Hz, 2H), 6.48 (t, J = 7.6 Hz, 1H), 5.92 (d, J = 7.2 Hz, 1H), 4.36 (s, 2H), 4.03 (d, J = 11.6 Hz, 2H), 3.76 (t, J = 12.0 Hz, 2H), 3.45-3.14 (m, 5H), 2.17-2.08 (m, 2H); MS ESI 477.3 $[M + H]^+$, calcd for $[C_{30}H_{28}N_4O_2 + H]^+$ 477.2

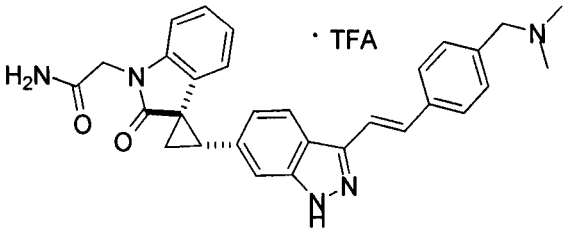
Optical Rotation $[\alpha]^{23}_D$ = -144° (c 0.34, MeOH).

Example A152. (1R*,2S*)-(E)-2-(3-(3-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



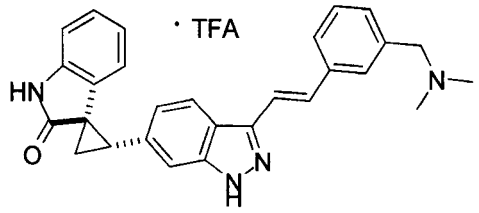
[00279] To a mixture of (1R*,2S*)-2-(3-vinyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (60.2 mg, 0.2 mmol) and 4-(3-bromobenzyl)morpholine (51.2 mg, 0.2 mmol) in DMF (1.5 mL) was added $^iPr_2NEt$ (0.07 mL), followed by $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $P(o\text{-}tol)_3$ (6.7 mg, 0.022 mmol). The resulting mixture was purged with argon, and then microwaved 2 h at 125 °C. Purification by prep-HPLC gave the title compound as a white solid (22 mg, 19%). NMR indicated 3% branched isomer. Spectral data was identical to that in obtained in Example A151.

Example A160. 2-((1R*,2S*)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-yl)acetamide 2,2,2-trifluoroacetate



[00280] The title compound (79 mg, 33%, TFA salt) was obtained as a pale yellow solid from 2-((1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-yl)acetamide (183 mg, 0.4 mmol) and (E)-N,N-dimethyl-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)methanamine (161 mg, 0.56 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 8 mL/4 mL, 5 mol% $Pd(PPh_3)_4$, 125 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.92 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.50-7.43 (m, 5H), 7.07 (t, J = 8.2 Hz, 1H, partially overlapping with the peak at 7.04 ppm), 7.04 (d, J = 9.2 Hz, partially overlapping with the peak at 7.07 ppm), 6.90 (d, J = 8.0 Hz, 1H), 6.60 (t, J = 7.6 Hz, 1H), 6.02 (d, J = 7.6 Hz, 1H), 4.58-4.54 (m, 2H), 4.30 (s, 2H), 3.39 (t, J = 8.4 Hz, 1H), 2.86 (s, 6H), 2.27-2.18 (m, 2H); MS ESI 492.3 $[M + H]^+$, calcd for $[C_{30}H_{29}N_5O_2 + H]^+$ 492.2.

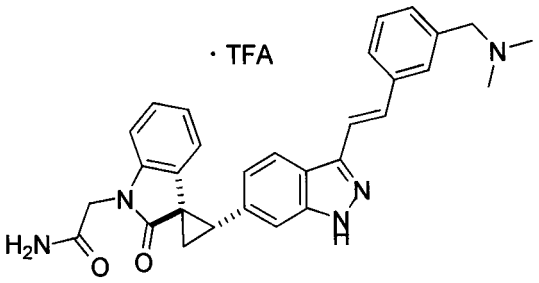
Example A162. (1R*,2S*)-(E)-2-(3-(3-((dimethylamino)methyl)styryl)-1H-indazol-6-yl) spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00281] To a mixture of (1R*,2S*)-2-(3-vinyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (60.2 mg, 0.2 mmol) and 1-(3-bromophenyl)-N,N-dimethylmethanamine (42.8 mg, 0.2 mmol) in DMF (2 mL) was added $^iPr_2NEt$ (0.07 mL), followed by $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $P(o\text{-}tol)_3$ (6.7 mg, 0.022 mmol). The resulting mixture was purged with argon, and then microwaved 2 h at 125 °C. Purification by prep-HPLC gave the title compound (24 mg, 22%, TFA salt) as a white solid. NMR indicated 5% of the branched isomer. ^1H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 8.4 Hz, 1H), 7.78-7.75 (m, 2H), 7.55-7.49 (m, 3H), 7.47 (s, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.08-7.00 (m, 2H), 6.94 (d, J = 7.6 Hz, 1H), 6.57 (t, J = 7.4 Hz, 1H), 5.98 (d, J = 8.4 Hz, 1H), 4.36 (s, 2H), 3.35 (t, J = 8.4 Hz, 1H,

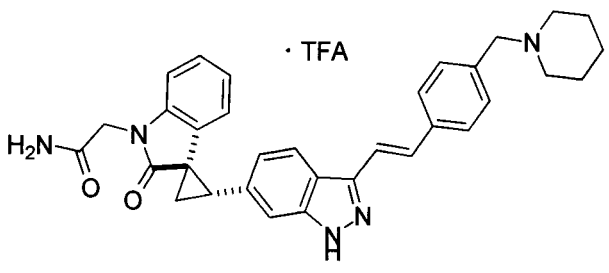
partially overlapping with MeOH residue), 2.90 (s, 6H), 2.23 (dd, J = 8.0 Hz, J = 4.8 Hz, 1H), 2.08 (dd, J = 9.2 Hz, J = 4.8 Hz, 1H); MS ESI 435.2 $[M + H]^+$, calcd for $[C_{28}H_{26}N_4O + H]^+$ 435.2.

Example A164. 2-((1R*,2S*)-(E)-2-(3-(3-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-yl)acetamide 2,2,2-trifluoroacetate



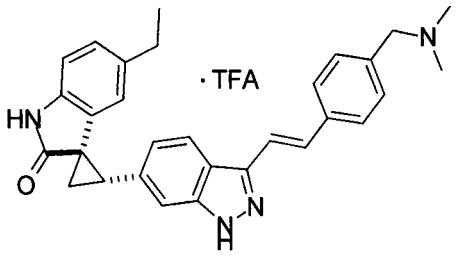
[00282] The title compound (6.9 mg, 23%, TFA salt) was obtained as a white solid from 2-((1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-yl)acetamide (22.9 mg, 0.05 mmol) and (E)-N,N-dimethyl-1-(3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)methanamine (21.6 mg, 0.075 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 2 mL/1 mL, 4 mol% $Pd(PPh_3)_4$, 120 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 8.01 (d, J = 8.4 Hz, 1H), 7.80 (s, 1H, partially overlapping with the peak at 7.79 ppm), 7.79 (d, J = 9.2 Hz, 1H, partially overlapping with the peak at 7.80 ppm), 7.57-7.52 (m, 4H), 7.42 (d, J = 7.2 Hz, 1H), 7.15-7.08 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H), 6.64 (t, J = 7.8 Hz, 1H), 6.03 (d, J = 7.6 Hz, 1H), 4.60 (d, J = 16.4 Hz, 1H), 4.55 (d, J = 17.2 Hz, 1H), 4.37 (s, 2H), 3.44 (t, J = 8.6 Hz, 1H), 2.91 (s, 6H), 2.33-2.24 (m, 2H); MS ESI 492.3 $[M + H]^+$, calcd for $[C_{30}H_{29}N_5O_2 + H]^+$ 492.2.

Example A165. 2-((1R*,2S*)-(E)-2'-oxo-2-(3-(4-(piperidin-1-ylmethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indoline]-1'-yl)acetamide 2,2,2-trifluoroacetate



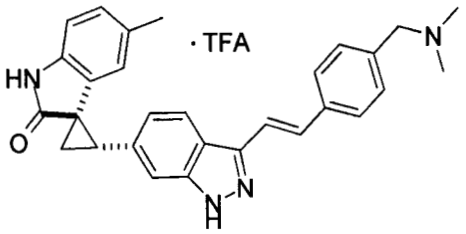
[00283] The title compound (12 mg, 37%, TFA salt) was obtained as a white solid from 2-((1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-2'-oxospiro[cyclopropane-1,3'-indoline]-1'-yl)acetamide (22.9 mg, 0.05 mmol) and (E)-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)piperidine (24.6 mg, 0.075 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 2 mL/1 mL, 4 mol% $Pd(PPh_3)_4$, 120 °C, 2 h). ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.57-7.50 (m, 5H), 7.15-7.08 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H), 6.64 (t, J = 7.4 Hz, 1H), 6.03 (d, J = 7.6 Hz, 1H), 4.60 (d, J = 16.8 Hz, 1H), 4.55 (d, J = 16.8 Hz, 1H), 4.30 (s, 2H), 3.52-3.40 (m, 3H), 2.98 (t, J = 11.6 Hz, 2H), 2.32-2.22 (m, 2H), 2.00-1.68 (m, 5H), 1.60-1.46 (m, 1H); MS ESI 532.4 $[M + H]^+$, calcd for $[C_{33}H_{33}N_5O_2 + H]^+$ 532.3.

Example A167. (1R*,2S*)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-5'-ethylspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



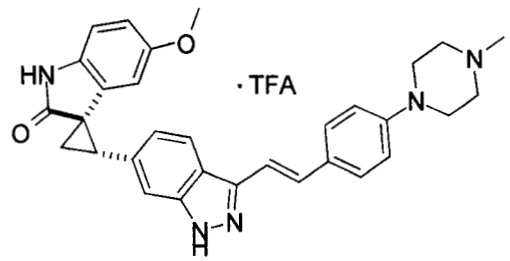
[00284] The title compound (19.5 mg, 34%, TFA salt) was obtained as a light yellow solid from (1*R,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-ethylspiro[cyclopropane-1,3'-indolin]-2'-one (42.9 mg, 0.1 mmol) and (E)-N,N-dimethyl-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)methanamine (29 mg, 0.1 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 2 mL/1 mL, 2.5 mol% $Pd(PPh_3)_4$, 120 °C, 2 h). ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.54-7.50 (m, 4H), 7.44 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 5.77 (s, 1H), 4.33 (s, 2H), 3.34 (t, J = 8.0 Hz, 1H, partially overlapping with MeOH residue), 2.88 (s, 6H), 2.25-2.10 (m, 4H), 0.65 (t, J = 7.6 Hz, 3H); MS ESI 463.3 $[M + H]^+$, calcd for $[C_{30}H_{30}N_4O + H]^+$ 463.2.

Example A169. (1R*,2S*)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-5'-methylspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00285] The title compound (27 mg, 48%, TFA salt) was obtained as a light yellow solid from (1*R,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (41.5 mg, 0.1 mmol) and (E)-N,N-dimethyl-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)methanamine (43 mg, 0.15 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 2 mL/1 mL, 2.5 mol% $Pd(PPh_3)_4$, 120 °C, 2 h). ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.53 (s, 2H, partially overlapping with the peak at 7.52 ppm), 7.52 (d, J = 8.8 Hz, 2H, partially overlapping with the peak at 7.53 ppm), 7.46 (s, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 7.6 Hz ,1H), 5.83 (s, 1H), 4.33 (s, 2H), 3.32 (t, J = 8.4 Hz, 1H, partially overlapping with MeOH residue), 2.88 (s, 6H), 2.22-2.13 (m, 2H), 1.88 (s, 3H); MS ESI 449.2 $[M + H]^+$, calcd for $[C_{29}H_{28}N_4O + H]^+$ 449.2.

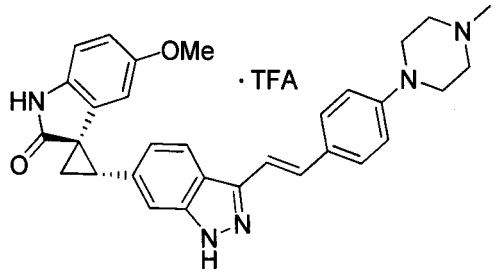
Example A174. (1R*,2S*)-(E)-5'-methoxy-2-(3-(4-(4-methylpiperazin-1-yl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00286] To a mixture of crude (1R*,2S*)-5'-methoxy-2-(3-vinyl-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one (97 mg, 0.2 mmol) and 1-(4-bromophenyl)-4-methylpiperazine (51 mg, 0.2 mmol) in DMF (2 mL) was added ^{i}Pr$_2$NEt (0.07 mL), followed by $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $P(o\text{-}tol)_3$ (6.7 mg, 0.022 mmol). The resulting mixture was purged with argon, then microwaved 2 h at 125 °C. Purification by prep-HPLC followed by trituration from MeOH gave the title compound (4 mg, 3%, TFA salt) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.46 (s, 1H, partially overlapping with the peak at 7.44 ppm), 7.44 (d, J = 16.4

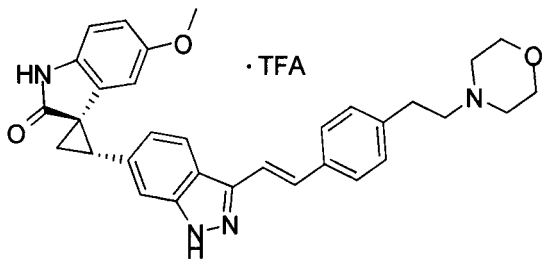
Hz, 1H, partially overlapping with the peak at 7.46 ppm), 7.31 (d, J = 16.8 Hz, 1H), 7.10-7.00 (m, 3H), 6.84 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 7.2 Hz, 1H), 5.59 (s, 1H), 4.01-3.00 (m, 12H), 2.99 (s, 3H), 2.30-2.15 (m, 2H); MS ESI 506.3 $[M + H]^+$, calcd for $[C_{31}H_{31}N_5O_2 + H]^+$ 506.2.

Example A175. (1R,2S)-(E)-5'-methoxy-2-(3-(4-(4-methylpiperazin-1-yl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00287] The title compound was prepared in a similar manner to Example A51B using (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (36.0 mg, 0.083 mmol) and (E)-1-methyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine (31.9 mg, 0.097 mmol). The reaction mixture was diluted with MeOH (3 mL) and poured onto a 20 cc PoraPak Rxn Cx cartridge. After rinsing with MeOH (20 mL), the title compound was eluted using 2M NH_3:MeOH (20 mL). After removal of the solvents in vacuo, the title compound was purified by preparative HPLC to yield the title compound as the TFA salt (yellow solid, 23.3 mg, 45%). ^{1}H NMR was identical to Example A174; MS ESI 506.3 $[M + H]^+$, calcd for $[C_{31}H_{31}N_5O_2 + H]^+$ 506.3.

Example A177. (1R,2S)-(E)-5'-methoxy-2-(3-(4-(2-morpholinoethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

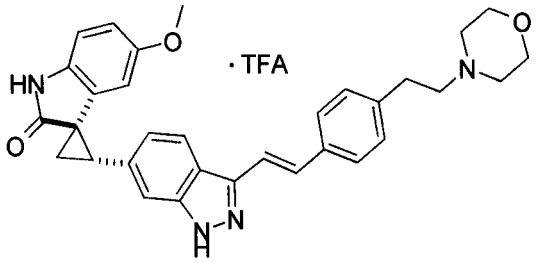


[00288] To a mixture of 4-(4-bromophenethyl)morpholine (731 mg, 2.71 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.5 mL, 2.95 mmol, 1.1 eq.) in a 20 mL microwave vial was added Et_3N (0.76 mL, 5.4 mmol, 2 eq.), followed by $Pd(P^tBu_3)_2$ (14 mg, 0.027 mmol, 1 mol%). The resulting mixture was purged with argon, then capped and heated at 80 °C (oil temp.) for 2 h. After cooling to rt, the reaction was quenched with sat. $NaHCO_3$ (10 mL), H_2O (10 mL), extracted with EtOAc (30 mL x 2) and dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by Biotage column system (EtOAc/hex gradient: 0-100%) to give (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenethyl)morpholine as a white solid (714 mg, 77%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 19.0 Hz, 1H), 7.19 (d, J = 7.8 Hz, 2H), 6.13 (d, J = 18.3 Hz, 1H), 3.75 (t, J = 4.4 Hz, 4H), 2.84-2.77 (m, 2H), 2.63-2.56 (m, 2H), 2.53 (br, pseudo s, 4H), 1.32 (s, 12H).

[00289] To a mixture of (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro [cyclopropane-1,3'-indolin]-2'-one (172 mg, 0.4 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenethyl)morpholine (138 mg, 0.4 mmol) in $PhCH_3$/EtOH (8 mL/4 mL) in a 20 mL microwave vial was added 1 M Na_2CO_3 (0.8 mL, 0.8 mmol), followed by $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 5 mol%). The resulting mixture was purged with argon, and then microwaved 2 h at 125 °C. After cooling to rt, the mixture was diluted with H_2O (20 mL), extracted with EtOAc (30 mL x 2) and dried over Na_2SO_4. After removal of the solvents, the residue was redissolved in DMF (4 mL) and purified by prep-HPLC to give the title compound as a pale yellow solid (115 mg, 45%). ^1H NMR (400 MHz, CD_3OD) δ 7.90 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.43 (s, 1H), 7.37 (d, J = 6.4 Hz, 2H), 7.28 (d, J = 7.2 Hz, 2H), 6.95 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 5.57 (s, 1H), 4.06 (d, J = 11.2 Hz, 2H), 3.80 (t, J = 11.2 Hz, 2H), 3.56 (d, J = 11.2 Hz, 2H), 3.38 (t, J = 7.6 Hz, 2H), 3.27-3.12 (m, 5H), 3.09-3.05 (m, 2H),, 2.20-2.10 (m, 2H); MS ESI 521.4 $[M + H]^+$, calcd for $[C_{32}H_{32}N_4O_3 + H]^+$ 521.2.

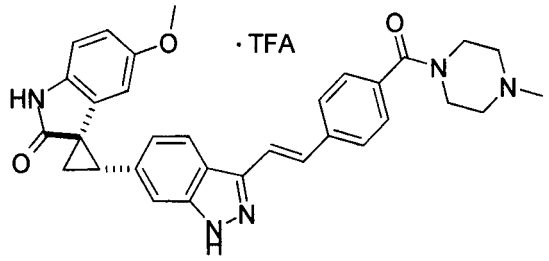
Optical Rotation $[\alpha]^{23}_D = -90°$ (c 0.67, MeOH).

Example A178. (1R*,2S*)-(E)-5'-methoxy-2-(3-(4-(2-morpholinoethyl) styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



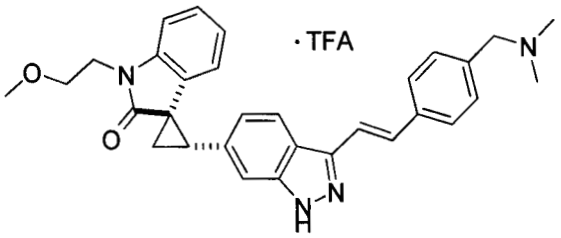
[00290] To a mixture of crude (1R*,2S*)-5'-methoxy-2-(3-vinyl-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (100 mg, 0.2 mmol) and 4-(4-bromophenethyl)morpholine (54 mg, 0.2 mmol) in DMF (2 mL) was added $^{i}Pr_2NEt$ (0.07 mL), followed by $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $P(o\text{-}tol)_3$ (6.7 mg, 0.022 mmol). The resulting mixture was purged with argon, and then microwaved 2 h at 125 °C. The mixture was purification by prep-HPLC gave the title compound as a white solid 36 mg, 28%, TFA salt. Spectral data was identical to that in obtained in Example A177.

Example A179. (1R*,2S*)-(E)-5'-methoxy-2-(3-(4-(4-methylpiperazine-1-carbonyl) styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



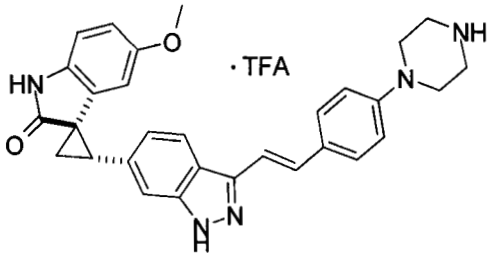
[00291] To a mixture of crude (1R*,2S*)-5'-methoxy-2-(3-vinyl-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one (100 mg, 0.2 mmol) and (4-bromophenyl)(4-methylpiperazin-1-yl)methanone (56.6 mg, 0.2 mmol) in DMF (2 mL) was added $^{i}Pr_2NEt$ (0.07 mL), followed by $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $P(o\text{-}tol)_3$ (6.7 mg, 0.022 mmol). The resulting mixture was purged with argon, and then microwaved 2 h at 125 °C. LC-MS showed incompletion and it was microwaved an additional 90 min at 130 °C. Purification by prep-HPLC gave the title compound (32 mg, 25%) as a pale yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.55-7.45 (m, 5H), 7.01 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.59 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 5.58 (d, J = 2.4 Hz, 1H), 3.65-3.10 (m, 12H), 2.96 (s, 3H), 2.25-2.14 (m, 2H); MS ESI 534.4 $[M + H]^+$, calcd for $[C_{32}H_{31}N_5O_3 + H]^+$ 534.3.

Example A180. (1R*,2S*)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-1'-(2-methoxyethyl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00292] The title compound (30 mg, 25%, TFA salt) was obtained as a colorless sticky oil from (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-1'-(2-methoxyethyl)spiro[cyclopropane-1,3'-indolin]-2'-one (92 mg, 0.2 mmol) and (E)-N,N-dimethyl-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)methanamine (86 mg, 0.3 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 3 mL/1.5 mL, 2.5 mol% $Pd(PPh_3)_4$, 120 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.55-7.45 (m, 5H), 7.13-7.07 (m, 2H), 7.01 (d, J = 8.4 Hz, 1H), 6.61 (dd, J = 8.0 Hz, 1H), 6.01 (d, J = 7.2 Hz, 1H), 4.32 (s, 2H), 4.05 (t, J = 5.4 Hz, 2H), 3.71 (t, J = 5.6 Hz, 2H), 3.41-3.35 (m, 4H), 2.89 (s, 6H), 2.28-2.18 (m, 2H); MS ESI 493.4 $[M + H]^+$, calcd for $[C_{31}H_{32}N_4O_2 + H]^+$ 493.3.

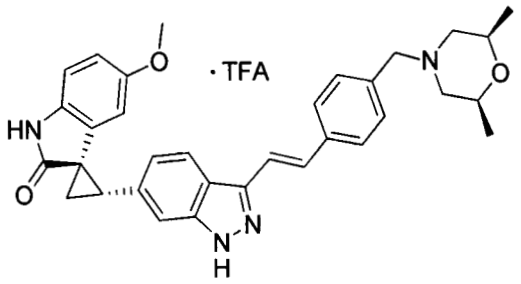
Example A182. (1R*,2S*)-5'-methoxy-2-(3-(4-(piperazin-1-yl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00293] The title compound (42 mg, 35%, TFA salt) was obtained as a yellow solid from (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (86.2 mg, 0.2 mmol) and (E)-1-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine (62.8 mg, 0.2 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 3 mL/1.5 mL, 2.5 mol% $Pd(PPh_3)_4$, 125 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.89 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.47 (s, 1H), 7.35 (d, J = 16.8 Hz, 1H), 7.22 (d, J = 16.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.4 Hz,

1H), 6.86 (d, J = 8.8 Hz, 1H), 6.60 (dd, J = 8.6 Hz, J = 2.2 Hz, 1H), 5.58 (s, 1H), 3.49-3.43 (m, 4H), 3.40-3.30 (m, 5H), 3.23 (s, 3H), 2.25-2.15 (m, 2H); MS ESI 492.3 $[M + H]^+$, calcd for $[C_{30}H_{29}N_5O_2 + H]^+$ 492.2.

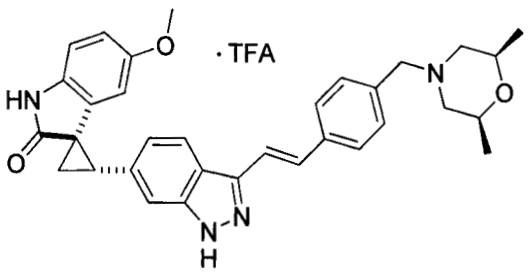
Example A185. (1R,2S)-(E)-2-(3-(4-trans-2,6-dimethylmorpholino)methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00294] The title compound (445 mg, 57%, TFA salt) was obtained as a pale yellowish white solid from three identical batches of (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (172 mg, 0.4 mmol) and cis-2,6-dimethyl-4-(4-((E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (150 mg, 0.42 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 9 mL/4.5 mL, 2.5 mol% $Pd(PPh_3)_4$, 110 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.75 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.42 (s, 1H), 7.35 (d, J = 16.8 Hz, 1H), 7.30 (d, J = 16.4 Hz, 1H), 6.82 (d, J = 9.2 Hz, 1H, partially overlapping with the peak at 6.80 ppm), 6.80 (d, J = 8.8 Hz, partially overlapping with the peak at 6.82 ppm), 6.51 (d, J = 8.4 Hz, 1H), 5.19 (s, 1H), 4.28 (s, 2H), 3.92-3.80 (m, 2H), 3.40-3.30 (m, 2H), 3.27(t, J = 8.4 Hz, 1H), 3.15 (s, 3H), 2.70 (t, J = 11.4 Hz, 2H), 2.15-2.05 (m, 2H), 1.18 (d, J = 6.0 Hz, 6H); MS ESI 535.3 $[M + H]^+$, calcd for $[C_{33}H_{34}N_4O_3 + H]^+$ 535.3.

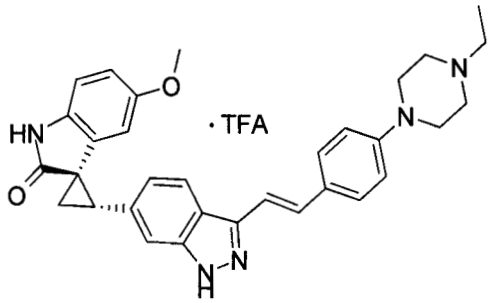
Optical Rotation $[\alpha]^{23}_D$ = -91° (c 0.31, MeOH).

Example A186. (1R*,2S*)-(E)-2-(3-(4-trans-2,6-dimethylmorpholino) methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00295] To a mixture of (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (431 mg, 1 mmol), (E)-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzaldehyde (284 mg, 1.1 mmol) in $PhCH_3$/EtOH (8 mL/4 mL) was added 1 M Na_2CO_3 (2 mL, 2 mmol), followed by $Ph(PPh_3)_4$ (29 mg, 0.025 mmol). The resulting mixture was purged with argon and then microwaved 2 h at 125 °C. After aqueous workup (extraction with EtOAc) and removal of solvents, the residue was redissolved in DCE/THF (45 mL/15 mL). Cis-2,6-dimethylmorpholine (115 mg, 1 mmol) and $NaBH(OAc)_3$ (254 mg, 1.2 mmol) were added, followed by AcOH (0.2 mL). The resulting mixture was stirred for 3 h at rt and quenched with sat. $NaHCO_3$ (20 mL), H_2O (20 mL), sat. brine (20 mL). The solution was extracted with EtOAc (60 mL x 2) and dried over Na_2SO_4. After removal of solvent, the residue was purifed by prep-HPLC to give the title compound as a pale yellow solid (132 mg, 20% over 2 steps). Spectral data was identical to that in obtained in Example A185.

Example A187. (1R,2S)-(E)-2-(3-(4-(4-ethylpiperazin-1-yl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

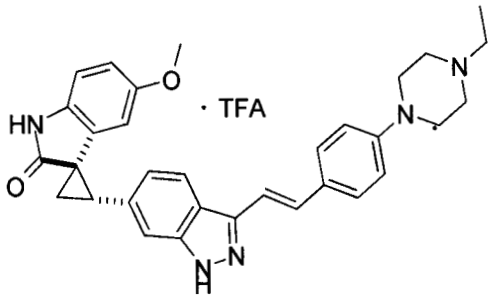


[00296] The title compound (414 mg, 55%, TFA salt) was obtained as a white solid (prep-HPLC, followed by trituration from MeOH) from three identical batches of (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (172 mg, 0.4 mmol) and (E)-1-ethyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl) phenyl)piperazine (impure, 205 mg, 0.6 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 6 mL/6mL, 2.5 mol% $Pd(PPh_3)_4$, 110 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.96 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.45 (s, 1H), 7.41 (d, J = 16.8 Hz, 1H), 7.28 (d, J = 16.8 Hz, 1H), 7.03-6.98 (m, 3H), 6.83 (d, J = 8.4 Hz, 1H), 6.60 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 5.59 (d, J = 2.0 Hz, 1H), 3.91 (d, J = 12.8 Hz, 2H), 3.66 (d, J = 11.6 Hz, 2H), 3.35 (t, J = 8.4 Hz, 1H, partially overlapping with MeOH residue), 3.29 (q, J = 7.2 Hz, 2H, partially overlapping with the peak at 3.25 ppm), 3.25 (s, 3H, partially overlapping with the peaks at 3.29 ppm and 3.20 ppm), 3.20 (t, J = 11.8 Hz, 2H,

partially overlapping with the peak at 3.25 ppm), 3.08 (t, J = 12.2 Hz, 2H), 2.25-2.15 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H); MS ESI 520.4 $[M + H]^+$, calcd for $[C_{32}H_{33}N_5O_2 + H]^+$ 520.3.

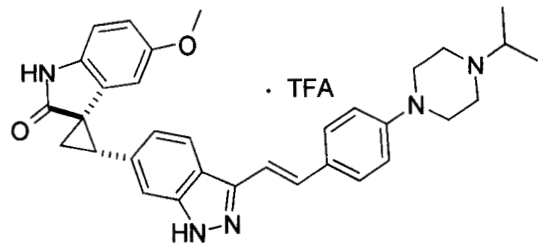
Optical Rotation $[\alpha]^{23}_D = -108^\circ$ (c 0.37, MeOH).

Example A188. (1R*,2S*)-(E)-2-(3-(4-(4-ethylpiperazin-1-yl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00297] The title compound (53 mg, 42%, TFA salt) was obtained as a light yellow solid from (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (86.2 mg, 0.2 mmol) and (E)-1-ethyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine (75 mg, 0.22 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 3 mL/1.5mL, 5 mol% $Pd(PPh_3)_4$, 125 °C, 2 h). Spectral data was identical to that in obtained in Example A187.

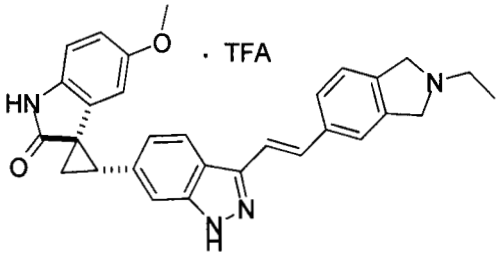
Example A189. (1R*,2S*)-(E)-2-(3-(4-(4-isopropylpiperazin-1-yl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



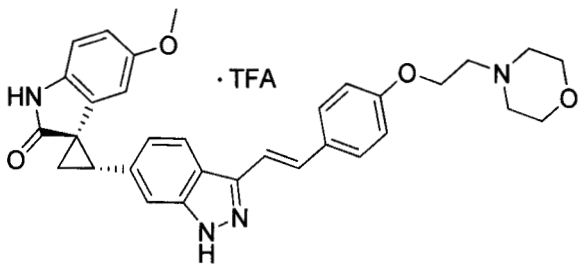
[00298] The title compound (85 mg, 66%, TFA salt) was obtained as a light yellow solid from (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (86.2 mg, 0.2 mmol) and (E)-1-isopropyl-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)piperazine (78.3 mg, 0.22 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 3 mL/1.5mL, 5 mol% $Pd(PPh_3)_4$, 125 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.46 (s, 1H, partially overlapping with the peak at 7.44 ppm), 7.44 (d, J = 16.4 Hz, 1H, partially

overlapping with the peak at 7.46 ppm), 7.31 (d, J = 16.4 Hz, 1H), 7.08-7.00 (m, 3H), 6.84 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.59 (s, 1H), 3.96 (d, J = 13.6 Hz, 2H), 3.65-3.55 (m, 3H), 3.40-3.30 (m, 6H), 3.08 (t, J = 9.0 Hz, 2H), 2.26-2.15 (m, 2H), 1.43 (d, J = 5.6 Hz, 6H); MS ESI 534.4 $[M + H]^+$, calcd for $[C_{33}H_{35}N_5O_2 + H]^+$ 534.3.

Example A190. (1R*,2S*)-2-(3-((E)-2-(2-ethylisoindolin-5-yl)vinyl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00299] The title compound (54 mg, 46%, TFA salt) was obtained as a pale yellow semi-solid from (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (86.2 mg, 0.2 mmol) and crude (E)-2-methyl-5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)isoindoline (73.0 mg, 0.24 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 3 mL/1.5mL, 5 mol% $Pd(PPh_3)_4$, 125 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.93 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H, partially overlapping with the peak at 7.60 ppm), 7.60 (d, J = 8.0 Hz, 1H, partially overlapping with the peak at 7.61 ppm), 7.48-7.37 (m, 4H), 6.90 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.59 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 5.58 (d, J = 1.2 Hz, 1H), 4.95-4.80 (m, 2H), 4.60-4.54 (m, 2H), 3.50 (q, J = 7.2 Hz, 2H), 3.31 (t, 1H, overlapping with MeOH residue), 3.24 (s, 3H), 2.23-2.13 (m, 2H), 1.44 (t, J = 7.2 Hz, 1H); MS ESI 477.3 $[M + H]^+$, calcd for $[C_{30}H_{28}N_4O_2 + H]^+$ 477.2.Example A194. (1R,2S)-(E)-5'-methoxy-2-(3-(4-(2-morpholinoethoxy)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

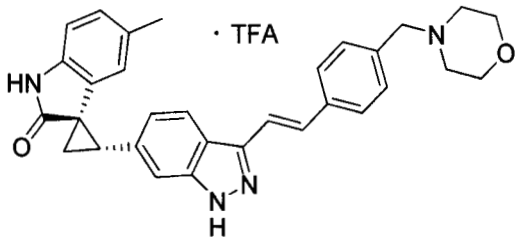


[00300] The title compound (431 mg, 66%, TFA salt) was obtained as a white solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one

(431 mg, 1 mmol) and ((E)-4-(2-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) vinyl)phenoxy)ethyl)morpholine (359 mg, 1 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 4.5 mL/9mL, 2 mol% $Pd(PPh_3)_4$, 125 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.72 (d, J = 8.4 Hz, 1H), 7.40-7.34 (m, 3H), 7.22 (d, J = 16.4 Hz, 1H), 7.10 (d, J = 16.4 Hz, 1H), 6.89 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 10.0 Hz, 1H, partially overlapping with the peak at 6.78 ppm), 6.78 (d, J = 9.2 Hz, 1H, partially overlapping with the peak at 6.80 ppm), 6.49 (d, J = 8.4 Hz, 1H), 5.55 (s, 1H), 4.31 (s, 2H), 4.05-3.97 (m, 4H), 3.62-3.50 (m, 4H), 3.30-3.15 (m, 3H; t, J = 8.2 Hz, 1H overlapping with m, 2H), 3.12 (s, 3H), 2.10-2.00 (m, 2H); MS ESI 537.4 $[M + H]^+$, calcd for $[C_{32}H_{32}N_4O_4 + H]^+$ 537.2.

Optical Rotation $[\alpha]^{23}_D$ = -85° (c 0.24, MeOH).

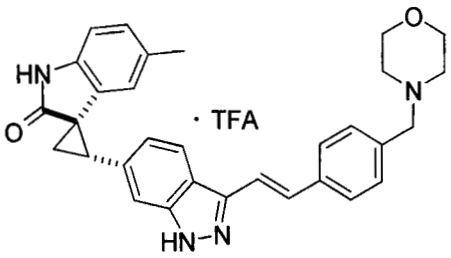
Example A195. (1R,2S)-(E)-5'-methyl-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00301] The title compound (470 mg, 78%, TFA salt) was obtained as a yellow solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (415 mg, 1 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl) benzyl)morpholine (329 mg, 1 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 4.5 mL/9mL, 2 mol% $Pd(PPh_3)_4$, 110 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.73 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.38 (s, 1H), 7.32 (d, J = 16.8 Hz, 1H), 7.27 (d, J = 16.8 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 5.78 (s, 1H), 4.29 (s, 2H), 3.99 (d, J = 11.2 Hz, 2H), 3.75 (t, J = 11.6 Hz, 2H), 3.42-3.32 (m, 2H), 3.21 (t, J = 8.4 Hz, 1H), 3.18-3.08 (m, 2H), 2.09-2.01 (m, 2H), 1.72 (s, 3H); MS ESI 491.3 $[M + H]^+$, calcd for $[C_{31}H_{30}N_4O_2 + H]^+$ 491.2.

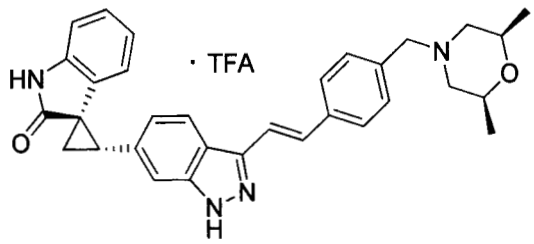
Optical Rotation 89° $[\alpha]^{23}_D$ = -89° (c 0.28, MeOH).

Example A196. (1R*,2S*)-(E)-5'-methyl-2-(3-(4-(morpholinomethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00302] The title compound (27 mg, 22%, TFA salt) was obtained as a yellow solid from (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl)-5'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (83 mg, 0.2 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (66 mg, 0.2 mmol) using the method for the preparation of Example A51B. Spectral data was identical to that in obtained in Example A195.

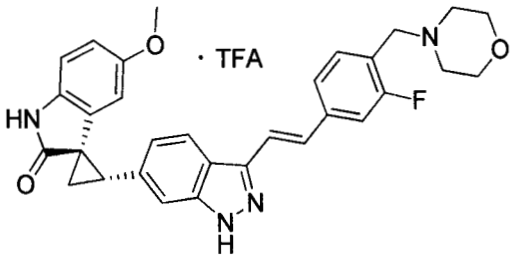
Example A198. (1R,2S)-(E)-2-(3-(4-cis-2,6-dimethylmorpholino)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00303] The title compound (284 mg, 57%, TFA salt) was obtained as a white solid from two batches of (1R,2S)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (160 mg, 0.4 mmol) and cis-2,6-dimethyl-4-(4-((E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (157 mg, 0.42 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 9 mL/4.5mL, 2.5 mol% $Pd(PPh_3)_4$, 110 °C, 2.5 h). ^1H NMR (400 MHz, CD_3OD) δ 7.74 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.40-7.28 (m, 3H), 6.96-6.99 (m, 2H), 6.82 (d, J = 8.4 Hz, 1H), 6.40 (t, J = 7.4 Hz, 1H), 5.89 (d, J = 7.6 Hz, 1H), 4.28 (s, 2H), 3.93-3.80 (m, 2H), 3.34 (d, J = 13.6 Hz, 2H, overlapping with MeOH residue), 3.24 (t, J = 7.6 Hz, 1H), 2.70 (t, J = 7.4 Hz, 2H), 2.08 (p, J = 7.6 Hz, 2H), 1.18 (d, J = 6.0 Hz, 6H); MS ESI 505.3 $[M + H]^+$, calcd for $[C_{32}H_{32}N_4O_2 + H]^+$ 505.3.

Optical Rotation $[\alpha]^{23}_D$ = -134° (c 0.27, MeOH).

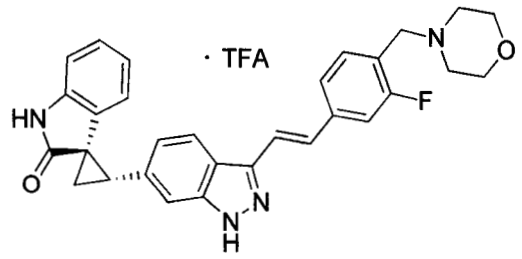
Example A199. (1R,2S)-(E)-2-(3-(3-fluoro-4-(morpholinomethyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00304] The title compound (154 mg, 60%, TFA salt) was obtained as a white solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (172 mg, 0.4 mmol) and (E)-4-(2-fluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (145 mg, 0.42 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 6 mL/6mL, 2.5 mol% $Pd(PPh_3)_4$, 110 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.78 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.45-7.35 (m, 4H), 7.29 (d, J = 16.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 5.56 (s, 1H), 4.40 (s, 2H), 4.10-3.90 (m, 4H), 3.50-3.20 (m, 5H), 3.18 (s, 3H), 2.18-2.08 (m, 2H); MS ESI 525.3 $[M + H]^+$, calcd for $[C_{31}H_{29}FN_4O_3 + H]^+$ 525.2.

Optical Rotation $[\alpha]^{23}_D = 88°$ (c 0.27, MeOH).

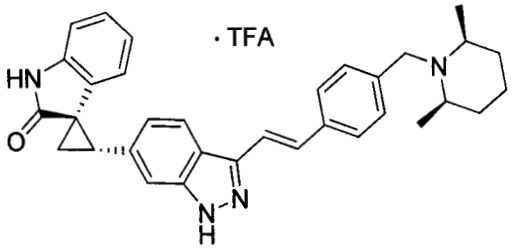
Example A200. (1R,2S)-(E)-2-(3-(3-fluoro-4-(morpholinomethyl)styryl)-1H-indazol-6-yl) spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00305] The title compound (228 mg, 75%, TFA salt) was obtained as a white solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (200 mg, 0.5 mmol) and (E)-4-(2-fluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl) benzyl)morpholine (190 mg, 0.55 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 7 mL/7mL, 2 mol% $Pd(PPh_3)_4$, 110 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.50 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.40-7.30 (m, 4H), 7.24 (d, J = 16.8 Hz, 1H), 6.97-6.82 (m, 3H), 6.42 (t, J = 7.4 Hz, 1H), 5.90 (d, J = 7.6 Hz, 1H), 4.36 (s, 2H), 4.10-3.70 (m, 4H), 3.50-3.15 (m, 5H), 2.12-2.03 (m, 2H); MS ESI 495.3 $[M + H]^+$, calcd for $[C_{30}H_{27}FN_4O_2 + H]^+$ 495.2.

Optical Rotation $[\alpha]^{23}_D$ = -130° (c 0.40, MeOH).

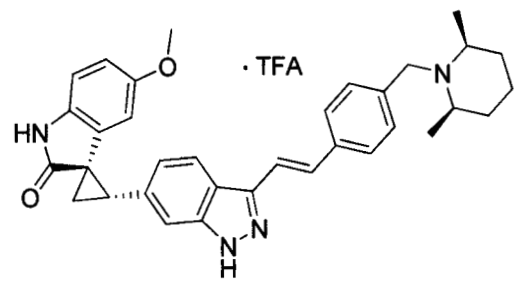
Example A201. (1R,2S)-(E)-2-(3-(4-((cis-2,6-dimethylpiperidin-1-yl)methyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00306] The title compound (91 mg, 74%, TFA salt) was obtained as a light yellow solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (80.2 mg, 0.2 mmol) and cis-2,6-dimethyl-1-(4-((E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)piperidine (78.5 mg, 0.22 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 1.5 mL/3mL, 2 mol% $Pd(PPh_3)_4$, 110 °C, 2 h). ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (d, J = 8.4 Hz, 1H), 7.68-7.60 (s, 1H at 7.51 ppm and d, J = 16.8 Hz, 1H at 7.50 ppm overlapping, 1H), 7.64 (d, J = 8.8 Hz, 1H, partially overlapping with the peak at 7.66 ppm), 7.55-7.38 (m, 5H), 7.00 (t, J = 7.6 Hz, 1H), 6.96-6.90 (m, 2H); 6.50 (t, J = 7.6 Hz, 1H), 5.96 (d, J = 7.2 Hz, 1H), 4.54 (s, 1.2H), 4.26 (s, 0.8H), 3.60-3.50 (m, 0.7 H), 3.28 (t, J = 8.0, 1H, partially overlapping with MeOH residue), 3.20-3.10 (m, 1.2 H), 2.20-2.08 (m, 2H), 1.96-1.35 (m, 12H); MS ESI 503.3 $[M + H]^+$, calcd for $[C_{33}H_{34}N_4O + H]^+$ 503.3.

Optical Rotation $[\alpha]^{23}_D$ = -133° (c 0.22, MeOH).

Example A203. (1R,2S)-(E)-2-(3-(4-((cis-2,6-dimethylpiperidin-1-yl)methyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

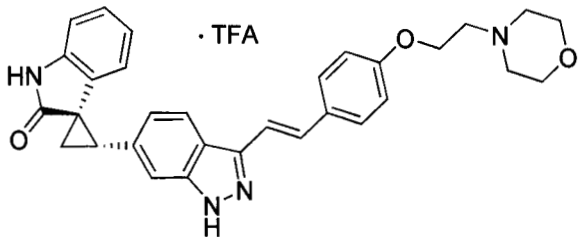


[00307] The title compound (78 mg, 60%, TFA salt) was obtained as a white solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one

(86.2 mg, 0.2 mmol) and cis-2,6-dimethyl-1-(4-((E)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)piperidine (78.5 mg, 0.22 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 1.5 mL/3mL, 2 mol% $Pd(PPh_3)_4$, 110 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.91 (d, J = 8.4 Hz, 1H), 7.68-7.63 (s, 1H at 7.66 ppm and d, J = 16.4 Hz, 1H at 7.66 ppm overlapping; 2H), 7.53 (d, J = 7.6 Hz, 1H), 7.50-7.40 (m, 4H), 6.96 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 5.58 (s, 1H), 4.56 (s, 1.2 H), 4.28 (s, 0.8H), 3.60-3.50 (m, 0.7H), 3.31 (t, 1H, overlapping with MeOH residue), 3.23-3.13 (m, 4.3H; OMe and 1.3H), 2.22-2.12 (m, 2H), 2.00-1.35 (m, 12H); MS ESI 533.4 $[M + H]^+$, calcd for $[C_{34}H_{36}N_4O_2 + H]^+$ 533.3.

Optical Rotation $[\alpha]^{23}_D$ = -93° (c 0.27, MeOH).

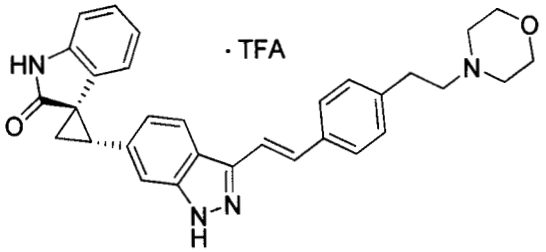
Example A204. (1R,2S)-(E)-2-(3-(4-(2-morpholinoethoxy)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00308] The title compound (94 mg, 74%, TFA salt) was obtained as a light yellow solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (80 mg, 0.2 mmol) and (E)-4-(2-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl) phenoxy)ethyl)morpholine (72 mg, 0.2 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 1.5 mL/3mL, 2 mol% $Pd(PPh_3)_4$, 110 °C, 2 h). ^1H NMR (400 MHz, CD_3OD) δ 7.83 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.38 (s, 1H), 7.32 (d, J = 16.8 Hz, 1H), 7.19 (d, J = 16.4 Hz, 1H), 7.02-6.93 (m, 3H), 6.91 (d, J = 7.2 Hz, 1H, partially overlapping with the peak at 6.89 ppm), 6.89 (d, J = 8.0 Hz, 1H, partially overlapping with the peak at 6.91 ppm), 6.48 (t, J = 7.2 Hz, 1H), 5.93 (d, J = 7.6 Hz, 1H), 4.36 (t, J = 4.0 Hz, 2H), 4.10-3.76 (m, 4H), 3.65-3.50 (m, 4H), 3.30-3.18 (m, 3H), 2.15-2.05 (m, 2H); MS ESI 507.3 $[M + H]^+$, calcd for $[C_{31}H_{30}N_4O_3 + H]^+$ 507.2.

Optical Rotation $[\alpha]^{23}_D$ = -139° (c 0.29, MeOH).

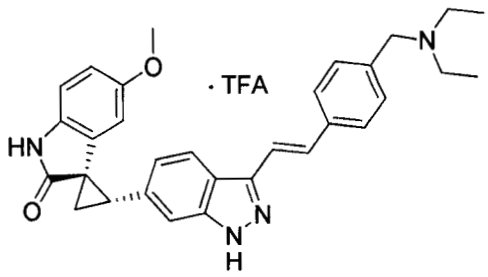
Example A205. (1R,2S)-(E)-2-(3-(4-(2-morpholinoethyl)styryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00309] The title compound (89 mg, 74%, TFA salt) was obtained as a light yellow solid from (1R,2S)-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (80 mg, 0.2 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenethyl) morpholine (69 mg, 0.2 mmol) using the method for the preparation of Example A51B ($PhCH_3$/EtOH = 1.5 mL/3mL, 2 mol% $Pd(PPh_3)_4$, 110 °C, 2 h). ^{1}H NMR (400 MHz, CD_3OD) δ 7.86 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 16.4 Hz, 2H), 7.34 (s, 1H), 7.26 (d, J = 7.6 Hz, 2H), 6.97 (t, J = 7.2 Hz, 1H), 6.91 (d, J = 7.2 Hz, 2H), 6.49 (t, J = 7.4 Hz, 1H), 5.94 (t, J = 7.6 Hz, 1H), 4.04 (d, J = 12.0 Hz, 2H), 3.80 (t, J = 11.8 Hz, 2H), 3.54 (d, J = 12.0 Hz, 2H), 3.36 (t, J = 8.8 Hz, 2H), 3.27 (t, J = 8.6 Hz, 1H), 3.15 (t, J = 11.0 Hz, 2H), 3.05 (t, J = 8.4 Hz, 2H), 2.16-2.06 (m, 2H); MS ESI 491.3 $[M + H]^+$, calcd for $[C_{31}H_{30}N_4O_2 + H]^+$ 491.2.

Optical Rotation $[\alpha]^{23}_D$ = -141° (c 0.22, MeOH).

Example A206. (1*R*,2*S*)-(E)-2-(3-(4-((diethylamino)methyl)styryl)-1H-indazol-6-yl)-5'-methoxy spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

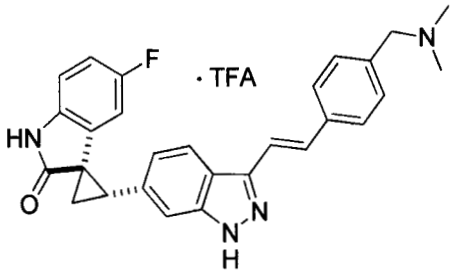


[00310] The title compound was synthesized according to the method of Example A51B, by using (1R,2S)-2-(3-iodo-1H-indazol-6-yl-)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (700 mg, 1.62 mmol) and (E)-N-ethyl-N-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)ethanamine (588.5 mg, 1.86 mmol). Purification by preparative HPLC gave the title compound as a cream solid (448 mg, 46%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.54-7.49 (m, 5H), 7.04

(s, J = 8.4 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 5.58 (s, 1H), 4.36 (s, 2H), 3.36 (t, J = 8.4 Hz, 1H), 3.31-3.18 (bm, 7H), 2.26-2.23 (m,1H), 2.20-2.17 (m, 1H), 1.37 (t, J = 7.2 Hz, 6H); MS ESI 493.4 $[M + H]^+$, calcd for $[C_{31}H_{32}N_4O_2 + H]^+$ 493.26.

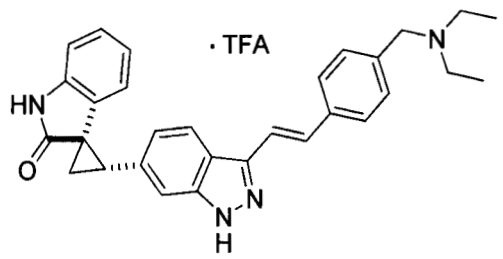
Optical Rotation: $[\alpha]^{22}_D$ = -80° (c 0.286, Methanol).

Example A208. (1*R**,2*S**)-(E)-2-(3-(4-((dimethylamino)methyl)styryl)-1H-indazol-6-yl)-5'-flurorospiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00311] The title compound was synthesized according to the method of Example A51B, by using (1R*,2S*)-5'-fluoro-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin] -2'-one (75 mg, 0.178 mmol) and (E)-N,N-dimethyl-1(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)methanamine (63.9 mg, 0.222 mmol). Purification by preparative HPLC gave the title compound as a cream solid (42 mg, 41.4%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.57 (s, 2H), 7.56-7.50 (m, 3H), 7.05 (d, J = 8.4 Hz, 1H), 6.91-6.88 (m, 1H), 6.82-6.77 (m, 1H), 5.77 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 4.33(s, 2H), 3.42-3.38 (m, 1H), 2.88 (s, 6H), 2.32-2.29 (m, 1H), 2.24-2.20 (m, 1H); MS ESI 453.2 $[M + H]^+$, calcd for $[C_{28}H_{25}FN_4O + H]^+$ 453.2.

Example A211. (1*R**,2*S**)-(E)-2-(3-(4-((diethylamino)methyl)styryl)-1H-indazol-6-yl)spiro-[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



A. N-ethyl-N-(4-ethynylbenzyl)ethanamine

[00312] Sodium triacetoxyborohydride (1.22 g, 5.76 mmol) was added to a solution of 4-ethynylbenzaldehyde (0.50 g, 3.84 mmol) in 1,2-dichloroethane (18.75 mL) at rt. Diethylamine (0.61 mL, 5.76 mmol) and acetic acid (0.12 mL, 1.92 mmol) were then added under N_2 atmosphere to the mixture at rt and the reaction was stirred for 18 h. The reaction was quenched with sat. sodium bicarbonate solution (10 mL) and the mixture was stirred for 15 min. Dichloromethane (18.75 mL) was then added and the layers were separated. The aqueous layer was extracted using dichloromethane (10 mL), and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was then removed under vacuum at 40°C/200 mbar. The resultant oily residue was purified by silica gel column chromatography using dichloromethane: methanol (100 to 90:10) gradient to give the title compound as pale yellow thick oil (0.455 g, 63.2%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H), 3.78 (s, 2H), 3.08 (s, 1H), 2.72-2.66 (m, 4H), 1.13 (t, J = 7.2 Hz, 6H); MS ESI 187.9 $[M + H]^+$, calcd for $[C_{13}H_{17}N + H]^+$ 187.14.

B. (E)-N-ethyl-N-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) vinyl) benzyl)ethananamine

[00313] According to procedure for the synthesis of example A42A , by using N-ethyl-N-(4-ethynylbenzyl)ethanamine (0.70 g, 3.73 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.62 mL , 11.21 mmol) to give the title compound as a yellowish orange oil (1.02 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (m, 3H), 7.30-7.27 (m, 2H), 6.12 (d, J = 18.4 Hz, 1H), 3.56 (s, 2H), 2.54-2.49 (m, 4H), 1.32 (s, 12H), 1.04 (t, J = 7.2 Hz, 6H); MS ESI 316.1 $[M + H]^+$, calcd for $[C_{29}H_{30}BNO_2 + H]^+$ 316.24.

This intermediate can also be prepared by the following method:

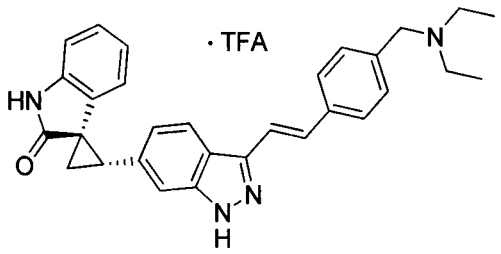
[00314] According to procedure for the synthesis of Example A211A , by using (E)-4-(2-(4,4,5,5-tetramethyl-1,3,2-dooxaborolan-2-yl)vinyl)benzaldehyde (1.93 g, 7.48 mmol), sodium triacetoxyborohydride (2.38 g, 11.22 mmol) and diethylamine (1.16 mL, 11.22 mmol) to give the title compound after purification using Biotage on SNAP 25g column with hexane:ethylacetate (100 to 72:25) gradient as a pale yellow thick oil (1.55 g, 66 %).

D. (1R,2S*)-2-(3-(4-((diethylamino)methyl)styryl)-1H-indazol-6-yl)spiro-[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate*

[00315] The title compound was synthesized according to the method of Example A51B, by using (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl-)spiro[cyclopropane-1,3'-indolin]-2'-one (70.0 mg, 0.174 mmol) and (E)-N-ethyl-N-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)ethanamine (68.76 mg, 0.218 mmol). Purification by preparative HPLC

gave the title compound as a cream solid (29 mg, 29%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.56-7.52 (m, 4H), 7.48 (s, 1H), 7.04 (d, J = 7.2 Hz, 2H), 6.93 (d, J = 7.6 Hz, 1H), 6.58 (t, J = 7.2 Hz, 1H), 5.98 (d, J = 7.6 Hz, 1H), 4.36 (s, 2H), 3.29-3.17 (m, 5H), 2.25 (t, J = 4.8 Hz, 1H), 2.21-2.17 (m, 1H), 1.37 (t, J = 7.2 Hz, 6H); MS ESI 463.3 $[M + H]^+$, calcd for $[C_{30}H_{30}N_4O + H]^+$ 463.25.

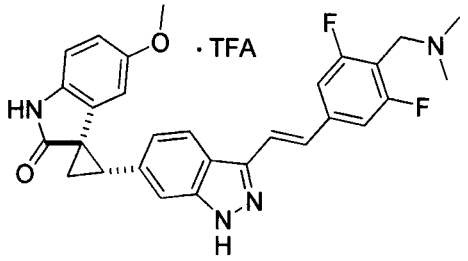
Example A212. (1*R*,2*S*)-(E)-2-(3-(4-((diethylamino)methyl)styryl)-1H-indazol-6-yl)spiro-[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00316] The title compound was synthesized according to the method of Example A51B, by using (1R,2S)-2-(3-iodo-1H-indazol-6-yl-)spiro[cyclopropane-1,3'-indolin]-2'-one (600 mg, 1.50 mmol) and (E)-N-ethyl-N-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) vinyl) benzyl)ethanamine (589.3 mg, 1.87 mmol). Purification by preparative HPLC gave the title compound as a cream solid (360 mg, 42%). Spectral data was identical to that obtained for Example A211D.

Optical Rotation: $[\alpha]^{23}_D$ = -194° (c 0.577, Methanol).

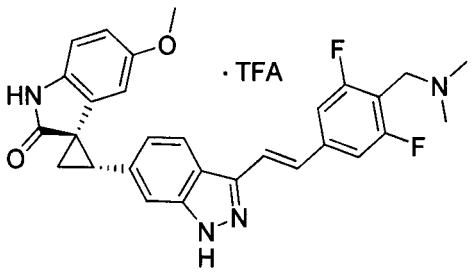
Example A215. (1*R**,2*S**)-(E)-2-(3-(4-((dimethylamino)methyl)-3,5-difluorostyryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoro acetate



[00317] A mixture of (1R*,2S*)-5'-methoxy-2-(3-vinyl-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one (50.0 mg, 0.15 mmol), 1-(4-bromo-2,6-difluorophenyl)-N,N-dimethylmethanamine (41.51 mg, 0.165 mmol), $Pd(OAc)_2$ (1.69 mg, 0.0075 mmol), $P(oTol)_3$ (5.0 mg, 0.016 mmol) and DIPEA (39.0 mg, 0.30 mmol) in DMF (1.0 mL) was

sealed and heated with stirring under microwave irradiation at 125°C for 2 h. The reaction was then diluted with ethyl acetate (20 mL) and water (5 mL) and the layers were separated. The aqueous layer was extracted using ethyl acetate (10 mL), and the combined ethyl acetate layer was washed with brine (4.0 mL) and was dried over sodium sulfate and then concentrated vacuum at 40°C/100 mbar to yield a yellowish residue. The crude product was purified by prep. HPLC to give the title compound as a pale yellow solid (9.5 mg, 10%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 8.4 Hz, 1H), 7.47 (s, 1H), 7.43 (d, J = 16.4 Hz, 1H), 7.30-7.25 (m, 3H), 6.87 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 8.8 Hz, 1H), 5.56 (s, 1H), 4.43 (s, 2H), 3.28 (t, J = 10.0 Hz, 1H), 3.19 (s, 3H), 2.96 (s, 6H), 2.18-21.2 (m,2H); MS ESI 501.3 $[M + H]^+$, calcd for $[C_{29}H_{26}F_2N_4O_2 + H]^+$ 501.21.

Example A216. (1*R*,2*S*)-(E)-2-(3-(4-((dimethylamino)methyl)-3,5-difluorostyryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



A. (E)-1-(2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaorolan-2-yl)vinyl)phenyl)-N,N-dimethylmethanamine

This intermediate was prepared via 2 different synthetic methods.

Method 1.

a.1-(4-bromo-2,6-difluorophenyl)-N,N-dimethylmethanamine

[00318] According to procedure for the synthesis of Example A211A, by using 4-bromo-2,6-difluorobenzaldehyde (500 mg, 2.26 mmol), sodium triacetoxyborohydride (959 mg, 4.52 mmol) and 2M dimethylamine solution (2.626 mL, 4.52 mmol) to give the title compound as a colorless oil (452 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 6.8 Hz, 2H), 3.54 (s, 2H), 2.26 (s, 6H); MS ESI 249.9 $[M + H]^+$, calcd for $[C_9H_{10}BrF_2N + H]^+$ 249.0.

b.1-(4-ethylnyl-2,6-difluorophenyl)-N,N-dimethylmethanamine

[00319] A mixture of 1-(4-bromo-2,6-difluorophenyl)-N,N-dimethylmethanamine (0.45g, 1.79 mmol), trimethylsilylacetylene (0.356 mL, 2.24 mmol), $Pd(PPh_3)_2Cl_2$ (50.49 mg, 0.071 mmol), CuI (3.42 mg, 0.017 mmol) and DIPEA (0.46 mL, 2.69 mmol) in DMF (3.0 mL) was sealed under argon atmosphere and heated with stirring under microwave irradiation at 100°C for 2 h. The reaction was diluted with methanol (9 mL) and the resulting precipitate was filtered off. The mother liquor was concentrated under vacuum at 45°C/75mbar to give a brown, thick oil. The residue was purified on Biotage using SNAP 25g column with hexane: ethyl acetate (100 to 80:20) gradient to give yellow oil as a trimethylsilyl ether (0.250 g, 52%); MS ESI 268.0 $[M + H]^+$,calcd for $[C_{14}H_{19}F_2NSi + H]^+$ 268.13.

[00320] Deprotection of above trimethylsilyl ether was carried out in methanol (10 mL) and 10% K_2CO_3 solution (1.67 mL) at rt for 1.5 h. The solvents were removed in vacuo below 40°C and then water (5 mL) was added at room temperature. The product was extracted using dichloromethane (2 x 15 mL) and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under vacuum at 40°C/200 mbar to give brownish oil, which was purified on Biotage using SNAP 25g column with hexane: ethyl acetate (100 to 75:75) gradient to give yellow oil (98 mg, 54%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 6.8 Hz, 2H), 3.68 (s, 2H), 3.17 (s, 1H), 2.35 (s, 6H); MS ESI 195.8 $[M + H]^+$, calcd for $[C_{11}H_{11}F_2N + H]^+$ 195.09.

c. (E)-1-(2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaorolan-2-yl)vinyl) phenyl)-N,N-dimethylmethanamine

[00321] According to procedure for the synthesis of example A42A, by using 1-(4-ethylnyl-2,6-difluorophenyl)-N,N-dimethylmethanamine (97 mg, 0.496 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane(0.21 mL, 1.488 mmol) to give the title compound after purification on Biotage using KPNH SNAP 25 gm column with hexane : ethyl acetate (100 to 50:50) gradient as a brown semi solid (67 mg, 41%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 18.4 Hz, 1H), 6.99 (d, J = 7.6 Hz, 2H), 6.13 (d, J = 18.4 Hz, 1H), 3.57 (s, 2H), 2.28 (s, 6H), 1.32 (s, 12H); MS ESI 324.2 $[M + H]^+$, calcd for $[C_{17}H_{24}BrF_2NO_2 + H]^+$ 323.19.

Method 2

a. (E)-2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) vinyl) benzaldehyde

[00322] According to procedure for the synthesis of example A51A , by using 4-bromo-2,6-difluorobenzaldehyde (1.10 g, 4.98 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-

dioxaborolane (0.97 mL , 5.72 mmol) to give the title compound as a colorless oil (1.10 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.05 (d, J = 9.6 Hz, 2H), 7.22 (d, J = 8.8 Hz, 1H), 6.28 (d, J = 18.8 Hz, 1H), 1.33 (s, 12H); MS ESI 295.1 $[M + H]^+$, calcd for $[C_{15}H_{17}BF_2O_3 + H]^+$ 295.13.

b.(E)-1-(2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaorolan-2-yl)vinyl)phenyl)-N,N-dimethylmethanamine

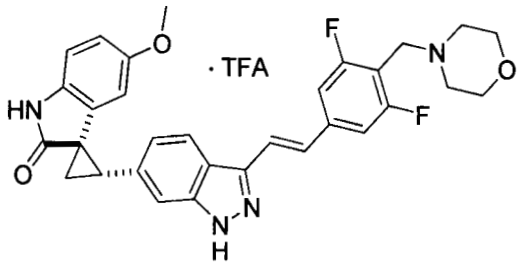
[00323] According to procedure for the synthesis of example A211A, by using (E)-2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzaldehyde (1.10 g, 3.74 mmol), sodium triacetoxyborohydride (1.19 g, 5.61 mmol) and 2M dimethylamine solution (3.74 mL, 7.48 mmol) to give the title compound as a colorless thick oil (0.571 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 18.4 Hz, 1H), 6.99 (d, J = 7.6 Hz, 2H), 6.13 (d, J = 18.4 Hz, 1H), 3.57 (s, 2H), 2.28 (s, 6H), 1.32 (s, 12H) ; MS ESI 324.2 $[M + H]^+$, calcd for $[C_{17}H_{24}BrF_2NO_2 + H]^+$ 323.19.

B. (1R,2S)-2-(3-(4-((dimethylamino)methyl)-3,5-difluorostyryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

[00324] The title compound was synthesized according to the method of Example A51B, by using (1R,2S)-2-(3-iodo-1H-indazol-6-yl-)-5'-methoxyspioro[cyclopropane-1,3'-indolin]-2'-one (500 mg, 1.15 mmol) and (E)-1-(2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)phenyl)-N,N-dimethylmethanamine (393.4mg, 1.21 mmol). Purification by preparative HPLC gave the title compound as a cream solid (400 mg, 56.1%). Spectral data was identical for that obtained in Example A215.

Optical Rotation: $[\alpha]^{22}_D$ = -88° (c 0.354, Methanol).

Example A217. (1*R**,2*S**)-(E)-2-(3-(3,5-difluoro-4-(morpholinomethyl)styryl-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



A. 1-(4-bromo-2,6-difluorophenyl)-morpholine

[00325] According to procedure for the synthesis of Example A211A by using 4-bromo-2,6-difluorobenzaldehyde (1.0 g, 4.52 mmol), sodiumtriacetoxyborohydride (1.438 g, 6.78 mmol) and morpholine (0.59 mL, 6.78 mmol) to give the title compound as a pale yellow oil (1.30 g, 98.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 6.4 Hz, 2H), 3.69 (d, J = 4.4 Hz, 4H), 3.63 (s, 2H), 2.49 (bm, 4H); MS ESI 292.1 $[M + H]^+$,calcd for $[C_{11}H_{12}BrF_2NO+ H]^+$ 293.0.

B .1-(4-ethylnyl-2,6-difluorophenyl)morpholine

[00326] According to procedure for the synthesis of Example A216A method 1b, by using 1-(4-bromo-2,6-difluorophenyl)-morpholine (1.32 g, 4.51 mmol) to give the title compound as a light brown oil (0.65 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 7.2 Hz, 2H), 3.71-3.67 (m, 6H), 3.16 (s, 1H), 2.50 (bm, 4H); MS ESI 238.0 $[M + H]^+$, calcd for $[C_{13}H_{13}F_2NO + H]^+$ 238.10.

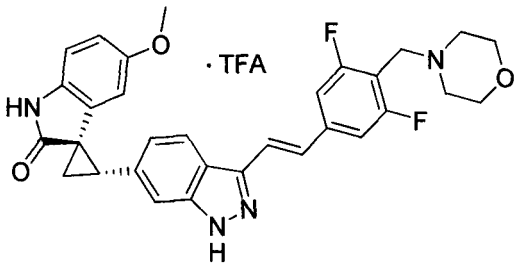
C. (E)-4-(2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) vinyl) benzyl)morpholine

[00327] According to procedure for the synthesis of example A42A , by using 1-(4-ethylnyl-2,6-difluorophenyl)morpholine (0.97 g, 4.08 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxa borolane (1.78 mL , 12.24 mmol) to give the title compound as a cream solid (1.21 g, 81%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 18.4 Hz, 1H), 6.99 (d, J = 7.6 Hz, 2H), 6.13 (d, J = 18.4 Hz, 1H), 3.59-3.66 (m, 6H), 2.51 (bm, 4H), 1.32 (s, 12H); MS ESI 366.1 $[M + H]^+$, calcd for $[C_{19}H_{26}BF_2NO_3 + H]^+$ 366.2.

D. (1R,2S*)-2-(3-(3,5-difluoro-4-(morpholinomethyl)styryl-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate*

[00328] The title compound was synthesized according to the method of Example A51B, by using (1R*,2S*)-2-(3-iodo-1H-indazol-6-yl-)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (60 mg, 0.139 mmol) and (E)-4-(2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (58.44 mg, 0.16 mmol). Purification by preparative HPLC gave the title compound as a cream solid (29 mg, 27%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 16.8 Hz, 1H), 7.52-7.49 (m, 4H), 7.06 (s, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 5.57 (s, 1H), 4.51 (s, 2H), 4.10-3.72 (bm, 4H), 3.47-3.42 (bm, 5H), 3.26 (s, 3H), 2.26-2.23 (m, 1H), 2.21-2.17 (m, 1H); MS ESI 543.3 $[M + H]^+$, calcd for $[C_{31}H_{28}F_2N_4O_3 + H]^+$ 543.22.

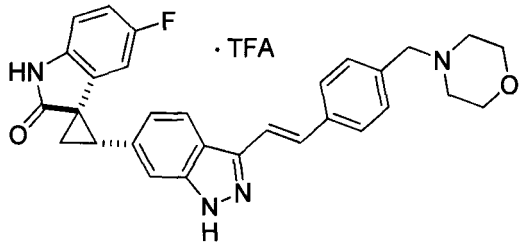
Example A218. (1R,2S)-(E)-2-(3-(3,5-difluoro-4-(morpholinomethyl)styryl)-1H-indazol-6-yl)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00329] The title compound was synthesized according to the method of Example A51B, by substituting (1R,2S)-2-(3-iodo-1H-indazol-6-yl-)-5'-methoxyspiro[cyclopropane-1,3'-indolin]-2'-one (600 mg, 1.50 mmol) and (E)-4-(2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (579.6 mg, 1.06 mmol). Purification by preparative HPLC gave the title compound as a cream solid (345 mg, 40%). Spectral data was identical for that obtained in Example A217.

Optical Rotation: $[\alpha]^{22}_{D}$ = -74° (c 0.34, Methanol).

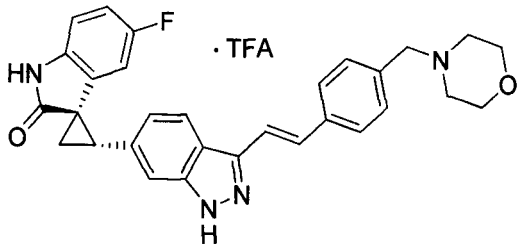
Example A219. (1*R**,2*S**)-(E)-5'-fluoro-2-(3-(4-(morpholinomethyl)styryl-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00330] The title compound was synthesized according to the method of Example A51B, by using (1R*,2S*)-5'-fluoro-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one(60.0 mg, 0.139 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)morpholine (54.83 mg, 0.173 mmol). Purification by preparative HPLC gave the title compound as a cream solid (31.0 mg, 37%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 7.2 Hz, 2H), 7.59-7.52 (m, 5H), 7.05 (d, J = 8.0 Hz, 1H), 6.91-6.88 (m, 1H), 6.79 (t, J = 8.0 Hz, 1H), 5.74(d, J = 8.8 Hz, 1H), 4.39 (s, 2H), 4.08-4.05 (bm, 2H), 3.76-3.70 (bt, 2H),3.42-3.35 (m, 3H), 3.26-3.23 (bm, 2H), 2.30 (t, J =

5.6 Hz, 1H), 2.24-2.20 (m, 1H); MS ESI 495.3 $[M + H]^+$, calcd for $[C_{30}H_{27}FN_4O_2 + H]^+$ 495.22.

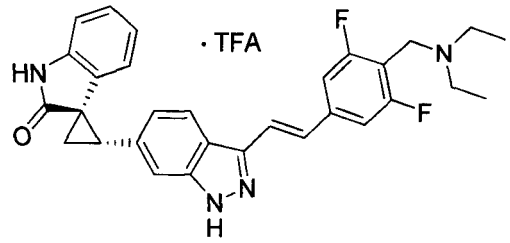
Example A220. (1*R*,2*S*)-(E)-5'-fluoro-2-(3-(4-(morpholinomethyl)styryl-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



[00331] The title compound was synthesized according to the method of Example A51B, by using (1R,2S)-5'-fluoro-2-(3-iodo-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (240 mg, 0.571 mmol) and (E)-4-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) vinyl) benzyl) morpholine (216.7 mg, 0.658 mmol). Purification by preparative HPLC gave the title compound as a cream solid (230 mg, 66%). Spectral data was identical to that obtained for Example A219.

Optical Rotation: $[\alpha]^{22}_D$ = -136° (c 0.404, Methanol).

Example A221. (1*R*,2*S*)-(E)-2-(3-(4-((diethylamino)methyl)-3,5-difluorostyryl)-1H-indazol-6-yl)spiro[cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate



A.N-(4-bromo-2,6-difluorobenzyl-)N-ethylethanamine

[00332] According to procedure for the synthesis of Example A211A, by using 4-bromo-2,6-difluorobenzaldehyde (610 mg, 2.76mmol), sodium triacetoxyborohydride (883.35 mg, 4.15 mmol) and diethylamine (425.21 mmL, 4.15 mmol) to give the title compound as a colorless oil (660 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 6.4 Hz, 2H), 3.61 (s, 2H), 2.55-2.50 (m, 4H), 1.07 (t, J = 6.8 Hz, 6H); MS ESI 279.9 $[M + H]^+$, calcd for $[C_{11}H_{14}BrF_2N + H]^+$ 278.03.

B. N-ethyl-N-(4-ethynyl-2,6-difluorobenzyl)ethanamine

[00333] According to procedure for the synthesis of Example A216A method 1b, by using N-(4-bromo-2,6-difluorobenzyl-)N-ethylethanamine (660 mg, 2.37 mmol) to give the title compound as a light brown oil (252 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 7.2 Hz, 2H), 3.67 (s, 2H), 3.13 (s, 1H), 2.57-2.51 (m, 4H), 1.08 (t, J = 7.2 Hz, 6H); MS ESI 224.0 $[M + H]^+$, calcd for $[C_{13}H_{15}F_2N + H]^+$ 224.12.

C:(E)-N-(2,6-Difluoro-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)N-ethylethanamine

[00334] According to procedure for the synthesis of example A42A, by using N-ethyl-N-(4-ethynyl-2,6-difluorobenzyl)ethanamine (252 mg, 1.12 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.493 mL , 3.36 mmol) to give the title compound as a cream semi solid (410 mg, 90%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 13.2 Hz, 1H), 6.97 (d, J = 7.6 Hz, 2H), 6.12 (d, J = 17.6 Hz, 1H), 3.67 (s, 2H), 2.58-2.52 (m, 4H), 1.32 (s, 12H), 1.08 (t, J = 6.8 Hz, 6H); MS ESI 352.2 $[M + H]^+$, calcd for $[C_{27}H_{26}N_6O_2 + H]^+$ 351.22.

This intermediate can also be prepared by the following method:

[00335] According to procedure for the synthesis of Example A211A, by using (E)-2,6-difluoro-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzaldehyde (1.10 g, 3.74 mmol), sodium triacetoxyborohydride (1.19 g, 5.61 mmol) and diethylamine (0.58 mL, 5.61 mmol) to give the title compound as a cream color solid (0.54 g, 41%).

C. (1R,2S)-2-(3-(4-((diethylamino)methyl)-3,5-difluorostyryl)-1H-indazol-6-yl)spiro [cyclopropane-1,3'-indolin]-2'-one 2,2,2-trifluoroacetate

[00336] The title compound was synthesized according to the method of Example A51B, by using (1R,2S)-2-(3-iodo-1H-indazol-6-yl-)-spiro[cyclopropane-1,3'-indolin]-2'-one (125 mg, 0.311 mmol) and (E)-N-(2,6-difluoro-(4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzyl)-N-ethylethanamine (131.4 mg, 0.373 mmol). Purification by preparative HPLC gave the title compound as a cream solid (54 mg, 28.4%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 16.4 Hz, 1H), 7.55-7.45 (m, 4H), 7.04 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H), 6.55 (t, J = 7.6 Hz, 1H), 5.96 (d, J = 7.6 Hz, 1H), 4.46 (s, 2H), 3.35-3.28 (m, 5H), 2.24-2.21 (m,1H), 2.19-2.15 (m, 1H), 1.42 (t, J = 6.8 Hz, 6H); MS ESI 499.4 $[M + H]^+$, calcd for $[C_{30}H_{28}F_2NO_4 + H]^+$ 499.23.

Optical Rotation: $[\alpha]^{22}_D$ = -126° (c 0.46, Methanol).

Example B: PLK4 Inhibition Assay

[00337] 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 gluthione sepharose. The dephosphorylated GST-PLK4 was stored in aliquots at -80°C until use.

[00338] PLK4 activity was measured using an indirect ELISA detection system. Dephosphorylated GST-PLK4 (4 nM) was incubated in the presence of 15 μM ATP (Sigma cat# A7699), 50 mM HEPES-Na^{2+} pH 7.4, 10 mM $MgCl_2$, 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).

[00339] Compound inhibition was determined at either a fixed concentration (10 μM) or at a variable inhibitor concentration (typically 50 μM to 0.1 μM 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 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.

[00340] **Examples C-E Omitted:**

Example F: Aurora A Inhibition Assay

[00341] Aurora A inhibition was determined using the Z-Lyte assay kit from Invitrogen. The assay was performed using the recommended manufacturer's instructions with 20 μM ATP and 12 nM Aurora A (Invitrogen cat # PV3612). The % inhibition values were determined according to the manufacturer's directions and IC_{50} values were obtained using a non-linear 4 point logistic curve fit (XLfit4, IDBS)

Example G: Aurora B Inhibition Assay

[00342] Aurora B inhibition was determined using the Z-Lyte assay kit from Invitrogen. The assay was performed using the recommended manufacturer's instructions with 128 μM ATP and 28 nM Aurora B (Invitrogen cat # PV3970). The % inhibition values were determined according to the manufacturer's directions and IC_{50} values were obtained using a non-linear 4 point logistic curve fit (XLfit4, IDBS)

[00343] In Table 1 , IC_{50} values for PLK4,Aurora A and Aurora B Kinases are indicated as "A," "B," and "C," for those less than or equal to 0.1 μM; those greater than 0.1 μM and less than or equal to 1 μM; and those greater than 1 μM, respectively. The relative inhibition percentages at a dose of 1 μM are indicated as "X" and "Y" for those equal to or greater than 50% inhibition and those less than 50% inhibition, respectively. As shown in Table 1, numerous compounds of the invention are effective PLK4 inhibitors. With respect to PLK1, PLK2 and PLK3, Examples A22 amd A23 did not show greater than 50% inhibition at 10 μM. In addition, a number of compounds of the invention also inhibit Aurora kinases, in particular Aurora B kinase.

Table 1: Inhibition Data of PLK4, Aurora A and Aurora B Kinases

Compound #	**IC50 Ranges**		
	PLK4	**Aurora A**	**Aurora B**
Example A1	C	--	--
Example A2	C	Y	C
Example A3	C	--	--
Example A4	B	--	--
Example A5	C	--	--
Example A6	A	Y	B
Example A7	A	Y	B
Example A8	C	--	--

Compound #	IC50 Ranges		
	PLK4	Aurora A	Aurora B
Example A9	B	Y	B
Example A10	B	Y	B
Example A11	C	Y	C
Example A23	A	A	A
Example A24	A	X	A
Example A25	B	X	B
Example A26	A	X	A
Example A34	A	X	A
Example A35	A	B	A
Example A36	A	X	A
Example A40	B	Y	B
Example A41	A	X	A
Example A42	A	X	A
Example A51	A	A	A
Example A54	A	X	B
Example A55	A	X	A
Example A56	A	A	A
Example A57	A	X	B
Example A58	A	X	A
Example A59	A	X	A
Example A60	A	X	B
Example A61	A	X	A
Example A64	A	X	A
Example A65	A	X	A
Example A66	A	X	A
Example A70	A	Y	A
Example A71	A	Y	A
Example A72	A	X	A
Example A73	A	X	A
Example A74	A	X	A
Example A75	A	X	A
Example A76	A	Y	A
Example A78	A	X	A

Compound #	IC50 Ranges		
	PLK4	Aurora A	Aurora B
Example A79	A	X	A
Example A80	A	X	B
Example A81	A	X	A
Example A82	A	X	A
Example A83	A	X	A
Example A84	A	X	B
Example A87	A	X	A
Example A89	A	X	A
Example A90	A	X	A
Example A91	A	X	A
Example A92	A	X	A
Example A94	A	X	A
Example A95	A	X	A
Example A102	A	X	A
Example A106	A	X	A
Example A109	A	X	A
Example A112	A	X	A
Example A113	A	X	--
Example A115	A	Y	--
Example A116	A	X	A
Example A131	A	X	A
Example A132	A	B	A
Example A133	A	X	A
Example A134	A	B	A
Example A135	A	X	A
Example A146	A	Y	A
Example A147	A	X	B
Example A151	A	A	A
Example A152	A	X	B
Example A160	A	X	A
Example A162	A	X	A
Example A164	A	X	A
Example A165	A	X	A

Compound #	IC50 Ranges		
	PLK4	Aurora A	Aurora B
Example A167	A	X	A
Example A169	A	X	A
Example A174	A	X	A
Example A175	A	Y	A
Example A177	A	X	A
Example A178	A	A	A
Example A179	A	A	A
Example A180	A	A	A
Example A182	A	X	A
Example A185	A	X	A
Example A186	A	X	A
Example A187	A	X	A
Example A188	A	X	A
Example A189	A	X	A
Example A190	A	X	A
Example A194	A	X	A
Example A195	A	X	--
Example A196	A	X	A
Example A198	A	X	A
Example A199	A	X	A
Example A200	A	X	A
Example A201	A	X	A
Example A203	A	X	A
Example A204	A	X	A
Example A205	A	X	A
Example A206	A	X	A
Example A208	A	X	A
Example A211	A	X	A
Example A212	A	X	A
Example A215	A	A	A
Example A216	A	X	A
Example A217	A	X	A
Example A218	A	X	A

Compound #	IC50 Ranges		
	PLK4	Aurora A	Aurora B
Example A219	A	X	A
Example A220	A	X	A
Example A221	A	X	A

Example H: FLT3 Inhibition Assay

[00344] The enzymatic activity of FLT3 was determined using the Z-Lyte assay kit from Invitrogen (Invitrogen cat # PV3191). The assay was performed using the recommended manufacturer's instructions with 117.5 μM ATP and 1 nM FLT3 (Invitrogen cat # PV3182). The % inhibition values were determined according to the manufacturer's directions and IC_{50} values were obtained using a non-linear 4 point logistic curve fit (XLfit4, IDBS). In Table 2, IC_{50} values for FLT3 inhibiton are indicated as "A," "B," and "C," for those less than or equal to 0.1 μM; those greater than 0.1 μM and less than or equal to 1 μM; and those greater than 1 μM, respectively, for selected compounds of the invention.

Table 2. Inhibition Data of Flt3

Compound #	IC_{50} Ranges	Compound #	IC_{50} Ranges
Example A24	A	Example A131	C
Example A42	A	Example A132	A
Example A56	A	Example A134	A
Example A58	A	Example A175	A
Example A71	B	Example A185	B
Example A112	B	Example A217	A

Example I: Kinase Selectivity Assays

[00345] The inhibitory activity of selected compounds of the invention was evaluated against a panel of 45 different kinase enzymes by CEREP, France. The assays were performed using standard HTRF assay methods as documented by CEREP against the human orthologues of Abl kinase, Akt1/PKBa, AMPKa, BMX kinase (Etk), Brk, CaMK2a, CaMK4, CDC2/CDK1 (cycB), CHK1, CHK2, c-Met kinase, CSK, EphB4 kinase, ERK1, ERK2 (P42mapk), FGFR2 kinase, FGFR4 kinase, FLT-1 kinase (VEGFR1), FLT-3 kinase, Fyn kinase, IGF1R kinase, IRK (InsR), JNK 2, KDR kinase (VEGFR2), Lck kinase, Lyn

kinase, MAPKAPK2, MEK1/MAP2K1, p38a kinase, p38d kinase, p38g kinase, PDGFRb kinase, PDK1, PKA, PKCa, PKCb1, PKCb2, PKCg, Ret kinase, ROCK2, RSK2, Src kinase, Syk, and TRKA (Table 3). The % Inhibition was determined by the formula; % Inhibition = 100 x (1 – (experimental value – background value)/(high activity control – background value)).

Table 3: Percent Inhibition Values For Examples A2 and A26 at 10 μM Concentration

Kinase	Example A2 % Inhibition @ 10 uM	Example A26 % Inhibition @ 10 uM
Abl	3	100
Akt1/PKBalpha	-2	-4
AMPKalpha	57	69
BMX (Etk)	-3	39
Brk	1	53
CaMK2alpha	41	9
CaMK4	7	-4
CDC2/CDK1	57	60
CHK1	-4	43
CHK2	-10	-3
c-Met	15	61
CSK	9	75
EphB4	11	65
ERK1	4	1
ERK (P42mapk)	9	2
FGFR4	0	-12
FLT-1 (VEGFR1)	1	30
FLT-3	62	102
Fyn	7	55
IGF1R	20	0
IRK (InsR)	4	5
JNK 2	-2	5
KDR (VEGFR2)	14	58
Lck	17	100
Lyn	26	86

Kinase	Example A2 % Inhibition @ 10 uM	Example A26 % Inhibition @ 10 uM
MAPKAPK2	-4	2
MEK1/MAP2K1	4	-2
p38alpha	6	-22
p38delta	-10	5
p38gamma	4	-5
PDGFRbeta	4	59
PDK1	4	2
PKA	0	-7
PKCalpha	-2	6
PKCbeta 1	1	-2
PKCbeta 2	4	26
PKCgamma	7	10
Ret	14	86
ROCK2	39	32
RSK2	17	22
Src	-10	51
Syk	--	--
TRKA	54	101

[00346] Table 3 above shows the percent inhibition values obtained for Examples A2 and A24 at 10 μM concentration. From this inhibition data it is apparent that certain kinases, e.g. Abl, CSK, FLT-3, Lck, Lyn, Ret and TRKA kinase are inhibited by compounds of the invention. These activities may impart additional therapeutic benefit to these compounds.

[00347] The inhibitory activity of selected compounds of the invention was evaluated against a panel of 284 different 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)).

Table 4: Percent Inhibition Values for Example A42 at 0.1 μM Concentration

Kinase	% Inhibition @ 0.1 μM
Abl	77

Kinase	% Inhibition @ 0.1 μM
Abl(m)	92
Abl (H396P)	93
Abl (M351T)	91
Abl (Q252H)	83
Abl(T315I)	98
Abl(Y253F)	75
ALK	64
Arg	89
Arg(m)	90
ARK5	86
Aurora-A	100
Aurora-B	101
Bmx	92
EphA1	61
EphB1	54
FGFR1	96
FGFR1(V561M)	91
FGFR2	88
FGFR2(N549H)	87
FGFR3	90
Flt3	54
GCK	80
IRAK1	52
Itk	82
Lck	77
Lck activated	90
MuSK	90
Ret (V804L)	60
Ron	62
Ros	93
Tie2	98
Tie2(R849W)	83

Kinase	% Inhibition @ 0.1 μM
Tie2(Y897S)	92
TrkA	100
TrkB	101

[00348] Table 4 above shows the percent inhibition values obtained for Example A42 at 0.1 μM concentration. From the panel of 284 kinases, only examples which showed greater than 50% inhibition at 0.1 μM are reported in Table 4. From this inhibition data it is apparent that certain kinases, e.g. Abl, Arg, AurA, AurB, FGFR3, TrkA and TRKB kinase are inhibited by compounds of the invention. These activities may impart additional therapeutic benefit to these compounds.

Example J: Cancer Cell Line Data of Compounds of the Invention

[00349] Breast cancer cells (MCF-7, MDA-MB-468, HCC1954), colon cancer cells (SW620) and lung cancer cells (A549), together with human mammary epithelial primary cells (HMEC), were seeded (1000 to 4000 per 80 μl per well depending on the cell growth rate) into 96 well plates, 24 hours before compound overlay. Compounds were prepared as 10mM 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 μM. Aliquots (20 μl) from each concentration were overlaid to 80 μl of the pre-seeded cells in the 96 well plates to make final concentrations of 10 nM to 50 μM. The cells were cultured for 5 days before the Sulforhodamine B assay (SRB) was performed to determine the compound's cell growth inhibition activity.

[00350] 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 μl ice cold 10% Trichloroacetic Acid (TCA) per well and incubate at 4°C for 30-60 min, The plates are washed with water five times and allowed to air dry for 5 min. Addition of 50 μl 0.4%(w/v) SRB solution in 1% (v/v) acetic acid to each well and incubatation 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 µl of 10 mM Tris pH 10.5 per well. Absorbance is read at 570 nm.

[00351] 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.

[00352] In Table 5 below, GI_{50} value ranges for several compound examples against a luminal breast cancer cell line (MCF-7), two basal breast cancer cell line (MDA-MB-468, HCC1954), a lung cancer cell line (A549), a colon cancer cell line (SW-620) and primary breast cells (HMEC) are given. The example compounds demonstrated varying growth inhibition/cell killing activity against cancer cells of luminal breast cancer and basal breast cancer cell, lung cancer and colon cancer. In general, these compounds showed less or little activity against normal cells as exemplified by HMEC. The GI_{50} ranges are indicated as "A," "B," "C," and "D," for values less than or equal to 0.1 µM; those greater than 0.1 µM and less than or equal to 1 µM; those greater than 1 µM and less than or equal to 10 µM; and those greater than 10 µM, respectively.

Table 5: Cell Growth Inhibition Data

Example	**Cell Line GI_{50} Range**					
#	MCF-7	MDA-MB-468	A-549	SW-620	HCC-1954	HMEC
A2	D	D	D	D	D	--
A4	C	C	D	C	C	--
A6	B	B	B	B	B	--
A7	B	B	B	B	B	--
A23	A	A	A	A	C	D
A24	B	A	A	A		D
A25	C	B	B	C	D	--
A26	B	B	B	B	C	--
A34	--	--	--	B	C	--
A35	A	A	A	A	C	D
A41	A	A	A	C	C	--

A42	A	A	A	A	B	D
A51	A	A	A	A	A	--
A55	B	A	A	B	C	--
A56	B	A	A	A	B	D
A57	B	B	B	B	C	--
A58	D	A	A	A	C	D
A59	--	A	A	A	C	D
A60	A	A	A	B		--
A60	B	A	A	A	A	C
A61	C	A	A	A	C	--
A64	A	A	A	A	B	-
A65	B	A	A	A	A	D
A65	A	A	A	A	B	
A70	C	B	B	C	C	-
A71	B	B	B	B	B	-
A72	B	A	A	A	C	--
A73	C	A	A	A	C	--
A74	C	A	A	A	C	-
A75	B	A	A	A	D	-
A76	B	B	B	C	C	-
A78	C	A	A	A	B	--
A79	B	A	A	A	C	--
A83	C	A	A	A	C	--
A87	A	A	A	B	C	--
A89	C	A	A	B	C	--
A90	A	A	A	A	B	--
A91	A	A	A	A	C	--
A92	A	A	A	A	B	D
A94	A	A	A	A	B	--
A95	C	A	A	A	C	--
A102	C	A	A	B	D	--
A106	D	A	A	A	A	C
A109	A	A	A	A	A	--
A112	A	A	A	A	C	--

A115	C	A	A	A	B	--
A116	A	A	A	B	B	--
A119	A	A	A	A	B	
A131	C	A	A	A	B	--
A132	B	A	A	A	C	D
A133	A	A	A	B	D	--
A134	A	A	A	A	B	D
A135	A	A	A	B	D	--
A146	C	A	A	A	C	--
A147	A	A	A	B	C	--
A151	B	B	A	B	C	D
A152	B	A	A	B	C	--
A160	C	A	A	A	A	D
A162	B	A	A	B	C	--
A165	C	A	A	A	C	--
A167	B	A	A	A	C	--
A169	A	A	A		C	--
A174	A	A	A	A	B	--
A175	B	A	A	A	B	C
A177	A	A	A	A	A	--
A178	A	A	A	A	B	--
A179	A	A	A	A	C	--
A180	B	A	A	A	B	--
A182	A	A	A	A	A	--
A185	A	A	A	B	A	--
A186	B	A	A	A	C	--
A187	A	A	A	A	B	--
A188	A	A	A	A	B	--
A189	A	A	A	A	A	C
A190	A	A	A	A	A	C
A194	A	A	A	B	D	D
A196	A	A	A	A	B	--
A198	A	A	A	B	A	--
A199	A	A	A	A	D	--

A200	D	A	A	A	C	--
A201	B	A	A	A	B	--
A203	A	A	A	A	C	--
A204	C	A	A	A	D	--
A205	B	A	A	A	B	--
A206	A	A	A	A	C	--
A208	B	A	A	A	B	--
A211	B	A	A	B	C	--
A212	A	A	A	A	C	--
A215	A	A	A	A	A	--
A216	B	A	A	A	C	--
A217	A	A	A	B	B	--
A218	A	A	A	B	A	--
A219	B	A	A	A	B	--
A220	B	A	A	A	D	--
A221	D	A	A	B	C	--

[00353] In addition to the cell lines tested as described above, selected compounds have been assayed against an extended panel. These include: breast cancer cell lines (T47 D, MDA-MB-231, HS578T, BT474, SKBR3, HCC1954), a lung cancer cell line (H358), brain cancer cell lines (A172, Hs683, SK-N-SH), Colon cancer cell lines (Colo 205, CT-15, HCT116+/-, HCT116+/+), ovarian cancer cell lines (OVCAR-3, SK-OV-3, SW 626), a melanoma cell line (518A2), a prostate cancer cell line (PC-3) and an immortalized breast cell line (184A1). The sulforhodamine B assay (SRB) described above was use to assay test compounds against the extended panel (Table 6). The GI_{50} ranges are indicated as "A," "B," "C," and "D," for values less than or equal to 0.1 μM; those greater than 0.1 μM and less than or equal to 1 μM; those greater than 1μM and less than or equal to 50 μM; and those greater than 50 μM, respectively.

Table 6: Cell Growth Inhibition Data

Example # / Cell line	**GI_{50} Range**
	A23
T47 D	A
MDA-MB-231	A

Example # / Cell line	GI_{50} Range
	A23
HS578T	A
BT474	C
SKBR3	C
H358	A
A172	A
Hs683	A
SK-N-SH	A
Colo 205	A
HCT-15	C
HCT116+/-	C
HCT116+/+	C
OVCAR-3	A
SK-OV-3	C
SW 626	C
518A2	A
PC-3	C
184A1	C

Example K: In vitro Angiogenesis Assay.

[00354] Certain compounds of the invention exhibited micromolar and submicromolar activity against Receptor Tyrosine Kinaseas (RTKs) such as FGFR2, VEGFR1, VEGFR2 and PDGFDbeta. Activity against these RTKs can result in antiangiogenic activity which is associated with slowed tumor growth and/or tumor regression. To measure the antiangiogenic effects of compounds of the invention, selected examples were tested in an angiogenesis assay as described below. Note that compound Example A23 showed anti-agiogenic effects at submicromolar concentrations (The **Figure**).

[00355] HUV-EC-C cells were obtained from the American Type Culture Collection (ATCC, CRL-1730), and were used at early passage for the assay. The *in vitro* Angiogenesis Assay Kit (Chemicon) was used according to the manufacturer's recommendation. An ice-cold mixture of ECMatrix was transferred into a precooled 96-

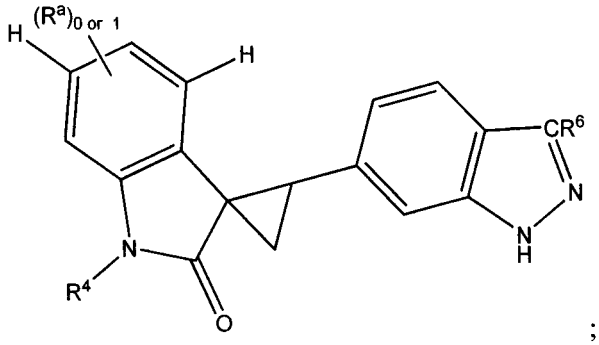
well plate. After the matrix solution had solidified (>1 hr incubation at 37 °C), 8,000 cells were mixed with the appropriate inhibitor concentration (in 100 microlitres EGM-2) and plated into each well. The clinical antiangiogenic, Sutent was used as a positive control in comparison to a compound of the invention, A13. After incubation at 37 °C for 4 hr, tube formation was inspected. Two methods, pattern recognition and branch point counting, were used to quantify the progression of angiogenesis and expressed as a percentage of the control tube count (The **Figure**).

[00356] While this invention has been particularly shown and described with reference to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof, wherein:

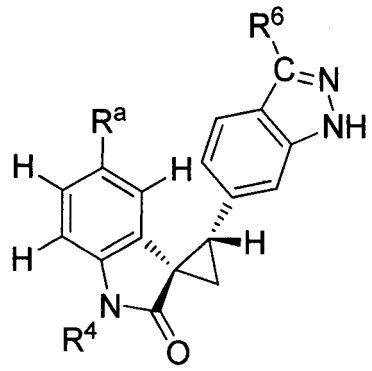
R^a is -F, methoxy, methyl or ethyl;

R_4 is –H, methyl, ethyl, 2-methoxyethyl or $-CH_2CONH_2$; and

R^6 is –C=C-(optionally substituted phenyl).

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

:



or a pharmaceutically acceptable salt thereof.

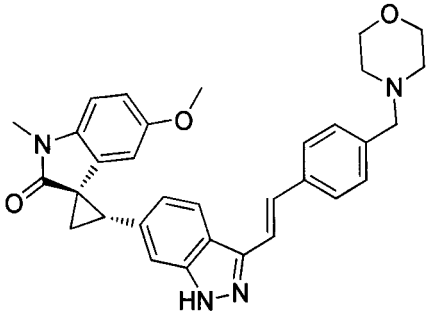
3. The compound of Claim 1 or 2 wherein:

wherein the phenyl in –CH=CH-(phenyl) is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} aminoalkyl), (C_{1-6} alkylamino)C_{1-6} alkyl, (C_{1-6} dialkylamino)C_{1-6} alkyl, (phenyl)C_{1-6} alkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, $-(CH_2)_{0-3}$-*N*-piperidinyl, $-(CH_2)_{0-3}$-*N*-morpholinyl, $-(CH_2)_{0-3}$-*N*-

pyrrolidinyl, -$(CH_2)_{0-3}$-*N*-piperazinyl and –$(CH_2)_{0-3}$-N-oxazepanyl, wherein the *N*-piperazinyl is optionally N'-substituted with C_{1-6} alkyl or C_{1-6} acyl; and

R^4 is –H or methyl.

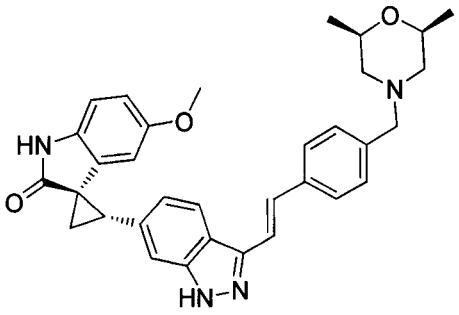
4. The compound of Claim 1, wherein the compound is represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof.

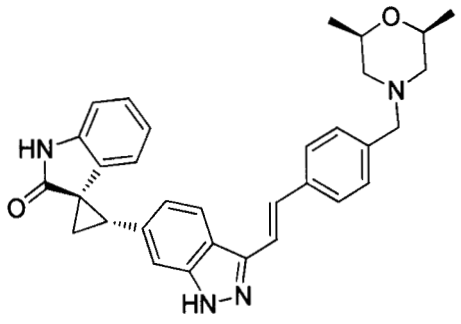
5. The compound of Claim 1, wherein the compound is represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof.

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



;

or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and a compound of any one of Claims 1-6 or a pharmaceutically acceptable salt thereof.

8. The pharmaceutical composition of Claim 7, further comprising an additional therapeutic agent.

9. The pharmaceutical composition of Claim 8, wherein the additional therapeutic agent is an anti-cancer drug.

10. A method of treating a subject with cancer, comprising administering an effective amount of a compound of any one of Claims 1-6 or a pharmaceutically acceptable salt thereof.

11. The method of Claim 10 wherein the cancer is selected from the group consisting of 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.

12. The method of Claim 11, wherein the cancer is selected from the group consisting of lung cancer, breast cancer or colon cancer.

13. The method of Claim 12, wherein the cancer is breast cancer.

14. The method of Claim 13, wherein the cancer is basal sub-type breast cancer or a luminal B sub-type breast cancer

15. The method of Claim 14, wherein the cancer is a basal sub-type breast cancer that overexpresses PLK4.
16. The method of Claim 13, wherein the cancer is basal sub-type breast cancer that is ER, HER2 and PR negative breast cancer.

17. The method of Claim 10, wherein the cancer is a soft tissue cancer.

18. The method of Claim 17, wherein 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.
19. The method of claim 10 wherin the cancer is an HPV associated cancer.
20. The method of claim 19 wherein the HPV associated neoplasm is cervical cancer, anogenital cancers, head and neck cancer and oropharyngeal cancer.
21. The method of any one of Claims 10-18, further comprising co-administering an additional therapeutic agent.
22. A use of an effective amount of a compound of any one of Claims 1-6 or a pharmaceutically acceptable salt thereof for treating a subject with cancer.
23. A use of an effective amount of a compound of any one of Claims 1-6 or a pharmaceutically acceptable salt thereof for the preparations of a medicament for treating a subject with cancer.