METHODS FOR PREPARING INDAZOLE COMPOUNDS

Field of the Invention

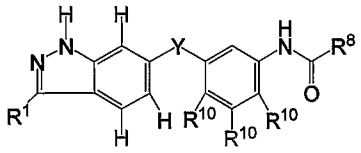
The present invention relates to methods for preparing indazole compounds, and intermediates thereof, which are useful as modulators and/or inhibitors of protein kinases.

Background of the Invention

The discussion of the background to the invention herein is included to explain the context of the invention. This is not to be taken as an admission that any of the material referred to was published, known or part of the common general knowledge in any country as of the priority date of any of the claims.

U.S. Patent Nos. 6,531,491 and 6,534,524 which are incorporated herein by reference in their entirety, are directed to indazole compounds that modulate and/or inhibit the activity of certain protein kinases such as VEGF-R (vascular endothelial cell growth factor receptor), FGF-R (fibroblast growth factor receptor), CDK (cyclin-dependent kinase) complexes, CHK1, LCK (also known as lymphocyte-specific tyrosine kinase), TEK (also known as Tie-2), FAK (focal adhesion kinase), and/or phosphorylase kinase. Such compounds are useful for the treatment of cancer and other diseases associated with angiogenesis or cellular proliferation mediated by protein kinases.

One group of indazole compounds discussed in the above-referenced U.S. Patents is represented by the formula shown below:



wherein:

R^1 is a substituted or unsubstituted aryl or heteroaryl, or a group of the formula $CH=CHR^3$ or $CH=NR^3$, where R^3 is a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Y is O, S, $C=CH_2$, C=O, S=O, SO_2, CH_2, $CHCH_3$, -NH-, or -N(C_1-C_8 alkyl);

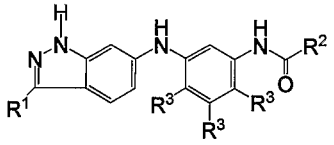
R^8 is a substituted or unsubstituted alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyl, or aryloxyl;

R^{10} is independently selected from hydrogen, halogen, and lower-alkyl; and pharmaceutically acceptable prodrugs, pharmaceutically acceptable metabolites, and pharmaceutically acceptable salts thereof.

Although methods for preparing such compounds were previously referred to, there remains a need in the art for new synthetic routes that are efficient and cost effective.

Summary of the Invention

The present invention relates to methods for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is a group of the formula -CH=CHR^4 or –CH=NR^4, and R^1 is substituted with 0 to 4 R^5 groups;

R^2 is (C_1 to C_{12}) alkyl, (C_2 to C_{12}) alkenyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, (5 to 12-membered) heteroaryl, (C_1 to C_{12}) alkoxy, (C_6 to C_{12}) aryloxy, and R^2 is substituted with 0 to 4 R^5 groups;

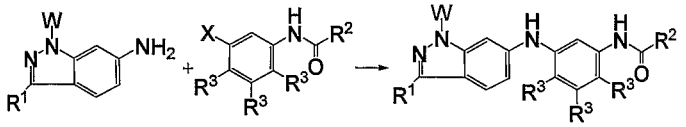
each R^3 is independently hydrogen, halogen, or (C_1 to C_8) alkyl, and the (C_1 to C_8) alkyl is substituted with 0 to 4 R^5 groups;

R^4 is (C_1 to C_{12}) alkyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, or (5 to 12-membered) heteroaryl, and R^4 is substituted with 0 to 4 R^5 groups;

each R^5 is independently halogen, (C_1 to C_8) alkyl, (C_2 to C_8) alkenyl, (C_2 to C_8) alkynyl,

-OH, -NO_2, -CN, -CO_2H, -O(C_1 to C_8 alkyl), (C_6 to C_{12}) aryl, (C_6 to C_{12}) aryl (C_1 to C_8) alkyl, -CO_2CH_3, -$CONH_2$, -OCH_2CONH_2, -NH_2, -SO_2NH_2, halo substituted (C_1 to C_{12}) alkyl, or –O(halo substituted (C_1 to C_{12}) alkyl); comprising:

a) reacting a compound of formula II with a compound of formula III to provide a compound of formula IV:



II III IV

wherein the reaction occurs in the presence of a catalyst and a base; W is a protecting group; X is an activated substituent group; R^1, R^2, R^3, R^4, and R^5 are as described above; and

b) deprotecting the compound of formula IV to provide the compound of formula I.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the catalyst is a palladium catalyst.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the catalyst is $Pd_2(dba)_3$ and the reaction further comprises a ligand that complexes with the $Pd_2(dba)_3$ catalyst.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the ligand is a phosphene ligand.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the ligand is 2-(di-*t*-butylphosphino)biphenyl.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the base is potassium carbonate, sodium carbonate, cesium carbonate, sodium *t*-butoxide, potassium *t*-butoxide, triethylamine, or mixtures thereof.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the base is sodium *t*-butoxide.

In another aspect, the invention relates to methods for preparing a compound of formula I, further comprising a solvent in the reaction between the compound of formula II and the compound of formula III.

In another aspect, the invention relates to methods for preparing a compound of formula I, further comprising a solvent.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the reaction is carried out at about 100°C.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein W is a tetrahydropyran protecting group or is a trimethylsilylethoxymethyl protecting group.

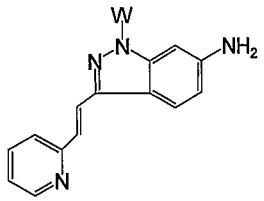
In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the activated substituent group X is chloride, bromide, or iodide.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the activated substituent group X is bromide.

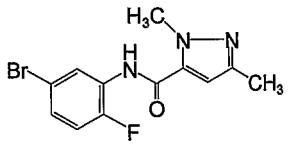
In another aspect, the invention relates to methods for preparing a compound of formula I, wherein W is a tetrahydropyran protecting group and the process of deprotecting comprises reacting the compound of formula IV with an acid in an alcoholic solvent.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the acid is methanesulfonic acid, and the alcoholic solvent is methanol, ethanol, n-propanol or isopropanol.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the compound of formula II has formula V, and the compound of formula III has formula VI:

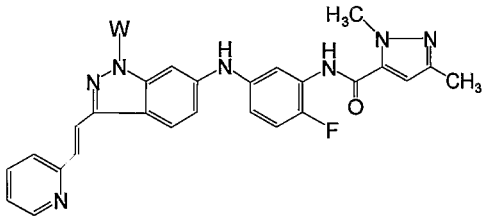


V



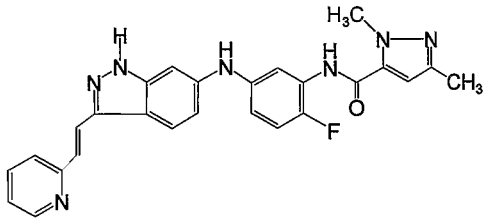
VI

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the compound of formula IV has formula VII:



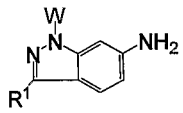
VII

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the compound of formula I has formula VIII:



VIII

In another aspect, the invention relates to methods for preparing a compound of formula II:



II

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is a group of the formula -CH=CHR^4 or –CH=NR^4, and R^1 is substituted with 0 to 4 R^5 groups;

R^4 is (C_1 to C_{12}) alkyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, or (5 to 12-membered) heteroaryl, and R^4 is substituted with 0 to 4 R^5 groups;

each R^5 is independently halogen, (C_1 to C_8) alkyl, (C_2 to C_8) alkenyl, (C_2 to C_8) alkynyl,

-OH, -NO_2, -CN, -CO_2H, -O(C_1 to C_8 alkyl), (C_6 to C_{12}) aryl, {(C_6 to C_{12}) aryl (C_1 to C_8) alkyl, -CO_2CH_3, -$CONH_2$, -OCH_2CONH_2, -NH_2, -SO_2NH_2, halo substituted (C_1 to C_{12}) alkyl, or –O(halo substituted (C_1 to C_{12}) alkyl);

W is a protecting group;

comprising:

a) protecting 6-nitro indazole with a nitrogen protecting group W;

b) functionalizing the C-3 position of the indazole ring with an R^1 group; and

c) reducing the 6-nitro group to a 6-amino group.

In another aspect, the invention relates to methods for preparing a compound of formula II, wherein the protecting group W is a tetrahydropyran protecting group or is a trimethylsilylethoxymethyl protecting group.

In another aspect, the invention relates to methods for preparing a compound of formula II, wherein the C-3 position of the indazole ring is functionalized by:

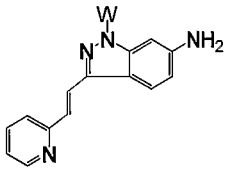
a) iodination with a metal halide to provide a N-1 protected (W) 3-iodo-6-nitro-indazole compound, and

b) coupling the N-1protected (W) 3-iodo-6-nitro-indazole compound with R^1 by a palladium catalyzed reaction.

In another aspect, the invention relates to methods for preparing a compound of formula II, wherein the metal halide is potassium iodide, and the palladium catalyzed reaction is a Heck reaction.

In another aspect, the invention relates to methods for preparing a compound of formula II, wherein R^1 is 2-vinyl pyridine.

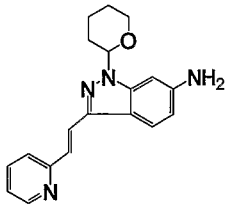
In another aspect, the invention relates to methods for preparing a compound of formula II, wherein the compound of formula II has formula IX:



IX

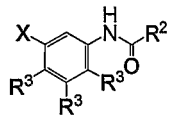
wherein W is a tetrahydropyran protecting group or is a trimethylsilylethoxymethyl protecting group.

In another aspect, the invention relates to methods for preparing a compound of formula II, wherein the compound of formula II has formula X:



X

In another aspect, the invention relates to methods for preparing a compound of formula III:



III

wherein:

R^2 is (C_1 to C_{12}) alkyl, (C_2 to C_{12}) alkenyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, (5 to 12-membered) heteroaryl, (C_1 to C_{12}) alkoxy, (C_6 to C_{12}) aryloxy, and R^2 is substituted with 0 to 4 R^5 groups;

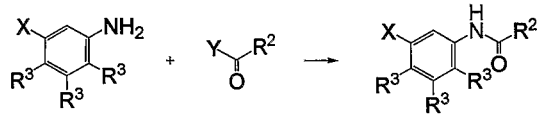
each R^3 is independently hydrogen, halogen, or (C_1 to C_8) alkyl, and the (C_1 to C_8) alkyl is substituted with 0 to 4 R^5 groups;

each R^5 is independently halogen, (C_1 to C_8) alkyl, (C_2 to C_8) alkenyl, (C_2 to C_8) alkynyl,

-OH, $-NO_2$, -CN, $-CO_2H$, -O(C_1 to C_8 alkyl), (C_6 to C_{12}) aryl, (C_6 to C_{12}) aryl (C_1 to C_8) alkyl, $-CO_2CH_3$, $-CONH_2$, $-OCH_2CONH_2$, $-NH_2$, $-SO_2NH_2$, halo substituted (C_1 to C_{12}) alkyl, or –O(halo substituted (C_1 to C_{12}) alkyl); and

X is an activated substituent group;

comprising, reacting a compound of formula XI with a compound of formula XII:

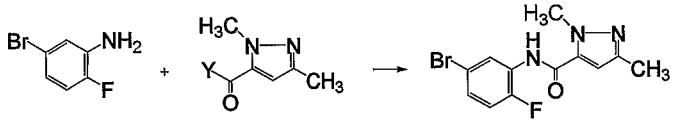


XI XII III

wherein Y is a leaving group, and X, R^2, and R^3 are as described above.

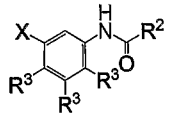
In another aspect, the invention relates to methods for preparing a compound of formula III, wherein the leaving group Y is chloride.

In another aspect, the invention relates to methods for preparing a compound of formula III, wherein the compound of formula XI has formula XIII, the compound of formula XII has formula XIV, and the compound of formula III has formula XV:



XIII XIV XV

In another aspect, the invention relates to methods for preparing a compound of formula III:



III

or pharmaceutically acceptable salt or solvate thereof, wherein:

R^2 is (C_1 to C_{12}) alkyl, (C_2 to C_{12}) alkenyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, (5 to 12-membered) heteroaryl, (C_1 to C_{12}) alkoxy, (C_6 to C_{12}) aryloxy, and R^2 is substituted with 0 to 4 R^5 groups;

each R^3 is independently hydrogen, halogen, or (C_1 to C_8) alkyl, and the (C_1 to C_8) alkyl is substituted with 0 to 4 R^5 groups;

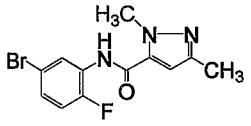
each R^5 is independently halogen, (C_1 to C_8) alkyl, (C_2 to C_8) alkenyl, (C_2 to C_8) alkynyl,

-OH, $-NO_2$, -CN, $-CO_2H$, -O(C_1 to C_8 alkyl), (C_6 to C_{12}) aryl, (C_6 to C_{12}) aryl (C_1 to C_8) alkyl,

$-CO_2CH_3$, $-CONH_2$, $-OCH_2CONH_2$, $-NH_2$, $-SO_2NH_2$, halo substituted (C_1 to C_{12}) alkyl, or –O(halo substituted (C_1 to C_{12}) alkyl); and

X is an activated substituent group.

In another aspect, the invention relates to methods for preparing a compound of formula III, wherein the compound of formula III has formula XV:



XV

or a pharmaceutically acceptable salt or solvate thereof.

In accordance with a convention used in the art,  is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure. When the phrase, "optionally substituted with one or more substituents" is used herein, it is meant to indicate that the group in question may optionally be substituted by one or more of the substituents provided. The number of substituents a group in the compounds of the invention may have depends on the number of positions available for substitution. An aryl ring in the compounds of the invention may contain from 1 to 5 additional substituents, depending on the degree of substitution present on the ring. The maximum number of substituents that a group in the compounds of the invention may have can be easily determined.

The terms "react", "reacted" and "reacting," as used herein, refers to a chemical process or processes in which two or more reactants are allowed to come into contact with each other to effect a chemical change or transformation. When reactant A and reactant B are allowed to come into contact with each other to afford a new chemical compound(s) C, A is said to have "reacted" with B to produce C.

The terms "protect," "protected," and "protecting" as used herein, refers to a process in which a functional group in a chemical compound is selectively masked by a non-reactive functional group in order to allow a selective reaction(s) to occur elsewhere on said chemical compound. Such non-reactive functional groups are herein termed "protecting groups." The term "nitrogen protecting group," as used herein refers to those groups that are capable of selectively masking the reactivity of a nitrogen (N) group. The term "suitable protecting group," as used herein refers to those protecting groups that are useful in the preparation of the compounds of the present invention. Such groups are generally able to be selectively introduced and removed using mild reaction conditions that do not interfere with other portions of the subject compounds. Protecting groups that are suitable for use in the processes and methods of the present invention are well known. The chemical properties of such protecting groups, methods for their introduction and their removal can be found in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons,

NY (1999), herein incorporated by reference in its entirety. The terms "deprotect," "deprotected," and "deprotecting," as used herein, are meant to refer to the process of removing a protecting group from a compound.

The term "leaving group," as used herein refers to a chemical functional group that generally allows a nucleophilic substitution reaction to take place at the atom to which it is attached. In acid chlorides of the formula Cl-C(O)R, wherein R is alkyl, aryl, or heterocyclic, the –Cl group is generally referred to as a leaving group because it allows nucleophilic substitution reactions to take place at the carbonyl carbon. Suitable leaving groups are well known, for example, halides, aromatic heterocycles, cyano, amino groups (generally under acidic conditions), ammonium groups, alkoxide groups, carbonate groups, formates, and hydroxy groups that have been activated by reaction with compounds such as carbodiimides. Suitable leaving groups include, but are not limited to, chloride, bromide, iodide, cyano, imidazole, and hydroxy groups that have been allowed to react with a carbodiimide such as dicyclohexylcarbodiimide (optionally in the presence of an additive such as hydroxybenzotriazole) or a carbodiimide derivative.

The term "activated substituent group," as used herein refers to a chemical functional group that generally allows a substitution reaction to take place at the atom to which it is attached. In aryl iodides, the –I group is generally referred to as an activated substituent group because it allows substitution reactions to take place at the aryl carbon. Suitable activated substituent groups are well known and can include halides (chloride, bromide, iodide), activated hydroxyl groups (e.g., triflate, mesylate, and tosylate), and diazonium salts.

As used herein, the term "alkyl" represents a straight- or branched-chain saturated hydrocarbon, containing 1 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. Exemplary alkyl substituents include, but are not limited to methyl (Me), ethyl (Et), propyl, isopropyl, butyl, isobutyl, t-butyl, and the like.

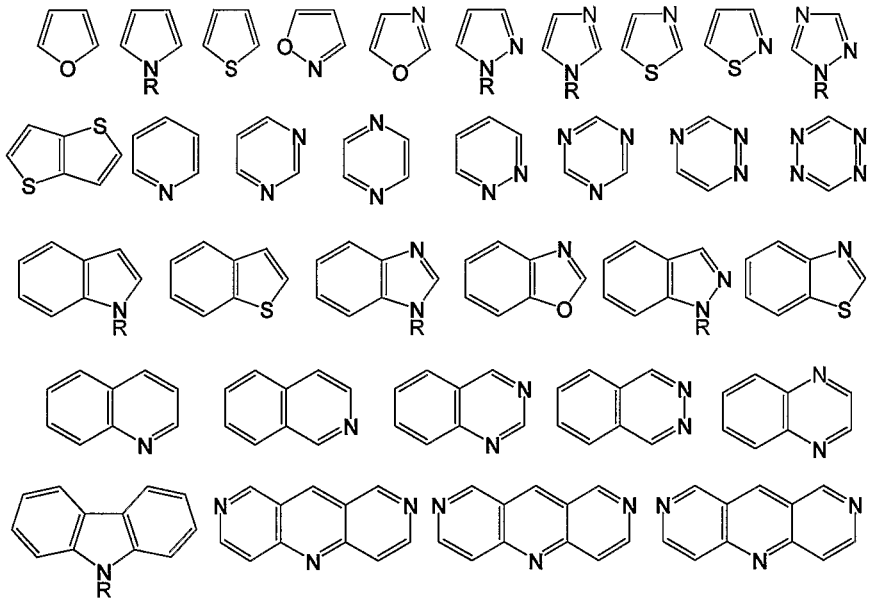
The term "alkenyl" represents a straight- or branched-chain hydrocarbon, containing one or more carbon-carbon double bonds and having 2 to 10 carbon atoms which may be unsubstituted or substituted by one or more of the substituents described below. Exemplary alkenyl substituents include, but are not limited to ethenyl, propenyl, butenyl, allyl, pentenyl and the like.

The term "phenyl," as used herein refers to a fully unsaturated 6-membered carbocyclic group. A "phenyl" group may also be referred to herein as a benzene derivative.

The term "heteroaryl," as used herein refers to a group comprising an aromatic monovalent monocyclic, bicyclic, or tricyclic group, containing 5 to 18 ring atoms, including 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents described below. As used herein, the term "heteroaryl" is also intended to encompass the N-oxide derivative (or N-oxide derivatives, if the heteroaryl group contains more than one nitrogen such that more than one N-oxide

derivative may be formed) of the nitrogen-containing heteroaryl groups described herein. Illustrative examples of heteroaryl groups include, but are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, benzo[b]thienyl, naphtho[2,3-b]thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathienyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxyalinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, and phenoxazinyl. Illustrative examples of N-oxide derivatives of heteroaryl groups include, but are not limited to, pyridyl N-oxide, pyrazinyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, triazinyl N-oxide, isoquinolyl N-oxide, and quinolyl N-oxide.

Further examples of heteroaryl groups include the following moieties:



wherein R is H, alkyl, hydroxyl or is a suitable nitrogen protecting group.

The terms “halide,” “halogen” and “halo” represent fluoro, chloro, bromo or iodo substituents.

The terms "comprising" and "including" are used in an open, non-limiting sense.

The term “polymorph” refers to a crystalline form of a compound with a distinct spatial lattice arrangement as compared to other crystalline forms of the same compound.

The term “amorphous” refers to a non-crystalline form of a compound.

"A pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a

pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, y-hydroxybutyrates, glycollates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If an inventive compound or an intermediate in the present invention is a base, a desired salt may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If an inventive compound or an intermediate in the present inventon is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine; ammonia; primary, secondary, and tertiary amines; and cyclic amines, such as piperidine, morpholine, and piperazine; as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

The compounds of the present invention may contain at least one chiral center and may exist as single stereoisomers (e.g., single enantiomers or single diastereomers), any mixture of stereoisomers (e.g., any mixture of enantiomers or diastereomers) or racemic mixtures thereof. It is specifically contemplated that, unless otherwise indicated, all stereoisomers, mixtures and racemates of the present compounds are encompassed within the scope of the present invention. Compounds identified herein as single stereoisomers are meant to describe compounds that are present in a form that contains at least from at least about 90% to at least about 99% of a single stereoisomer of each chiral center present in the compounds. Where the stereochemistry of the chiral carbons present in the chemical

structures illustrated herein are not specified, it is specifically contemplated that all possible stereoisomers are encompassed therein. The compounds of the present invention may be prepared and used in stereoisomerically pure form or substantially stereoisomerically pure form.

As used herein, the term "stereoisomeric" purity refers to the "enantiomeric" purity and/or "diastereomeric" purity of a compound. The term "stereoisomerically pure form," as used herein, is meant to encompass those compounds that contain from at least about 95% to at least about 99%, and all values in between, of a single stereoisomer.

The term "substantially enantiomerically pure," as used herein is meant to encompass those compounds that contain from at least about 90% to at least about 95%, and all values in between, of a single stereoisomer.

The term "diastereomerically pure," as used herein, is meant to encompass those compounds that contain from at least about 95% to at least about 99%, and all values in between, of a single diastereoisomer.

The term "substantially diastereomerically pure," as used herein, is meant to encompass those compounds that contain from at least about 90% to at least about 95%, and all values in between, of a single diastereoisomer.

The terms "racemic" or "racemic mixture," as used herein, refer to a mixture containing equal amounts of stereoisomeric compounds of opposite configuration. A racemic mixture of a compound containing one stereoisomeric center would comprise equal amount of that compound in which the stereoisomeric center is of the (S)- and ®-configurations.

The term "enantiomerically enriched," as used herein, is meant to refer to those compositions wherein one stereoisomer of a compound is present in a greater amount than the opposite stereoisomer.

Similarly, the term "diastereomerically enriched," as used herein, refers to those compositions wherein one diastereomer of compound is present in amount greater than the opposite diastereomer. The compounds of the present invention may be obtained in stereoisomerically pure (i.e., enantiomerically and/or diastereomerically pure) or substantially stereoisomerically pure (i.e., substantially enantiomerically and/or diastereomerically pure) form. Such compounds may be obtained synthetically, according to the procedures described herein using stereoisomerically pure or substantially stereoisomerically pure materials. Alternatively, these compounds may be obtained by resolution/separation of mixtures of stereoisomers, including racemic and diastereomeric mixtures, using well known procedures. Exemplary methods that may be useful for the resolution/separation of stereoisomeric mixtures include derivitation with stereochemically pure reagents to form diastereomeric mixtures, chromatographic separation of diastereomeric mixtures, chromatographic separation of enantiomeric mixtures using chiral stationary phases, enzymatic resolution of covalent derivatives, and crystallization/re-crystallization. Other useful methods may be found

in Enantiomers, Racemates, and Resolutions, J. Jacques, et al., 1981, John Wiley and Sons, New York, NY, the disclosure of which is incorporated herein by reference. Preferred stereoisomers of the compounds of this invention are described herein.

Brief Description of the Drawings

Having thus described the invention in general terms, reference will now be made to the accompanying drawings, wherein:

FIG. 1A is an X-ray powder diffraction diagram of polymorph Form I of the invention;

FIG. 1B is a Differential Scanning Calorimetry (DSC) thermogram of polymorph Form I of the invention;

FIG. 1C is a Raman spectral diagram of polymorph Form I of the invention;

FIG. 2A is an X-ray powder diffraction diagram of polymorph Form II of the invention;

FIG. 2B is a DSC thermogram of polymorph Form II of the invention;

FIG. 2C is a Raman spectral diagram of polymorph Form II of the invention;

FIG. 3A is an X-ray powder diffraction diagram of polymorph Form III of the invention;

FIG. 3B is a DSC thermogram of polymorph Form III of the invention;

FIG. 3C is a Raman spectral diagram of polymorph Form III of the invention;

FIG. 4A is an X-ray powder diffraction diagram of polymorph Form IV of the invention;

FIG. 4B is a DSC thermogram of polymorph Form IV of the invention;

FIG. 4C is a Raman spectral diagram of polymorph Form IV of the invention;

FIG. 5A is an X-ray powder diffraction diagram of polymorph Form V of the invention;

FIG. 5B is a DSC thermogram of polymorph Form V of the invention;

FIG. 5C is a Raman spectral diagram of polymorph Form V of the invention;

FIG. 6A is an X-ray powder diffraction diagram of polymorph Form Ia of the invention;

FIG. 6B is a DSC thermogram of polymorph Form Ia of the invention;

FIG. 7A is an X-ray powder diffraction diagram of polymorph Form Ib of the invention;

FIG. 7B is a DSC thermogram of polymorph Form Ib of the invention;

FIG. 7C is a Raman spectral diagram of polymorph Form Ib of the invention;

FIG. 8A is an X-ray powder diffraction diagram of polymorph Form IIa of the invention;

FIG. 8B is a DSC thermogram of polymorph Form IIa of the invention;

FIG. 9A is an X-ray powder diffraction diagram of polymorph Form IIb of the invention;

FIG. 9B is a DSC thermogram of polymorph Form IIb of the invention;

FIG. 9C is a Raman spectral diagram of polymorph Form IIb of the invention;

FIG. 10A is an X-ray powder diffraction diagram of polymorph Form IIIa of the invention;

FIG. 11A is an X-ray powder diffraction diagram of polymorph Form IIIb of the invention;

FIG. 11B is a DSC thermogram of polymorph Form IIIb of the invention;

FIG. 11C is a Raman spectral diagram of polymorph Form IIIb of the invention;

FIG. 12A is an X-ray powder diffraction diagram of polymorph Form IVa of the invention;

FIG. 12B is a DSC thermogram of polymorph Form IVa of the invention;

FIG. 13A is an X-ray powder diffraction diagram of polymorph Form Va of the invention;

FIG. 13B is a DSC thermogram of polymorph Form Va of the invention;

FIG. 13C is a Raman spectral diagram of polymorph Form Va of the invention;

FIG. 14A is an X-ray powder diffraction diagram of polymorph Form VI of the invention;

FIG. 14B is a DSC thermogram of polymorph Form VI of the invention;

FIG. 14C is a Raman spectral diagram of polymorph Form VI of the invention;

FIG. 15A is an X-ray powder diffraction diagram of an amorphous form of the invention;

FIG. 15B is a Raman spectral diagram of an amorphous form of the invention; and

FIG 16 is an X-ray powder diffraction diagram of polymorph Form Ibm-2 of the invention

Detailed Description of the Invention

The indazole compounds of formula I can be prepared from 6-nitroindazole. The indazole ring can be substituted at the C-3 position with an R^1 group as described herein, using known reagents and reactions. For example, the C-3 position of the indazole ring can be functionalized by reacting 6-nitroindazole with iodine (I_2) in the presence of a base such as potassium carbonate (K_2CO_3), and in a solvent such as DMF, to provide 3-iodo-6-nitro-indazole.



The C-3 position of the indazole ring can then be elaborated to a desired R^1 group using known reactions, such as a Suzuki reaction or a Heck reaction.

Before elaboration of the C-3 R^1 group, however, the intermediates useful for the preparation of the compounds of formula I may require the use of protecting groups. The indazole ring nitrogen (N-1) may require masking through use of a suitable protecting group. Furthermore, if the substituents on these intermediates are themselves not compatible with the synthetic methods of this invention, the substituents may be protected with suitable protecting groups that are stable to the reaction conditions used in these methods. The protecting groups may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the

methods for protecting and deprotecting different substituents using such suitable protecting groups are well known, examples of which may be found in T. Greene and P. Wuts, supra.

A suitable nitrogen protecting group, W, is one that is stable to the reaction conditions in which the compounds of formula II are allowed to react with the compounds of formula III to provide the compounds of formula IV. Furthermore, such a protecting group should be chosen so that it can be subsequently removed to provide the compounds of formula I.

As indicated above, suitable nitrogen protecting groups are well known and any nitrogen protecting group that is useful in the methods of preparing the compounds of this invention or may be useful in the protein kinase inhibitory compounds of this invention may be used. Exemplary nitrogen protecting groups include silyl, substituted silyl, alkyl ether, substituted alkyl ether, cycloalkyl ether, substituted cycloalkyl ether, alkyl, substituted alkyl, carbamate, urea, amide, imide, enamine, sulfenyl, sulfonyl, nitro, nitroso, oxide, phosphinyl, phosphoryl, silyl, organometallic, borinic acid and boronic acid groups. Examples of each of these groups, methods for protecting nitrogen moieties using these groups and methods for removing these groups from nitrogen moieties are disclosed in T. Greene and P. Wuts, supra.

Thus, suitable nitrogen protecting groups useful as W include, but are not limited to, silyl protecting groups (e.g., SEM: trimethylsilylethoxymethyl, TBDMS: *t*-butyldimethylsilyl); alkyl ether protecting groups such as cycloalkyl ethers (e.g., THP: tetrahydropyran); carbamate protecting groups such as alkyloxycarbonyl (e.g., Boc: t-butyloxycarbonyl), aryloxycarbonyl (e.g., Cbz: benzyloxycarbonyl, and FMOC: fluorene-9-methyloxycarbonyl), alkyloxycarbonyl (e.g., methyloxycarbonyl), alkylcarbonyl or arylcarbonyl, substituted alkyl, especially arylalkyl (e.g., trityl (triphenylmethyl), benzyl and substituted benzyl), and the like.

If W is a silyl protecting group (e.g., SEM: trimethylsilylethoxymethyl, TBDMS: *t*-butyldimethylsilyl), such groups may be applied and subsequently removed under known conditions. Such silyl protecting groups may be attached to nitrogen and moieties and hydroxyl groups via their silyl chlorides (e.g., SEMCl: trimethylsilylethoxymethyl chloride, TBDMSCl: *t*-butyldimethylsilyl chloride) in the presence of a suitable base (e.g., potassium carbonate), catalyst (e.g., 4-dimethylaminopyridine (DMAP)), and solvent (e.g, DMF or N,N-dimethylformamide). Such silyl protecting groups may be cleaved by exposure of the subject compound to a source of fluoride ions, such as the use of an organic fluoride salt such as a tetraalkylammonium fluoride salt, or an inorganic fluoride salt. Suitable fluoride ion sources include, but are not limited to, tetramethylammonium fluoride, tetraethylammonium fluoride, tetrapropylammonium fluoride, tetrabutylammonium fluoride, sodium fluoride, and potassium fluoride. Alternatively, such silane protecting groups may be cleaved under acidic conditions using organic or mineral acids, with or without the use of a buffering agent. Suitable acids include, but are not limited to, hydrofluoric acid, hydrochloric acid, sulfuric acid, nitric acid, acetic acid, citric acid, and methanesulfonic acid. Such silane protecting groups may also be cleaved using appropriate Lewis acids. Suitable Lewis acids include, but are not limited to,

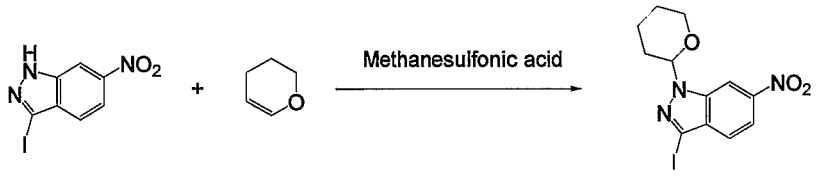
dimethylbromo borane, triphenylmethyl tetrafluoroborate, and certain Pd (II) salts. Such silane protecting groups can also be cleaved under basic conditions that employ appropriate organic or inorganic basic compounds. Such basic compounds include, but are not limited to, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, and potassium hydroxide. The cleavage of a silane protecting group may be conducted in an appropriate solvent that is compatible with the specific reaction conditions chosen and will not interfere with the desired transformation. Such suitable solvents include alkyl esters, alkylaryl esters, aryl esters, alkyl ethers, aryl ethers, alkylaryl esters, cyclic ethers, hydrocarbons, alcohols, halogenated solvents, alkyl nitriles, aryl nitriles, alkyl ketones, aryl ketones, alkylaryl ketones, or non-protic heterocyclic compounds. Suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, N,N-dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1, 4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Finally, such reactions may be performed at an appropriate temperature from –20 °C to 100 °C, depending on the specific reactants used. Further suitable reaction conditions may be found in T. Greene and P. Wuts, supra.

If W is a cyclic ether protecting group (e.g., a tetrahydropyran (THP) group), such groups may be applied and subsequently removed under known conditions. Such cyclic ethers may be attached to nitrogen moieties and hydroxyl groups via their enol ethers (e.g., dihydropyran (DHP)) in the presence of a suitable acid (e.g., para-toluenesulfonic acid or methanesulfonic acid), and solvent (e.g., methylene chloride). Such cyclic ether groups may be cleaved by treating the subject compound with organic or inorganic acids or Lewis acids. The choice of a particular reagent will depend upon the type of ether present as well as the other reaction conditions. The choice of a suitable reagent for cleaving such a cyclic ether are well known. Examples of suitable reagents include, but are not limited to, hydrochloric acid, sulfuric acid, nitric acid, para-toluenesulfonic acid, methanesulfonic acid, or Lewis acids such as boron trifluoride etherate.

These reactions may be conducted in solvents that are compatible with the specific reaction conditions chosen and will not interfere with the desired transformation. Among such suitable solvents include alkyl esters, alkylaryl esters, aryl esters, alkyl ethers, aryl ethers, alkylaryl esters, cyclic ethers, hydrocarbons, alcohols, halogenated solvents, alkyl nitriles, aryl nitriles, alkyl ketones, aryl ketones, alkylaryl ketones, or non-protic heterocyclic compounds. Suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl

acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, N,N-dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in this transformation if necessary. Finally, such reactions may be performed at an appropriate temperature from –20 °C to 100 °C, depending on the specific reactants used. Further suitable reaction conditions may be found in T. Greene and P. Wuts, supra.

Protection of the N-1 indazole ring nitrogen is accomplished by reacting 3-iodo-6-nitroindazole with 3,4-dihydro-2*H*-pyran and methanesulfonic acid in a solvent, such as DMF, tetrahydrofuran (THF), and methylene chloride (CH_2Cl_2) to provide 3-iodo-6-nitro-1-(tetrahydropyran-2-yl)-1H-indazole.



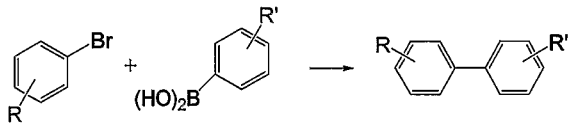
The various substituents contemplated for the compounds of formula I, and their intermediates, may require the use suitable protecting groups. The choice of a suitable nitrogen protecting group (described above), hydroxyl protecting group, carboxylic acid protecting group, amide protecting group, or sulfonamide protecting group, their application and their subsequent deprotection, are well known and are disclosed in T. Greene and P. Wuts, supra.

Suitable hydroxyl protecting groups that are useful in the present invention include, but are not limited to, alkyl or aryl esters, alkyl silanes, aryl silanes or alkylaryl silanes, alkyl or aryl carbonates, benzyl groups, substituted benzyl groups, ethers, or substituted ethers. The various hydroxyl protecting groups can be applied and suitably cleaved utilizing a number of known reaction conditions. The particular conditions used will depend on the particular protecting group as well as the other functional groups contained in the subject compound. Furthermore, suitable conditions include the use of an appropriate solvent that is compatible with the reaction conditions utilized and will not interfere with the desired transformation. Suitable solvents useful in applying the various protecting groups and their subsequent removal may include alkyl esters, alkylaryl esters, aryl esters, alkyl ethers, aryl ethers, alkylaryl esters, cyclic ethers, hydrocarbons, alcohols, halogenated solvents, alkyl nitriles, aryl nitriles, alkyl ketones, aryl ketones, alkylaryl ketones, and non-protic heterocyclic compounds. Suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl

acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, N,N-dimethyl formamide, dimethyl acetamide, propionitrile, butyronitrile, t-amyl alcohol, acetic acid, diethyl ether, methyl-t-butyl ether, diphenyl ether, methylphenyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, pentane, hexane, heptane, methanol, ethanol, 1-propanol, 2-propanol, t-butanol, n-butanol, 2-butanol, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, benzonitrile, acetone, 2-butanone, benzene, toluene, anisole, xylenes, and pyridine, or any mixture of the above solvents. Additionally, water may be used as a co-solvent in these transformations if necessary. Finally, such reactions may be performed at an appropriate temperature from –20 °C to 100 °C, depending on the specific reactants used. Further suitable reaction conditions may be found in T. Greene and P. Wuts, supra.

After functionalization of the C-3 position with Iodine, and protection of the indazole ring nitrogen (N-1) with a suitable nitrogen protecting group W, the C-3 position of the indazole ring can be elaborated to a desired R^1 group through a Suzuki or Heck reaction, using the appropriate catalyst, ligand, aryl, heteroaryl and/or olefinic species.

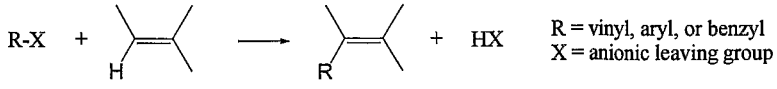
The Suzuki reaction is a palladium catalyzed coupling reaction in which the reaction of an optionally substituted aryl boronic acid or an optionally substituted heteroaryl boronic acid is coupled with a substituted aryl group or a substituted heteroaryl group, in which the substituents on the aryl group or the heteroaryl group are halide, triflate, or a diazonium salt, which produces a di-aryl species.



Useful palladium catalysts for the Suzuki reaction includes but are not limited to $Pd(C_{17}H_{14}O)_x$, $Pd(PPh_3)_4$, and $[Pd(OAc)_2]_3$, and the like. A base such as an inorganic base or an organic base (e.g., organic amine) is also required to neutralize the liberated acid. In general, Suzuki coupling reactions require milder conditions than Heck reactions.

When R^1 is a substituted or unsubstituted aryl group, or is a substituted or unsubstituted heteroaryl group, the compounds of formula I can be prepared by a Suzuki reaction between an optionally substituted aryl or heteroaryl boronic acid and a substituted aryl or heteroaryl group, in which the substituents on the aryl or heteroaryl group are halide, triflate, or a diazonium salt.

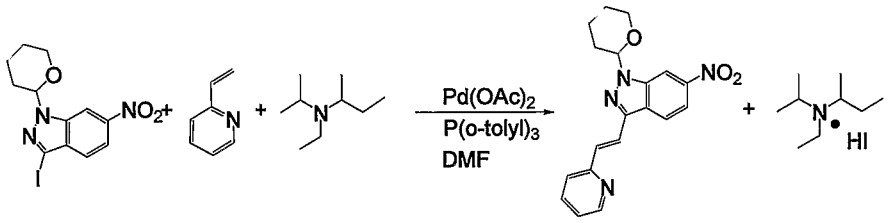
A Heck reaction involves the catalytic coupling of C-C bonds, where a vinylic hydrogen is replaced by a vinyl, aryl, or benzyl group, with the latter being introduced as a halide, diazonium salt, aryl triflate or hypervalent iodo compound.



Palladium in the form of Pd(II) salts or complexes and Pd(0), with 1-5% mole concentration, is the most widely used metal catalyst for these types of reactions. A base such as an inorganic base or an organic base (e.g., organic amine) is also required to neutralize the liberated acid. Typical catalysts for use in the Heck reaction include but are not limited to $Pd(dppf)Cl_2/CH_2Cl_2$, $[Pd(OAc)_2]_3$, trans-$PdCl_2(CH_3CN)_2$, $Pd(C_{17}H_{14}O)_x$, and Pd(0)-phosphine complexes such as $Pd(PPh_3)_4$ and trans-$PdCl_2(PPh_3)_2$ or in situ catalysts such as $Pd(OAc)_2/PPh_3$, and the like. Chelated phosphines with larger bite angles such as $Cp_2Fe(PPh_2)_2$ and $Ph_2P(CH_2)_{2\text{-}4}PPh_2$ are useful with catalysts such as $Pd(OAc)_2$, (pi-allyl)Pd complexes, $Pd_2(dba)_3$, $Pd(dba)_2$ and $PdCl_2$, and the like. The presence of phosphines "stabilize" these catalysts. Generally, these types of reactions are conducted in polar aprotic mediums (sigma donor type solvents such as acetonitrile, N,N-dimethyl formamide, dimethyl sulfoxide or dimethylacetamide). The reaction time and temperature depend on the nature of the organic halide to be activated. Iodo derivatives are more reactive and hence auxiliary ligands (phosphines) may not be required. In these cases polar solvents such as N,N-dimethyl formamide, dimethylacetamide and N-methylpyrrolidine in combination with sodium acetate as a base are especially beneficial.

When R^1 is a group of the formula $CH=CHR^4$ or $CH=NR^4$, wherein R^4 is as described herein, the compounds of formula I can be prepared by a Heck reaction between a compound containing a vinylic hydrogen and a compound containing a vinyl, aryl, or benzyl group which is substituted with a halide, halide, diazonium salt, aryl triflate or hypervalent iodo compound.

A Heck reaction between 3-iodo-6-nitro-1-(tetrahydropyran-2-yl)-1H-indazole and 2-vinyl pyridine is accomplished by heating these reactants in the presence of a catalyst such as palladium(II) acetate ($Pd(OAc)_2$), a ligand such as tri-o-tolylphosphine, a suitable base such as N,N-diisopropylethyl-amine, and a solvent such as DMF to provide 6-nitro-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole.

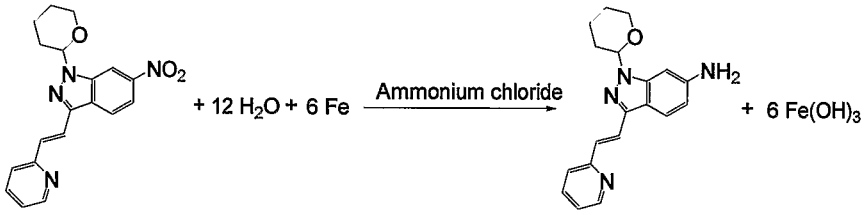


The compounds of formula I contain an indazole ring and phenyl ring that are bridged by an amino group. Such amino linked ring structures are obtained by coupling a 6-amino indazole (compound of formual II) with an aryl derivative which is substituted with an activated substituent group X (compound of formula III). Suitable activated substituent groups for X include but are not limited to halides (e.g., chloride, bromide, iodide), hydroxyl derivatives (e.g., triflate, mesylate, and tosylate groups), and diazonium salts.

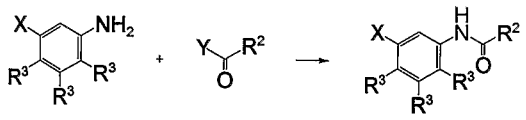
6-nitroindazole ring compounds can be converted to 6-amino indazole compounds by a reduction. The reduction of nitro groups to amino groups are well known. Metals, such as

Fe (iron), Zn (zinc), Sn (tin) and In (indium) can be used with a H^+ source to reduce a nitro group to an amino group by a sequence of single electron transfer (SET)/protonation reactions.

6-nitro-3-(E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole is reduced to the 6-amino compound by treatment with iron metal in the presence of an aqueous solution of ammonium chloride to provide 6-amino-3-(E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole.



The compounds of formula III are prepared by coupling an aryl amino compound of formula XI with a carboxylic acid derivative of formula XII:



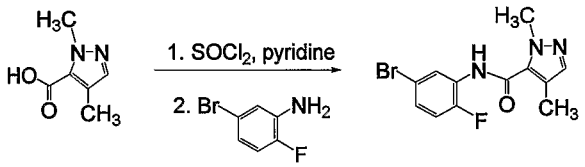
XI XII III

wherein Y is a leaving group, and R^2, R^3, R^4, R^5 and X are as described herein.

In general, the leaving group Y should be sufficiently reactive in order to be displaced by an aryl amino compound to provide the amido compounds of formula III. Compounds that contain such suitable leaving groups may be prepared and isolated and/or purified, or reacted without isolation or further purification. Among suitable leaving groups as Y, are halides, aromatic heterocycles, sulfonic acid esters, phosphoric acid esters, anhydrides, or groups derived from the reaction of carboxylic acids, wherein Y is hydroxyl, with reagents such as carbodiimides or carbodiimide species. Examples of suitable leaving groups include, but are not limited to, chloride, bromide, iodide, imidazole, -OC(O)alkyl, -OC(O)aryl, -OC(O)Oalkyl, -OC(O)Oaryl, -$OS(O_2)$alkyl, –$OS(O_2)$aryl, -$OPO(Oaryl)_2$, $OPO(Oalkyl)_2$, and those derived from the reaction of carboxylic acids wherein Y is –OH with carbodiimides. Other suitable leaving groups are known and may be found in Humphrey, J.M.; Chamberlin, A.R. *Chem. Rev.* 1997, 97, 2243; Comprehensive Organic Synthesis; Trost, B. M., Ed.; Pergamon: New York, (1991); Vol. 6, pp 301-434; and Comprehensive Organic Transformations; Larock, R. C.; VCH: New York, (1989), Chapter 9.

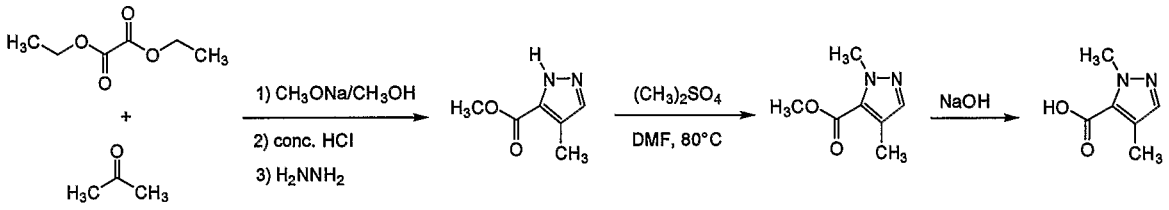
Compounds of formula XII, where in Y is a halogen can be prepared by reaction of a carboxylic acid (Y is hydroxyl) with a suitable agent such as thionyl chloride or oxalyl chloride in the presence of base to generate an acid chloride. Subsequent reaction of the intermediate acid chloride with an aryl amino compound provides the amido compounds of formula III.

1,3-dimethyl-5-pyrazolecarboxylic acid in ethyl acetate and DMF, and using pyridine as the base, is converted to the acid chloride by treatment with thionyl chloride. Addition of 5-bromo-2-fluoro-aniline to the intermediate acid chloride provides 3-bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide.

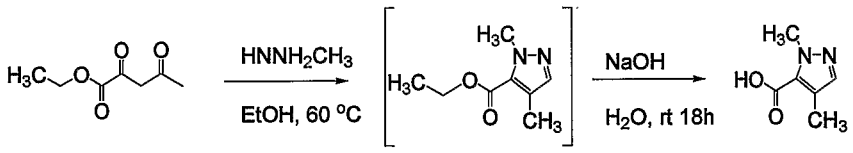


The compounds of formula XII are carboxylic acid derivatives that are either commercially available or are readily prepared using known reactions and reagents. For example, the carboxylic acid may be generated through hydrolysis of the corresponding ester.

1,3-dimethyl-5-pyrazolecarboxylic acid is prepared by the reaction of diethyl oxylate with acetone in the presence of base (sodium methoxide/methanol) to generate the aldol product, ethyl-2,4-dioxovalerate. Acidification and treatment of this aldol product with hydrazine provides the intermediate 3-methyl-pyrazole-5-carboxylic acid methylester. N-methylation of this intermediate with dimethylsulfate followed by base hydrolysis of the methyl ester, provides 1,3-dimethyl-5-pyrazolecarboxylic acid.

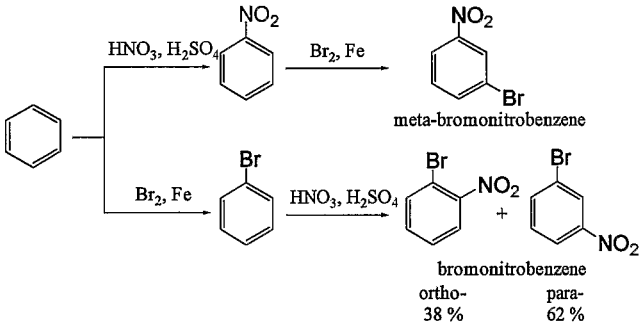


Alternatively, commercially available ethyl-2,4-dioxovalerate is reacted with methyl hydrazine in ethanol to provide the intermediate ethyl ester, which undergoes base hydrolysis to provide 1,3-dimethyl-5-pyrazolecarboxylic.



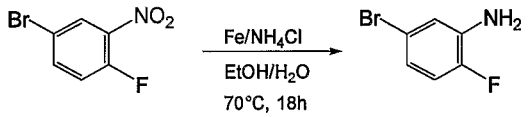
The compounds of formula XI are aryl amines that are commercially available or are readily prepared from commercially available aryl precursors using known methods and reagents. Various substituted aryl amines are easily prepared using readily available starting materials by an electrophilic aromatic substitution reaction. As shown below, the nitration/bromination (bromination/nitration) of benzene to meta- or ortho- and para-bromonitrobenzene is exemplary. The relative positions (ortho-, meta-, and para-) of the substituents on a phenyl ring can be controlled by the order in which the various substituents are introduced. In the preparation of bromonitrobenzenes, nitration followed by bromination provides the meta-substituted bromonitrobenzene, whereas, bromination followed by nitration

provides the ortho- and para-substituted bromonitrobenzenes. The ortho- and para-bromonitrobenzene isomers may be separated using known techniques (e.g., chromatography, distillation, recrystallization).

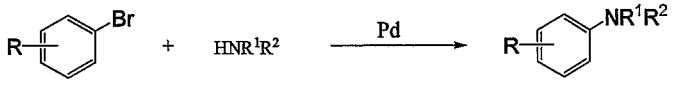


Subsequent reduction of the aryl nitro group provides the desired aryl amine compounds. As described herein, the reduction of nitro groups to amino groups are well known in the art. Metals, such as Fe (iron), Zn (zinc), Sn (tin) and In (indium) can be used with a H^+ source to reduce a nitro group to an amino group.

5-bromo-2-fluoro-nitrobenzene is reduced to the amino compound by treatment with iron metal in the presence of an aqueous solution of ammonium chloride to provide 5-bromo-2-fluoro-aniline.



The coupling reaction between the compounds of formula II and the compounds of formula III to provide the compounds of formula IV is accomplished in the presence of a catalyst, a base, and optionally, one or more solvents. The catalyst may be either a palladium or a copper catalyst. Methods that use palladium or copper catalysts to couple arylamines to aryl compounds containing an activated substituent X are well known. The Buchwald-Hartwig reaction is a palladium catalyzed coupling reaction between aryl halides (e.g., chlorides, bromides and iodides) and amines (e.g., alkyl, aryl, and heteroaryl amines) to form arylamines.



A wide variety of homogeneous Pd(0) catalysts can be used for the above reactions. Fully formed Pd(0) compounds such as $Pd(PPh_3)_4$ or catalysts made from precursors such as $[Pd(OAc)_2]_3$, and $Pd(dba)_x$ can be used with suitable phosphines such as triphenylphosphine (PPh_3). There are cases where the Pd precursor has been $PdCl_2$. PPh_3 is not the only phosphine which has been used. Bidentate chelating phosphines such as $Ph_2P(CH_2)_nPPh_2$ where n = 2, 3 or 4, and 1,1-bis(diphenylphosphino)-ferrocene have also been used.

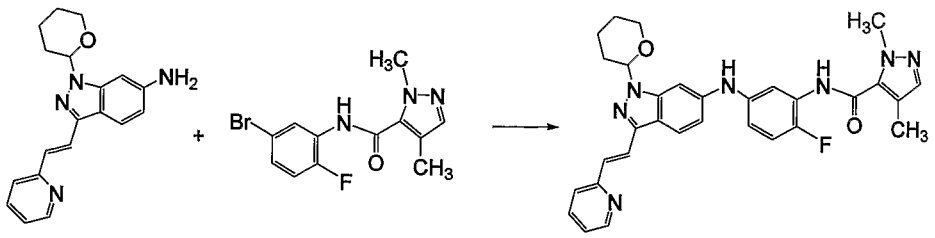
Other palladium catalysts which are useful in the above coupling reaction include but are not limited to $Pd(dppf)Cl_2$-CH_2Cl_2, $[Pd(P^t\text{-}Bu_3)(\mu\text{-}Br)]_2$, $Pd(PCy_3)_2Cl_2$, $Pd(P(o\text{-}tolyl)_3)_2Cl_2$,

$[Pd(P(OPh\text{-}2,4\text{-}t\text{-}Bu))_2Cl]_2$, FibreCat® 1007 ($PCy_2$-fibre/$Pd(OAc)_2$), FibreCat® 1026 ($PCy_2$-fibre/$PdCl_2/CH_3CN$), FibreCat® 1001($PPh_2$-fibre/$Pd(OAc)_2$), $Pd(dppf)Cl_2$, $Pd(dppb)Cl_2$, $Pd(dppe)Cl_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)Cl_2$, and the like. Other useful catalysts for the above transformation include those where one or more ligands, especially phosphine ligands, additionally complexes to the palladium catalyst include but are not limited to: $Pd_2(dba)_3$ complexed to a phospine ligand such as 2-(di-*t*-butylphosphino)biphenyl; $Pd(dba)_2$ complexed to $P(t\text{-}Bu)_3$; $Pd(OAc)_2$ complexed to (o-biphenyl)$P(t\text{-}Bu)_2$; and $Pd_2(dba)_3$ complexed to (o-biphenyl)$P(t\text{-}Cy)_2$. Copper catalysts which are useful in the above coupling reaction include those catalysts in which the copper is complexed with one or more ligands, including but not limited to CuI/ethylene glycol complex; CuBr/DBU complex, $Cu(PPh_3)Br$; and $Cu(PPh_3)Br$ additionally complexed to 1,10-phenanthroline or neocuproine (e.g., Cu(phen) $(PPh_3)Br$ and Cu(neocup)$(PPh_3)Br$, respectively), and the like.

Bases which are useful in the above coupling reaction include but are not limited to potassium carbonate, sodium carbonate, cesium carbonate, sodium *t*-butoxide, potassium *t*-butoxide, potassium phenoxide, triethylamine, and the like, or mixtures thereof. Solvents may be used in such coupling reactions including but not limited to toluene, xylenes, diglyme, tetrahydrofuran, dimethylethyleneglycol, and the like, or mixtures thereof.

In general, the activated substituent X in the compounds of formula III should be such that it provides sufficient reactivity to react with the compounds of formula II to provide the compounds of formula IV. Compounds of formula III that contain such activated substituents may be prepared, isolated and/or purified, and subsequently reacted with the compounds of formula II. Alternatively, compounds of formula III with suitable activated substituents may be prepared and further reacted without isolation or further purification with the compounds of formula II to afford the compounds of formula IV. Among suitable activated substituent groups for X are halogens (e.g., Cl, Br, and I); derivatized hydroxyl groups (e.g., triflate, mesylate, and tosylate); and diazonium salts. Other suitable activated substituent groups are well known and may be found in U.S. Patent No. 5,576,460 and in Humphrey, J.M.; Chamberlin, A.R. *Chem. Rev.* 1997, 97, 2243; Comprehensive Organic Synthesis; Trost, B. M., Ed.; Pergamon: New York, (1991); Vol. 6, pp 301-434; and Comprehensive Organic Transformations; Larock, R. C.; VCH: New York, (1989), Chapter 9.

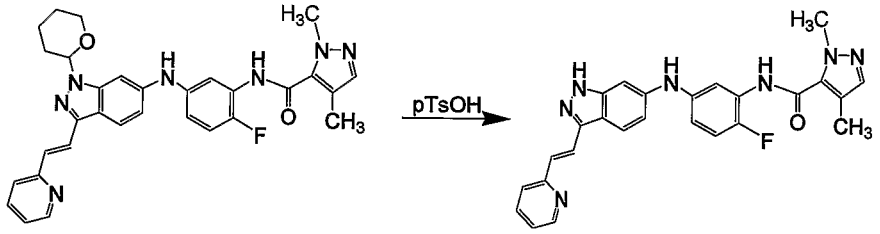
6-amino-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole is reacted with a catalytic amount of tris(dibenzylideneacetone) dipalladium in the presence of 2-(di-*t*-butylphosphino)biphenyl, sodium *t*-butoxide, and 3-bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide in toluene at 102 °C to provide 6-(2-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole .



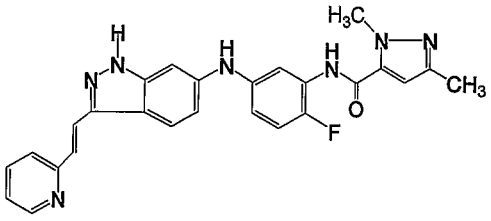
Other suitably functionalized aryl carboxamide compounds that are substituted with an X group, especially a bromide group, would be expected to react similarly with a 6-amino-indazole compound to provide a coupled product.

The choice of suitable reagents and reaction conditions for deprotecting the N-1 indazole ring nitrogen group, W, are well known. For example, when W is a tetrahydropyran protecting group, suitable reagents include, but are not limited to, hydrochloric acid, sulfuric acid, nitric acid, para-toluenesulfonic acid, methanesulfonic acid, or Lewis acids such as boron trifluoride etherate. These reactions may be conducted in solvents that are compatible with the specific reaction conditions chosen and will not interfere with the desired transformation.

The deprotection of 6-(2-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole using para-toluenesulfonic acid (p-TsOH) in methanol/water provides 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole.



The compounds of formula I may be present in an amorphous state or as one of several polymorph crystalline form, or mixtures thereof. For example, the compound of formula VII (2,5-dimethyl-2H-pyrazole-3-carboxylic acid {2-fluoro-5-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]phenyl}amide):



VIII

exists in the amorphous state as well as having several polymorph structures.

Each crystalline or amorphous form of this compound can be characterized by one or more of the following: X-ray powder diffraction pattern (i.e., X-ray diffraction peaks at various diffraction angles (2θ)), melting point onset (and onset of dehydration for hydrated forms) as

illustrated by endotherms of a Differential Scanning Calorimetry (DSC) thermogram, Raman spectral diagram pattern, aqueous solubility, light stability under International Conference on Harmonization (ICH) high intensity light conditions, and physical and chemical storage stability.

The polymorph or amorphous forms of the invention are preferably substantially pure, meaning each polymorph or amorphous form of the compound of formula I includes less than 10%, preferably less than 5%, preferably less than 3%, preferably less than 1% by weight of impurities, including other polymorph or amorphous forms of the compound.

The solid forms of the present invention may also exist together in a mixture. Mixtures of polymorphs and/or the amorphous form of the present invention will have X-ray diffraction peaks characteristic of each of the polymorphs and/or amorphous forms present in the mixture. For example, a mixture of two polymorphs will have a powder X-ray diffraction pattern that is a convolution of the X-ray diffraction patterns corresponding to the substantially pure polymorphs.

In particular, fourteen polymorphic forms and one amorphous form of the compound of formula VIII is provided. Form I is a substantially pure polymorph and has a powder X-ray diffraction (PXRD) pattern comprising the peaks at diffraction angles (2θ) of 5.5 and 28.4. More particularly, polymorph Form I has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 5.5, 9.5, 10.7, and 28.4. Even more particularly, polymorph Form I has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 1A. Still more particularly, polymorph Form I is characterized by a Raman spectra essentially the same as shown in Figure 1C.

Form II of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 12.1 and 16.7. More particularly, polymorph Form II has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 12.1, 13.0, 16.7, and 18.3. Even more particularly, polymorph Form II has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 2A. Still more particularly, polymorph Form II is characterized by a Raman spectra essentially the same as shown in Figure 2C.

Form III of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 6.4 and 23.4. More particularly, polymorph Form III has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 6.4, 23.4, 25.0, and 27.3. Even more particularly, polymorph Form III has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 3A. Still more particularly, polymorph Form III is characterized by a Raman spectra essentially the same as shown in Figure 3C.

Form IV of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 24.5 and 34.1. More

particularly, polymorph Form IV has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 12.8, 15.8, 24.5, and 34.1. Even more particularly, polymorph Form IV has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 4A. Still more particularly, polymorph Form IV is characterized by a Raman spectra essentially the same as shown in Figure 4C. Even more particularly, polymorph Form IV can be characterized by an onset of crystal melting endotherm at about 118 °C at a scan rate of 10 °C per minute. Still more particularly, polymorph Form IV has a DSC thermogram essentially the same as shown in Figure 4B.

Form V of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 8.4 and 26.0. More particularly, polymorph Form V has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 8.4, 14.2, 22.2, and 26.0. Even more particularly, polymorph Form V has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 5A. Still more particularly, polymorph Form IV is characterized by a Raman spectra essentially the same as shown in Figure 5C.

Form Ia of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 5.5 and 25.2. More particularly, polymorph Form Ia has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 5.5, 10.6, 18.9, and 25.2. Even more particularly, polymorph Form Ia has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 6A.

Form Ib of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 10.2 and 13.8. More particularly, polymorph Form Ib has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 10.2, 13.8, 20.1, and 26.2. Even more particularly, polymorph Form Ib has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 7A. Still more particularly, polymorph Form Ib is characterized by a Raman spectra essentially the same as shown in Figure 7C.

Form IIa of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 12.8 and 22.9. More particularly, polymorph Form IIa has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 12.8, 16.0, 22.9, and 31.2. Even more particularly, polymorph Form IIa has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 8A.

Form IIb of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 14.3 and 19.0. More particularly, polymorph Form IIb has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 7.9, 14.3, 19.0, and 27.0. Even more particularly, polymorph Form IIb has a

PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 9A. Still more particularly, polymorph Form IV is characterized by a Raman spectra essentially the same as shown in Figure 9C.

Form IIIa of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 24.9 and 36.2. More particularly, polymorph Form IIIa has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 14.7, 21.0, 24.9, and 36.2. Even more particularly, polymorph Form IIIa has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 10A.

Form IIIb of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 6.8 and 14.5. More particularly, polymorph Form IIIb has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 6.8, 14.5, 20.8, and 24.8. Even more particularly, polymorph Form IIIb has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 11A. Still more particularly, polymorph Form IIIb is characterized by a Raman spectra essentially the same as shown in Figure 11C.

Form IVa of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 13.5 and 32.5. More particularly, polymorph Form IVa has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 13.5, 15.8, 27.0, and 32.5. Even more particularly, polymorph Form IVa has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 12A. Still more particularly, polymorph Form IVa has an onset of dehydration endotherm at about 63 °C and an onset of crystal melting endotherm at about 123 °C at a scan rate of 10 °C per minute. Still further, polymorph Form IVa has a DSC thermogram essentially the same as shown in Figure 12B.

Form Va of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 19.2 and 33.9. More particularly, polymorph Form Va has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 11.5, 19.2, 24.4, and 33.9. Even more particularly, polymorph Form Va has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 13A. Still more particularly, polymorph Form Va is characterized by a Raman spectra essentially the same as shown in Figure 13C.

Form VI of the compound of formula VIII is a substantially pure polymorph and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 7.7 and 26.8. More particularly, polymorph Form VI has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 7.7, 12.9, 18.5, and 26.8. Even more particularly, polymorph Form VI has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 14A. Still more particularly, polymorph Form VI is characterized by a Raman

spectra essentially the same as shown in Figure 14C.

The amorphous form of the compound of formula VIII has a PXRD pattern exhibiting a broad peak at diffraction angles (2θ) ranging from 4 to 40° without any of the sharp peaks characteristic of a crystalline form. More particularly, the amorphous form is characterized by having a PXRD pattern essentially the same as shown in Figure 15A. Even more particularly, the amorphous form is characterized by a Raman spectra comprising shift peaks (cm^{-1}) essentially the same as shown in Figure 15B.

A solid form of the compound of formula VIII exists as a mixture comprising at least two of the following solid forms: polymorph Forms I, II, III, IV, V, Ia, Ib, IIa, IIb, IIIa, IIIb, IVa, Va, VI, and an amorphous form.

Form Ibm-2 of the compound of formula VIII is a substantially pure polymorph of the compound of formula VIII, which is a mixture of Forms Ib and VI, and has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 12.9 and 13.8. More particularly, polymorph Form Ibm-2 has a PXRD pattern comprising the peaks at diffraction angles (2θ) of 12.9, 13.8, 20.1, and 26.8. Even more particularly, polymorph Form Ibm-2 has a PXRD pattern comprising the peaks at diffraction angles (2θ) essentially the same as shown in Figure 16.

The following processes illustrate the preparation of indazole compounds of formula I which are useful as modulators and/or inhibitors of protein kinases. These compounds, prepared by the methods of the present invention, are useful as anti-angiogenesis agents and as agents for modulating and/or inhibiting the activity of protein kinases, thus providing treatments for cancer or other diseases associated with cellular proliferation mediated by protein kinases.

Unless otherwise indicated, variables according to the following processes are as defined above. Starting materials, the synthesis of which are not specifically described herein or provided with reference to published references, are either commercially available or can be prepared using methods known to those of ordinary skill in the art. Certain synthetic modifications may be done according to methods familiar to those of ordinary skill in the art.

Examples

In the examples described below, unless otherwise indicated, all temperatures in the following description are in degrees Celsius (°C) and all parts and percentages are by weight, unless indicated otherwise.

Various starting materials and other reagents were purchased from commercial suppliers, such as Aldrich Chemical Company or Lancaster Synthesis Ltd., and used without further purification, unless otherwise indicated.

The reactions set forth below were performed under a positive pressure of nitrogen, argon or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents. Analytical thin-layer chromatography was performed on glass-backed silica gel 60°F 254 plates (Analtech (0.25 mm)) and eluted with the appropriate solvent ratios (v/v).

The reactions were assayed by high-pressure liquid chromotagraphy (HPLC) or thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. The TLC plates were visualized by UV, phosphomolybdic acid stain, or iodine stain.

^{1}H-NMR spectra were recorded on a Bruker instrument operating at 300 MHz and ^{13}C-NMR spectra were recorded at 75 MHz. NMR spectra are obtained as DMSO-d_6 or $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or DMSO-d_6 (2.50 ppm and 39.52 ppm). Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Coupling constants, when given, are reported in Hertz.

Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrometer as neat oils, as KBr pellets, or as $CDCl_3$ solutions, and when reported are in wave numbers (cm^{-1}). The mass spectra were obtained using LC/MS or APCI. All melting points are uncorrected.All final products had greater than 95% purity (by HPLC at wavelengths of 220nm and 254nm).

The X-ray powder diffraction pattern for each polymorph or amorphous form of the invention was measured on a Shimadzu XRD-6000 X-ray diffractometer equipped with a Cu X-ray source operated at 40 kV and 50 mA. Samples were placed in a sample holder and then packed and smoothed with a glass slide. During analysis, the samples were rotated at 60 rpm and analyzed from angles of 4 to 40° (θ-2θ) at 5°/min with a 0.04° step or at 2°/min with a 0.02° step. If limited material was available, samples were placed on a silicon plate (zero background) and analyzed without rotation. One of skill in the art will appreciate that the peak positions (2θ) will show some inter-apparatus variability, typically as much as 0.1°. Accordingly, where the solid forms of the present invention are described as having a powder X-ray diffraction pattern essentially the same as that shown in a given figure, the term "essentially the same" is intended to encompass such inter-apparatus variability in diffraction peak positions.

The DSC thermographs were obtained using a Mettler Toledo DSC821^{e} instrument at a scan rate of 10 °C/min over a temperature range of 30-250°C. Samples were weighed into 40 µl aluminum crucibles that were sealed and punctured with a single hole. The extrapolated onset of melting temperature and, where applicable, the onset of dehydration temperature, were calculated.

Depending on several factors, the endotherms exhibited by the compounds of the invention may vary (by about 0.01-5 °C for crystal polymorph melting and by about 0.01-20°C for polymorph dehydration) above or below the endotherms depicted in the appended figures. Factors responsible for such variance include the rate of heating (i.e., the scan rate) at which the DSC analysis is conducted, the way the DSC onset temperature is defined and determined, the calibration standard used, instrument calibration, the relative humidity and the chemical purity of the sample. For any given sample, the observed endotherms may also

differ from instrument to instrument; however, it will generally be within the ranges defined herein provided the instruments are calibrated similarly.

Raman scattering spectra were obtained by using a Fourier transform Raman spectrophotometer Kaiser Optical Instruments, Ramen RXN1-785. The excitation light source was an Invictus NIR Laser operating at 785 nm wavelength. The detector was an Andor CCD. The resolution was 34 cm^{-1}.

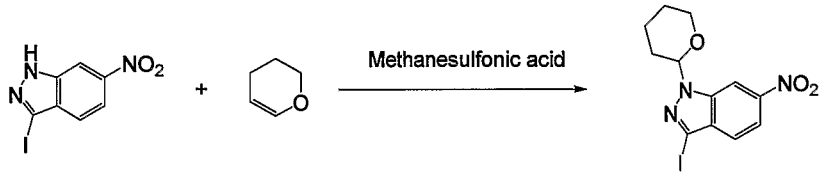
In the following examples and preparations, "DMF" means N,N-dimethyl formamide, "THF" means tetrahydrofuran, "Et" means ethyl, "Ac" means acetyl, "Me" means methyl, "Ph" means phenyl, "HCl" means hydrochloric acid, "EtOAc" means ethyl acetate, "Na_2CO_3" means sodium carbonate, "$NaHCO_3$" means sodium hydrogen carbonate (sodium bicarbonate), "NaOH" means sodium hydroxide, "$Na_2S_2O_3$" means sodium thiosulfate, "NaCl" means sodium chloride, "Et_3N" means triethylamine , "H_2O" means water, "KOH" means potassium hydroxide, "K_2CO_3" means potassium carbonate, "MeOH" means methanol, "i-PrOAc" means isopropyl acetate, "$MgSO_4$" means magnesium sulfate, "DMSO" means dimethylsulfoxide, "AcCl" means acetyl chloride, "CH_2Cl_2" means methylene chloride, "MTBE" means methyl t-butyl ether, "$SOCl_2$" means thionyl chloride, "H_3PO_4" means phosphoric acid, "CH_3SO_3H" means methanesulfonic acid, "Ac_2O" means acetic anhydride, "CH_3CN" means acetonitrile, "DHP" means 3,4-dihydro-2*H*-pyran.

Example 1: Preparation of 3-iodo-6-nitroindazole



6-Nitroindazole (45.08 Kg) is dissolved in N,N-dimethyl formamide (228 Kg) and powdered potassium carbonate (77 Kg) is added while the solution temperate is maintained at ≤ 30°C. A solution of iodine (123 Kg) dissolved in N,N-dimethyl formamide (100 Kg) is added over 5 to 6 hours while the reaction temperature is maintained ≤ 35°C. (Caution: the reaction is exothermic). The reaction mixture is agitated for 1 to 5 hours at 22°C (until the reaction is complete by HPLC). The mixture is then added to a solution of sodium thiosulfate (68 Kg) and potassium carbonate (0.46 Kg) dissolved in water (455 Kg) while the solution temperature is maintained ≤ 30°C. The mixture is agitated for 1.5 hours at 22°C. Water (683 Kg) is added which precipitates solids and the slurry is agitated for 1 to 2 hours at 22°C. The solids are filtered, washed with water (2 x 46 Kg), and dried in a vacuum oven for 24 to 48 hours (50°C and 25 mm Hg) to provide 74.7 Kg of 3-iodo-6-nitroindazole as a yellow white solid (93.6% yield with a purity of 86% by HPLC; KF is 0.2%).

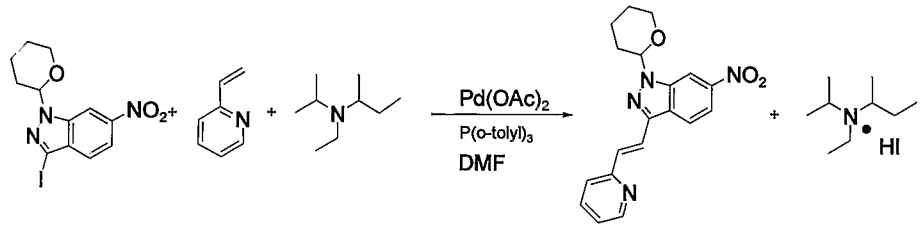
Example 2: Preparation of 3-iodo-6-nitro-1-(tetrahydropyran-2-yl)-1H-indazole



3-iodo-6-nitroindazole (74.6 Kg) is dissolved in methylene chloride (306 Kg) and tetrahydrofuran (211 L), and methanesulfonic acid (3.0 Kg) is carefully added. (Caution: residual sodium bicarbonate may cause CO_2 to be evolved. Monitor the pressure in the reactor). A solution of DHP (55 Kg) in methylene chloride (97 Kg) is added over 5 to 6 hours while the reaction temperature is maintained at ≤ 22°C. The mixture is agitated at 22°C for 2 to 6 hours (until the reaction is complete by HPLC). The mixture is then carefully added to an aqueous solution of 10% $NaHCO_3$ (37 Kg of $NaHCO_3$ dissolved in 370 Kg water) while the solution temperature is maintained at 22°C. (Caution: CO_2 is evolved. Monitor the pressure in the reactor). The mixture is agitated for 1 hour at 22°C and the layers separated. The organic layer is washed with an aqueous solution of 10% NaCl (407 Kg) and the layers separated. The organic layer is concentrated at 55°C and atmospheric pressure to cut the volume to half (ca. 500 L), then under reduced pressure to remove the remaining solvents. The concentrate (ca.138 L) is co-evaporated with acetonitrile (1 x 224 Kg, 1 x 75 Kg, 1 x 60 Kg) at 55°C under reduced pressure until the final volume is ca. 80 L. The resulting slurry is diluted with acetonitrile (60 Kg) and is agitated for 8 hours at -5°C. The slurry is filtered, and the solids are rinsed with cold acetonitrile (15 Kg). The solids are dried at room temperature

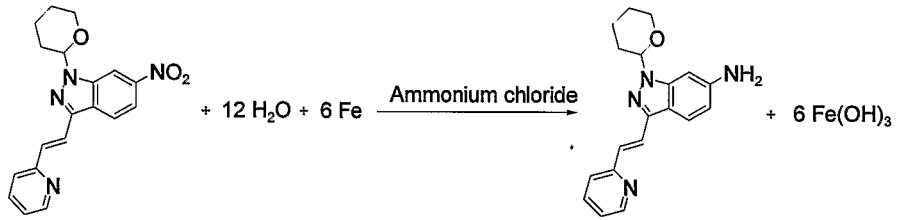
under reduced pressure to provide 77.6 Kg of 3-iodo-6-nitro-1-(tetrahydropyran-2-yl)-1H-indazole (80.5% yield with a purity of 95% by HPLC).

Example 3: Preparation of 6-nitro-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole



3-iodo-6-nitro-1-(tetrahydropyran-2-yl)-1H-indazole (77 Kg) is added to a solution of 2-vinyl pyridine (31 Kg), N,N-diisopropylethylamine (51 Kg), and tri-*o*-tolylphosphine (5.414 Kg) in N,N-dimethyl formamide (163 Kg). $Pd(OAc)_2$ (1.503 Kg) is added and the mixture is agitated for 12 to 18 hours at 100°C (until the reaction is complete by HPLC). The mixture is then cooled to 45°C and isopropanol (248 Kg) is added. The mixture is agitated for 30 minutes at 45°C, diluted with water (1,238 L), and the mixture is agitated at 22°C for 1 to 2 hours. The resulting slurry is filtered, rinsed with water (77 L), and the solids are combined with isopropanol (388 Kg). The mixture is agitated for 30 to 90 minutes at 55°C, then for 30 to 90 minutes at 10°C, filtered, and the solids are washed with cold (ca. 10°C) isopropanol (2 x 30 L). The solids are dried in a vacuum oven for 24 to 48 hours (50°C and 25 mm Hg) to provide 61.8 Kg of 6-nitro-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole (85% yield with a purity of 88% by HPLC).

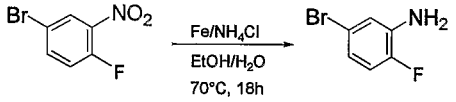
Example 4: Preparation of 6-amino-3-(E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole



6-nitro-3-(E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole (61.4 Kg) is dissolved in an aqueous solution of ammonium chloride (71.4 Kg of NH_4Cl in 257 Kg water) and ethanol (244 Kg) is added. Iron powder (39 Kg) is added and the mixture is agitated for 2 to 8 hours at 50°C (until the reaction is complete by HPLC). (Add more iron powder (ca. 9.8 Kg) if the reaction is not complete after 8 hours). The mixture is then cooled to 22°C and tetrahydrofuran (1,086 Kg) is added. The mixture is agitated for 1 hour at 22°C, and filtered through diatomaceous earth (ca. 5 Kg). The cake is rinsed with tetrahydrofuran (214 Kg), and the filtrate is concentrated at 50°C under reduced pressure to a volume of ca. 305 L. The concentrate is cooled to 22°C, diluted with water (603 Kg), and agitated at 22°C for 1 hour. The mixture is filtered, rinsed with heptanes (62 Kg), dried in a vacuum oven for 24 to 48

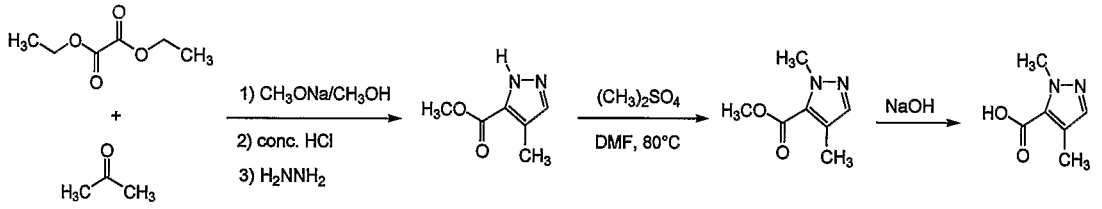
hours (50°C and 25 mm Hg) to provide 51.5 Kg of 6-amino-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole (91.8% yield with a purity of 95% by HPLC).

Example 5: Preparation of 5-Bromo-2-fluoro-aniline

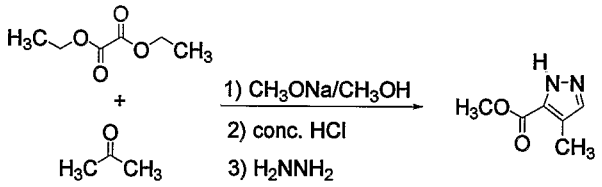


5-Bromo-2-fluoro-nitrobenzene (698 g) is dissolved in 95% ethanol (0.90 L) and is added to a mixture of iron powder (711 g) in a saturated aqueous ammonium chloride solution (2.0 L). The reaction mixture is agitated for 24 hours at 70°C (until the reaction is complete by HPLC). The reaction mixture is then cooled to room temperature, filtered through Celite, and the filtrate is evaporated under reduced pressure. The residue is extracted with ethyl acetate (2 L) and water (2 L) and the layers separated. The aqueous layer is extracted with ethyl acetate (1 L). The combined organic extracts are washed with water (1 L), dried over $MgSO_4$, filtered, and the solution is concentrated under reduced pressure. The residual ethyl acetate is removed from the product under high vacuum for five hours to provide 545.76 g of 5-bromo-2-fluoro-aniline (91 % yield). ^1H NMR 300MHz, $CDCl_3$ ppm: 6.85-6.65 (m, 3H), 3.78 (br s, 2H).

Example 6: Preparation of 1,3-dimethylpyrazole-5-carboxylic acid



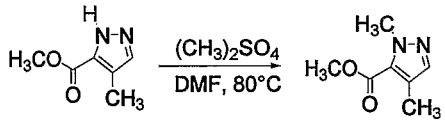
a. Synthesis of 3-methyl-pyrazole-5-carboxylic acid methylester



Diethyl oxalate (3.4 L) is dissolved in acetone (1.84 L) and the solution is added drop-wise over 7 hours at 0°C to a solution of 25% sodium methoxide in methanol (5.72 L) dissolved in anhydrous methanol (8 L). Throughout the process, the internal temperature should never exceed 20°C. Drop-wise addition is imperative, fast addition is detrimental to the reaction. The reaction mixture is stirred at 0 °C for 14 hours. Concentrated HCl (2.1 L) is added drop-wise over 3 hours at 0°C to the reaction mixture. Throughout the process, the internal temperature never exceeded 20 °C. Hydrazine monohydrate (1.21 L) is added drop-wise in over 5 hours at 0°C to the reaction mixture. By controlling the addition rate, the internal temperature is maintained approximately at room temperature. Throughout the process, the internal temperature never exceeded 24 °C. Upon complete addition, the

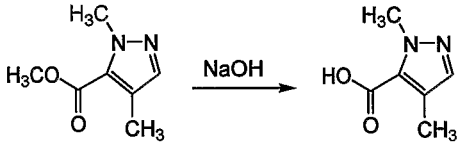
resulting mixture is allowed to stir for 18 hours at 22°C. The mixture is filtered and the filtrate is concentrated under reduced pressure to 7 L. The concentrate is diluted with ethyl acetate (16 L) and water (12 L), the mixture is extracted, and the layers are separated. The organic layer is dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure to provide 2.61 Kg of 3-methyl-pyrazole-5-carboxylic acid methylester (75 % yield with a purity of 95%). ^1H NMR 300MHz, $CDCl_3$ ppm; 6.57 (1 H, s), 3.89 (3 H, s), 2.37 (3 H, s).

b. Synthesis of 1,3-dimethyl-pyrazole-5-carboxylic acid methylester



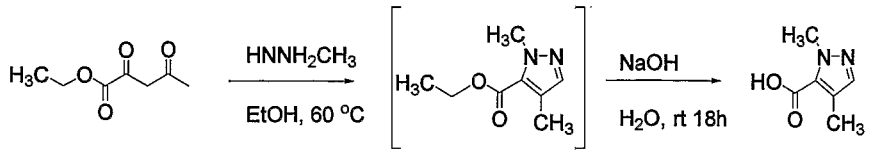
3-methyl-pyrazole-5-carboxylic acid methyl ester (6.8 Kg Kg) is dissolved in DMF (8L) and dimethyl sulfate (6.0 L) is added dropwise in over three hours. The reaction is exothermic and the addition of dimethyl sulfate must be controlled so that the internal temperature does not exceed 90°C. After complete addition, the mixture is heated for 18 hours at 80°C. The mixture is then cooled to room temperature, diluted with ice (3.4 Kg), and cooled in an ice bath. A solution of aqueous 28% ammonium hydroxide (8.6 L) is added to the reaction mixture over 3 hours. The resulting mixture is stirred for 18 hours, diluted with ethyl acetate (12 L) and water (16 L), extracted, and the layers are separated. The organic layer is washed with water (4L), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide 5.14 Kg of 1,3-dimethyl-pyrazole-5-carboxylic acid methylester (69 % yield with a purity of >90 % by HPLC). The crude product is used directly in the next step. ^1H NMR 300MHz, $CDCl_3$ ppm; 6.59 (1 H, s), 4.17 (3 H, s), 3.86 (3 H, s), 2.26 (3 H, s).

c. Synthesis of 1,3-dimethyl-pyrazole-5-carboxylic acid



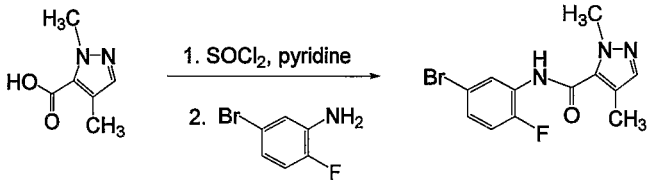
3,5-dimethyl-pyrazole-5-carboxylic acid methylester (5.14 Kg) is added to an aqueous solution of 20% sodium hydroxide (10 L) at 0°C. The reaction mixture is stirred at room temperature for 18 hours and cooled to 0°C. Concentrated hydrochloric acid (4.2 L) is then added to the reaction mixture in over 7 hours. The resulting thick slurry is stirred at room temperature for 18 hours. The mixture is filtered, and the solids are washed with water (500 mL), and dried in a vacuum oven for 18 hours (70°C and 25 mm Hg) to provide 3.8 Kg of 1,3-dimethyl-pyrazole-5-carboxylic acid (81 % yield with a purity of >97 % by HPLC). ^1H NMR 300MHz, $CDCl_3$ ppm; 6.63 (1 H, s), 4.98 (broad s, methanol), 4.06 (3 H, s), 2.23 (3 H, s).

d. Alternative synthesis of 1,3-dimethylpyrazole-5-carboxylic acid



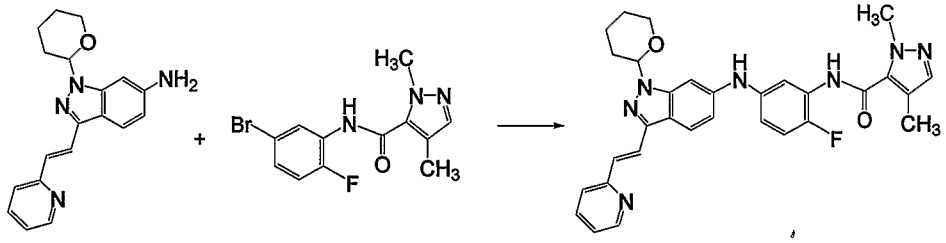
Ethyl-2,4-dioxovalerate (Kg) is added to a solution of methyl hydrazine (L) in ethanol (L) and heated to 60°C for 18 hours to provide the intermediate 3,5-dimethyl-pyrazole-5-carboxylic acid ethylester.

Example 7: Preparation of 3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide



1,3-dimethyl-5-pyrazolecarboxylic acid (50.0 g) is dissolved in ethyl acetate (1,150 mL), pyridine (29.0 mL) and DMF (0.5 mL) and the solution is warmed to 35°C. Thionyl chloride (50 mL) is added in over 15 minutes and the mixture is stirred for 1 hour at 35°C. A solution of 5-bromo-2-fluoro-aniline dissolved in ethyl acetate (150 mL) is added drop-wise over 1 hour. The reaction mixture is stirred for 18 hours at 35°C, cooled to room temperature, diluted with ethyl acetate (500 mL) and water (750 mL), extracted, and the layers are separated. The aqueous layer is extracted with ethyl acetate (500 mL), and the combined organic layers are dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue is stirred in a solution of 10% ethyl acetate in heptanes (250 mL), and the solids are filtered, washed with 10% ethyl acetate in heptanes (250 mL), and dried in a vacuum oven for 18 hours (40°C and 25 mm Hg) to provide 84.60 g of 3-bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide (78 %). (Note: If after the work up, there is residual starting material, this can be removed with a saturated sodium bicarbonate wash). ^1H NMR 300MHz, d6-DMSO ppm: 10.10 (s, 1H), 7.83 (dd, 1H, j=2.45, 6.78), 7.50-7.46 (s, 1H), 7.31 (dd, 1H, j=8.85, 10.55), 6.85 (s, 1H), 3.99 (s, 3H), 2.09 (s, 3H).

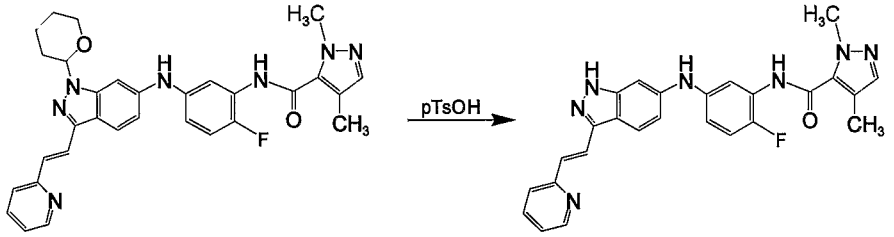
Example 8: Preparation of 6-(2-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole



6-amino-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole (50.0 g), 3-bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide (48.8 g), 2-(di-*t*-butylphosphino)biphenyl (2.42 g), sodium *t*-butoxide (19.30 g), tris(dibenzylideneacetone) dipalladium (2.85 g) and

toluene (500 mL) are combined and agitatede for 18 hours at 102°C). The reaction mixture is then cooled to 40°C, and THF (500 mL) and 10% cysteine on silica gel (250 g) is added. The resulting mixture is stirred for 24 hours and filtered through a pad of Celite (100 g). The pad is washed with THF (500 mL) and the combined filtrates are concentrated under reduced pressure to a volume of 1L. The concentrate is stirred with 10% cysteine on silica gel (250 g) for 48 hours and filtered through a pad of Celite (100 g). The pad is washed with THF (500 mL) and the combined filtrates are concentrated under reduced pressure to provide 75.67 g of 6-(2-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole (88 % yield).

Example 9: Preparation of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole



6-(2-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole (77.67 g) and *p*-toluenesulfonic acid monohydrate (78.76 g) are dissolved in methanol (500 mL) and agitated for 18 hours at 68°C. The resulting orange slurry is diluted with isopropanol (500 mL) and agitated for 2 hours at room temperature.

The mixture is filtered, and the solids are washed with isopropanol (500 mL). The solids are suspended isopropanol (500 mL), and a solution of K_2CO_3 (97.8 g) in water (700 mL) is added. The mixture is stirred for 3 hours at room temperature, filtered, washed with water (700 mL), and dried under reduced pressure for 96 hours at 40°C to provide 31.32 g of 6-(2-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole (47.6 % yield)^{1}H NMR 300MHz, d6-DMSO ppm: 8.61-8.57 (m, 1H), 8.39 (s, 1H), 8.01 (d, 1H, j=8.67Hz), 7.83 (d, 1H, j=16.39), 7.83-7.77 (m, 1H), 7.64 (d, 1H, j=7.91Hz), 7.49 (d, 1H, j=16.20Hz), 7.46-7.41 (m, 1H), 7.29-7.17 (m, 2H), 7.11 (bs, 1H), 7.06-6.93 (m, 2H), 6.88 (s, 1H), 4.00 (s, 3H), 2.19 (s, 3H).

Example 10: Polymorph Form I of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Polymorph Form I, an anhydrous form of the compound of formula VIII, is prepared by slurrying the compound of formula VIII (155 mg) in ethanol (5 mL) and heating to reflux for 30 minutes. The sample is slowly cooled to 23°C to provide a solid precipitate. The solids are collected by filtration and dried at 85°C under high vacuum. Form I was confirmed by X-ray diffraction and the HPLC purity was >98%. Form I has an aqueous solubility of about 39

μg/mL at pH 2 and about 0.4 μg/mL at pH 7.4. Form I is light-stable under ICH high intensity light conditions and chemically stable at 80°C and 40°C/75%RH for at least 14 days.

Form I is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 4.80, 5.49, 7.06, 7.90, 9.52, 10.67, 12.33, 14.10, 15.08, 15.80, 18.12, 18.80, 19.72, 20.40, 21.09, 21.95, 23.00, 23.48, 24.52, 25.52, 26.16, 27.92, 28.36, 29.08, 29.88, 30.32, 30.96, 31.68, 33.59, 34.32, 34.72, 35.20, 36.64, and 38.00. Figure 1A provides an X-ray powder diffraction pattern for Form I.

The DSC thermogram for Form I, shown in Figure 1B, indicates an onset of crystal melting endotherm at about 183°C, at a scan rate of 10°C/minute.

The Raman spectral diagram for Form I, shown in Figure 1C, includes Raman Shift peaks (cm^{-1}) at approximately 993, 1265, 1323, 1377, 1394, 1432, 1465, 1482, 1563, 1589, and 1640.

Example 11: Polymorph Form II of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Polymorph Form II, an anhydrous form of the compound of formula VIII, is prepared by dissolving the compound of formula VIII (Example 10, Form I) in THF at 60°C, and re-crystallizing by gradual addition of hexanes. Form II was confirmed by X-ray diffraction (HPLC purity >98%). Form II has an aqueous solubility of about 19 μg/mL at pH 2 and about 0.7 μg/mL at pH 7.4. Form II is light stable under ICH high intensity light conditions.

Form II is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 4.65, 6.9200, 7.36, 7.76, 9.81, 11.41, 12.08, 12.60, 13.03, 13.72, 14.24, 14.72, 16.06, 16.66, 17.80, 18.32, 18.80, 19.68, 20.32, 21.05, 21.89, 22.64, 23.00, 23.60, 25.45, 26.30, 27.18, 28.34, 29.04, 30.21, 31.14, 32.24, 34.14, 34.91, 36.97, 39.21, and 39.92. Figure 2A provides an X-ray powder diffraction pattern for Form II.

The DSC thermogram for Form II, shown in Figure 2B, indicates an onset of crystal melting endotherm at about 195°C, at a scan rate of 10°C/minute.

The Raman spectral diagram for Form II, shown in Figure 2C, includes Raman Shift peaks (cm^{-1}) at approximately 993, 1265, 1323, 1377, 1394, 1432, 1465, 1482, 1563, 1589, and 1640.

Example 12: Polymorph Form III of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Polymorph Form III, an anhydrous form of the compound of formula VIII, is prepared by slurrying the compound of formula VIII (Example 10, Form I) in light mineral oil at 192°C for about 1.5 hours. The mixture is allowed to cool to room temperature and the solids are washed with hexanes, filtered, and dried at 50°C under vacuum. Form III was confirmed by X-ray diffraction (HPLC purity >97%). Form III has an aqueous solubility of about 10 μg/mL

at pH 2 and about 0.6 µg/mL at pH 7.4. Form III is light-stable under ICH high intensity light conditions.

Form III is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 6.40, 6.87, 7.36, 9.73, 10.43, 13.20, 13.72, 14.04, 14.65, 15.20, 15.80, 17.60, 18.56, 19.56, 20.16, 20.56, 21.49, 21.96, 22.92, 23.40, 24.08, 24.98, 25.64, 27.32, 27.72, 28.35, 29.08, 29.56, 30.12, 30.58, 31.53, 33.58, 35.01, 36.84, 37.24, 37.60, and 39.51. Figure 3A provides an X-ray powder diffraction pattern for Form III.

The DSC thermogram for Form III, shown in Figure 3B, indicates an onset of crystal melting endotherm at about 210°C, at a scan rate of 10°C/minute.

The Raman spectral diagram for Form III, shown in Figure 3C, includes Raman Shift peaks (cm^{-1}) at approximately 991, 1261, 1379, 1431, 1589, and 1634.

Example 13: Polymorph Form IV of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form IV, an anhydrous form of the compound of formula VIII, is prepared by dissolving the compound of formula VIII (crude material from synthesis) in ethyl acetate and ethanol, and recrystallizing by addition of 1:1 $NaHCO_3$:Water. Form IV was confirmed by X-ray diffraction (HPLC purity>99%). Form IV has an aqueous solubility of about 7 µg/mL at pH 2. Form IV is light stable under ICH high intensity light conditions.

Form IV is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 4.85, 7.95, 9.85, 11.51, 12.80, 13.53, 14.56, 14.92, 15.80, 16.32, 17.43, 18.08, 18.44, 19.31, 20.08, 21.08, 21.61, 22.64, 23.24, 23.84, 24.48, 25.08, 26.24, 27.02, 27.92, 28.76, 30.12, 30.72, 31.40, 32.52, 34.07, 37.48, and 38.20. Figure 4A provides an X-ray powder diffraction pattern for Form IV.

The DSC thermogram for Form IV, shown in Figure 4B, indicates an onset of crystal melting endotherm at about 118°C, at a scan rate of 10°C/minute.

The Raman spectral diagram for Form IV, shown in Figure 4C, includes Raman Shift peaks (cm^{-1}) at approximately 998, 1269, 1314, 1340, 1371, 1436, 1463, 1483, 1562, 1592, and 1644.

Example 14: Polymorph Form V of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form V, an anhydrous form of the compound of formula VIII, is prepared by slurrying Form IV solids in heavy mineral oil at 130°C, and then 180°C for about 1.5 hours, followed by hexane wash and filtration. The solids are collected by filtration, washed with hexanes, and dried under vacuum. Form V was confirmed by X-ray diffraction (HPLC purity >99%).Form V has an aqueous solubility of about 8 µg/mL at pH 2 and about 0.2 µg/mL at pH 7.4. Form V is light stable under ICH high intensity light conditions

Form V is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 4.23, 8.38, 11.74, 12.00, 12.47, 12.95, 13.58, 14.17, 15.15, 16.76, 16.96, 17.44, 17.92, 18.28, 18.70, 19.37, 20.26, 21.16, 21.62, 21.84, 22.16, 22.54, 23.28, 23.64, 24.17, 24.84, 25.12, 25.58, 25.98, 26.48, 27.02, 28.16, 28.54, 29.14, 29.89, 31.40, 32.23, 32.66, and 39.68. Figure 5A provides an X-ray powder diffraction pattern for Form V.

The DSC thermogram for Form V, shown in Figure 5B, indicates an onset of crystal melting endotherm at about 210°C, at a scan rate of 10°C/minute.

The Raman spectral diagram for Form V, shown in Figure 5C, includes Raman Shift peaks (cm^{-1}) at approximately 989, 1230, 1298, 1374, 1433, 1466, 1481, 1562, 1586, and 1642.

Example 15: Polymorph Form Ia of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form Ia, a hydrate form of the compound of formula VIII, is prepared by slurrying Form I in water (approximately 20-40 mg/mL) at ambient temperature for seven days. Form Ia was confirmed by X-ray diffraction (HPLC purity > 99%). Form Ia is light-stable under ICH high intensity light conditions.

Form Ia is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 4.84, 5.49, 7.07, 7.90, 9.55, 10.60, 10.96, 11.48, 12.20, 12.72, 13.48, 14.10, 14.56, 15.78, 17.54, 18.08, 18.52, 18.88, 19.44, 21.11, 21.93, 22.48, 23.06, 23.72, 24.20, 24.48, 25.20, 25.56, 26.12, 26.72, 27.12, 27.78, 28.75, 30.36, 30.68, 31.20, 31.64, 32.04, 34.64, 34.97, 36.16, 36.60, 36.92, 37.24, 37.68, 38.12, 38.48, and 39.80. Figure 6A provides an X-ray powder diffraction pattern for Form Ia.

The DSC thermogram for Form Ia, shown in Figure 6B, indicates an onset of dehydration endotherm at about 60°C and an onset of crystal melting endotherm at about 185°C, at a scan rate of 10°C/minute.

Example 16: Polymorph Form Ib of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form Ib, a mono-hydrate of the compound of formula VIII, is prepared by slurrying Form I in water (approximately 20-40 mg/mL) at 90°C for three days, or by crystallization from ethanol:water at greater than 65°C. Form Ib is also obtained by crystallization from ethanol:water at 65°C. Form Ib was confirmed by X-ray diffraction (HPLC purity > 99%). Form Ib is physically and chemically stable for at least three months at 60°C and 40°C/75%RH and is also light-stable under ICH high intensity light conditions

Form Ib is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 7.93, 10.23, 11.04, 13.12, 13.79, 14.88, 15.24, 15.81, 16.81, 17.40, 17.89, 18.64, 19.00, 20.11, 20.96, 21.53, 22.14, 22.87, 23.80, 24.16, 25.20, 26.20, 26.64, 27.76, 28.38, 28.84, 29.52, 29.92, 30.28, 30.92, 31.87, 32.80, 33.24,

34.07, 34.68, 35.74, 36.54, and 37.96. Figure 7A provides an X-ray powder diffraction pattern for Form Ib.

The DSC thermogram for Form Ib, shown in Figure 7B, indicates an onset of dehydration endotherm at about 67°C and an onset of crystal melting endotherm at about 179°C, at a scan rate of 10°C/minute.

The Raman spectral diagram for Form Ib, shown in Figure 7C, includes Raman Shift peaks (cm^{-1}) at approximately 964, 1002, 1239, 1266, 1372, 1470, 1558, and 1641.

Example 17: Polymorph Form IIa of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form IIa, a mono-hydrate of the compound of formula VIII, is prepared by slurrying Form II in water (approximately 20-40 mg/mL) at ambient temperature for seven days. Form IIa was confirmed by X-ray diffraction (HPLC purity > 99%). Form IIa is light stable under ICH high intensity light conditions.

Form IIa is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 4.77, 7.64, 8.80, 9.82, 11.41, 12.75, 13.48, 14.23, 15.96, 16.64, 17.68, 18.76, 21.67, 22.85, 25.38, 27.16, 28.24, 30.12, 31.23, 32.16, 34.02, 34.80, 35.92, 36.92, 38.32, and 39.25. Figure 8A provides an X-ray powder diffraction pattern for Form IIa.

The DSC thermogram for Form IIa, shown in Figure 8B, indicates an onset of dehydration endotherm at about 51°C and an onset of crystal melting endotherm at about 194°C, at a scan rate of 10°C/minute.

Example 18: Polymorph Form IIb of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form IIb, which is a di-hydrate of the compound of formula VIII, is prepared by slurrying Form II in water (approximately 20-40 mg/mL) at 90°C for three days and then ambient temperature for 17 days. Form IIb is confirmed by X-ray diffraction. Form IIb is light stable under ICH high intensity light conditions.

Form IIb is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 4.80, 7.86, 8.73, 11.44, 12.70, 13.41, 14.33, 15.71, 16.60, 17.43, 18.32, 19.03, 20.08, 21.56, 21.88, 22.56, 23.10, 23.76, 24.40, 25.04, 25.56, 26.20, 26.64, 27.02, 27.80, 28.64, 30.63, 31.36, 31.80, 32.28, 33.88, 35.95, 37.03, 37.80, 38.16, and 39.88. Figure 9A provides an X-ray powder diffraction pattern for Form IIb.

The DSC thermogram for Form IIb, shown in Figure 9B, indicates an onset of dehydration endotherm at about 64°C and an onset of crystal melting endotherm at about 197°C, at a scan rate of 10°C/minute.

The Raman spectral diagram for Form IIb, shown in Figure 9C, includes Raman Shift peaks (cm^{-1}) at approximately 993, 1265, 1362, 1431, 1464, 1561, 1589, and 1639.

Example 19: Polymorph Form IIIa of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form IIIa, a di-hydrate of the compound of formula VIII, is prepared by slurrying Form III in water (approximately 20-40 mg/mL) at ambient temperature for seven days, or by placing Form III in 93% relative humidity at ambient temperature for ten days. Form IIIa is confirmed by X-ray diffraction.

Form IIIa is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 6.81, 7.36, 8.71, 9.37, 9.80, 10.51, 13.31, 13.72, 14.72, 15.28, 17.60, 18.20, 19.09, 19.92, 20.48, 21.03, 22.27, 22.68, 23.84, 24.36, 24.86, 25.60, 26.16, 26.66, 27.33, 28.22, 29.41, 30.29, 31.48, 32.27, 33.60, 35.35, 36.22, and 38.21. Figure 10A provides an X-ray powder diffraction pattern for Form IIIa.

Example 20: Polymorph Form IIIb of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form IIIb, an anhydrous form of the compound of formula VIII, is prepared by drying Form IIIa (Example 10) at 50°C under vacuum. Form IIIb was confirmed by X-ray diffraction.

Form IIIb is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 6.28, 6.84, 7.36, 8.66, 9.66, 13.13, 13.80, 14.4718, 15.40, 17.21, 18.39, 19.46, 20.78, 21.56, 22.70, 24.81, 25.52, 26.79, 27.60, 28.80, 29.45, 30.32, 31.22, 33.47, 34.69, 37.16, 37.88, and 39.45. Figure 11A provides an X-ray powder diffraction pattern for Form IIIb.

The DSC thermogram for Form IIIb, shown in Figure 11B, indicates an onset of crystal melting endotherm at about 210°C, at a scan rate of 10°C/minute.

The Raman spectral diagram for Form IIIb, shown in Figure 11C, includes Raman Shift peaks (cm^{-1}) at approximately 993, 1267, 1311, 1326, 1378, 1436, 1466, 1481, 1563, 1592, and 1636.

Example 21: Polymorph Form IVa of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form IVa, a di-hydrate of the compound of formula VIII, is prepared by slurrying Form IV in water (approximately 20-40 mg/mL) at ambient temperature for seven days. Form IVa is light-stable under ICH high intensity light conditions. Form IVa is confirmed by X-ray diffraction and DSC.

Form IVa is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 4.85, 7.95, 9.85, 11.51, 12.80, 13.53, 14.56, 14.92, 15.80, 16.32, 17.43, 18.08, 18.44, 19.31, 20.08, 21.08, 21.61, 22.64, 23.24, 23.84, 24.48, 25.08, 26.24, 27.02, 27.92, 28.76, 30.12, 30.72, 31.40, 32.52, 34.07, 37.48, and 38.20. Figure 12A provides an X-ray powder diffraction pattern for Form IIb.

The DSC thermogram for Form IVa, shown in Figure 12B, indicates an onset of dehydration endotherm at about 63°C and an onset of crystal melting endotherm at about 123°C, at a scan rate of 10°C/minute.

Example 22: Polymorph Form Va of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form Va, a di-hydrate form of the compound of formula VIII, is prepared by slurrying Form V in water (approximately 20-40 mg/mL) at ambient temperature for seven days. Form Va is light-stable under ICH high intensity light conditions. Form Va is confirmed by X-ray diffraction.

Form Va is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 4.26, 4.82, 7.92, 8.42, 8.96, 11.45, 12.70, 13.40, 14.21, 15.21, 15.70, 16.64, 16.96, 17.30, 18.28, 19.16, 20.24, 21.14, 21.60, 22.56, 23.20, 23.80, 24.44, 24.96, 26.60, 27.08, 27.96, 28.56, 29.04, 30.62, 31.34, 32.27, 32.84, 33.92, 34.83, 35.90, 36.99, and 37.44. Figure 13A provides an X-ray powder diffraction pattern for Form Va.

The DSC thermogram for Form Va, shown in Figure 13B, indicates an onset of dehydration endotherm at about 74°C and an onset of crystal melting endotherm at about 211°C, at a scan rate of 10°C/minute.

The Raman spectral diagram for Form Va, shown in Figure 13C, includes Raman Shift peaks (cm^{-1}) at approximately 989, 1228, 1298, 1372, 1430, 1465, 1561, 1584, and 1641.

Example 23: Polymorph Form VI of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form VI, an anhydrous form of the compound of formula VIII, is prepared by dehydration of Form Ib, such as by heating Form Ib at 140°C for 10 minutes. Form VI was confirmed by X-ray diffraction. Form VI is very hygroscopic and can be readily converted back to Form Ib under ambient humidity.

Form VI is characterized by an X-ray powder diffraction pattern with peaks at the following approximate diffraction angles (2θ): 7.74, 10.00, 11.56, 12.85, 15.56, 16.04, 17.80, 18.47, 19.20, 20.43, 21.72, 22.16, 23.28, 24.00, 25.83, 26.79, 28.23, 29.88, 30.36, 31.36, and 39.69. Figure 14A provides an X-ray powder diffraction pattern for Form VI.

The DSC thermogram for Form VI, shown in Figure 14B, indicates an onset of crystal melting endotherm at about 179°C, at a scan rate of 10°C/minute.

The Raman spectral diagram for Form VI, shown in Figure 14C, includes Raman Shift peaks (cm^{-1}) at approximately: 965, 993, 1201, 1230, 1267, 1320, 1368, 1412, 1426, 1469, 1557, 1587, and 1647.

Example 24: Polymorph Form Ibm-2 of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

Form Ibm-2, which is a mixture of polymorph Form Ib and Form VI of the compound of formula VIII, is prepared by heating Form Ib (Example 7) at 50 °C under vacuum. Form Ibm-2 is confirmed by X-ray diffraction to be a mixture of polymorph Form Ib and Form VI.

Example 25: Amorphous Form of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

The amorphous form of the compound of formula VII, is prepared by drop-wise dilution in water (approximately 1:10 ratio) of the compound of formula VIII in polyethylene glycol 400 solution, or roto-vaporation of the compound of formula VIII in methanol or THF solution, or lyophilization of the compound of formula VIII in t-butanol solution.

The X-ray powder diffraction pattern of the amorphous form is characterized by a typical amorphous broad hump-peak from 4 to 40°, without any sharp peaks characteristic of crystalline forms. Figure 15A provides an X-ray powder diffraction pattern for the amorphous form.

The Raman spectral diagram for the amorphous form, shown in Figure 15B, includes Raman Shift peaks (cm^{-1}) at approximately 995, 1265, 1366, 1435, 1468, 1562, 1589, and 1640.

Example 26: Mixtures of 6-(3-Bromo-6-fluoro-1,3-dimethylpyrazole-5-carboxamide)-3-((E)-2-pyridin-2-yl-vinyl)-1H-indazole

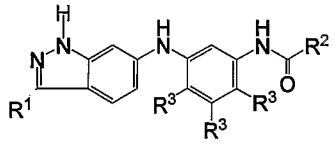
The crystalline and amorphous forms discussed above may also exist in mixtures, wherein the solid form exists as a mixture comprising at least two of the solid forms discussed above. For example, Form Ibm-2 is a meta-stable form that is a mixture of Forms Ib and VI. This meta-stable form can be prepared by dehydrating Form Ib under vacuum at temperatures of about 45 °C or greater. Partial hydration of Form VI will also result in the meta-stable Form Ibm-2. Form Ibm-2 will convert to Form Ib upon complete hydration under ambient humidity. Form Ibm-2 is characterized by an X-ray powder diffraction pattern with peaks as shown in Figure 16. This diffraction pattern matches the pattern that results from addition of the diffraction patterns of Form Ib and Form VI. The DSC thermogram for Form Ibm-2 indicates an onset of dehydration endotherm at about 73°C and an onset of crystal melting endotherm at about 177°C, at a scan rate of 10°C/minute.

While the invention has been illustrated by reference to specific and preferred embodiments, those skilled in the art will recognize that variations and modifications may be made through routine experimentation and practice of the invention. Thus, the invention is intended not to be limited by the foregoing description, but to be defined by the appended claims and their equivalents.

CLAIMS

What is claimed is:

1. A method for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is a group of the formula -CH=CHR^4 or –CH=NR^4, and R^1 is substituted with 0 to 4 R^5 groups;

R^2 is (C_1 to C_{12}) alkyl, (C_2 to C_{12}) alkenyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, (5 to 12-membered) heteroaryl, (C_1 to C_{12}) alkoxy, (C_6 to C_{12}) aryloxy, and R^2 is substituted with 0 to 4 R^5 groups;

each R^3 is independently hydrogen, halogen, or (C_1 to C_8) alkyl, and the (C_1 to C_8) alkyl is substituted with 0 to 4 R^5 groups;

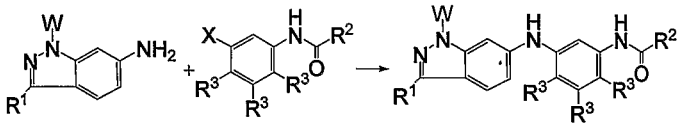
R^4 is (C_1 to C_{12}) alkyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, or (5 to 12-membered) heteroaryl, and R^4 is substituted with 0 to 4 R^5 groups;

each R^5 is independently halogen, (C_1 to C_8) alkyl, (C_2 to C_8) alkenyl, (C_2 to C_8) alkynyl,

-OH, -NO_2, -CN, -CO_2H, -O(C_1 to C_8 alkyl), (C_6 to C_{12}) aryl, (C_6 to C_{12}) aryl (C_1 to C_8) alkyl, -CO_2CH_3, -$CONH_2$, -OCH_2CONH_2, -NH_2, -SO_2NH_2, halo substituted (C_1 to C_{12}) alkyl, or –O(halo substituted (C_1 to C_{12}) alkyl);

comprising:

a) reacting a compound of formula II with a compound of formula III to provide a compound of formula IV:



II III IV

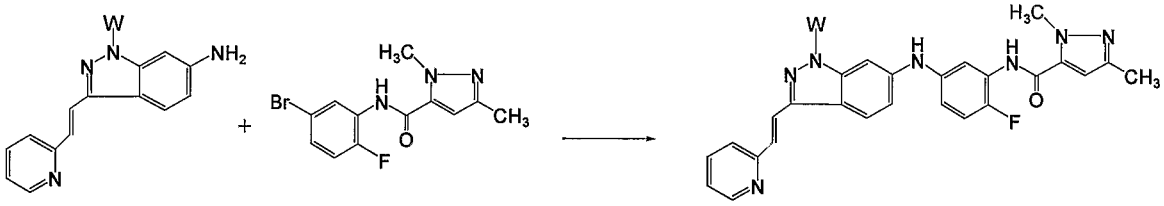
wherein the reaction occurs in the presence of a palladium catalyst such as $Pd_2(dba)_3$ and a phosphene ligand that complexes with the $Pd_2(dba)_3$ catalyst such as 2-(di-*t*-butylphosphino)biphenyl; and a base such as potassium carbonate, sodium carbonate, cesium carbonate, sodium *t*-butoxide, potassium *t*-butoxide, triethylamine or mixtures thereof; W is a protecting group; X is an activated substituent group; R^1, R^2, R^3, R^4, and R^5 are as described above; and

b) deprotecting the compound of formula IV to provide the compound of formula I.

2. The method of claim 1, further comprising a solvent in the reaction between the compound of formula II and the compound of formula III, wherein the reaction is carried out at about 100°C; W is a tetrahydropyran protecting group or is a trimethylsilylethoxymethyl protecting group; the activated substituent group X is chloride, bromide, or iodide.

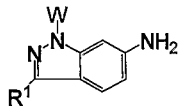
3. The method of claim 1, wherein W is a tetrahydropyran protecting group and the process of deprotecting comprises reacting the compound of formula IV with an acid such as methane sulfonic acid in an alcoholic solvent such as methanol, ethanol, n-propanol or isopropanol.

4. The method of claim 1, wherein the compound of formula II has formula V, the compound of formula III has formula VI, and the compound of formula IV has formula VII:



V VI VII

5. A method for preparing a compound of formula II:



II

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is a group of the formula -CH=CHR^4 or –CH=NR^4, and R^1 is substituted with 0 to 4 R^5 groups;

R^4 is (C_1 to C_{12}) alkyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, or (5 to 12-membered) heteroaryl, and R^4 is substituted with 0 to 4 R^5 groups;

each R^5 is independently halogen, (C_1 to C_8) alkyl, (C_2 to C_8) alkenyl, (C_2 to C_8) alkynyl,

-OH, -NO_2, -CN, -CO_2H, -O(C_1 to C_8 alkyl), (C_6 to C_{12}) aryl, (C_6 to C_{12}) aryl (C_1 to C_8) alkyl, -CO_2CH_3, -$CONH_2$, -OCH_2CONH_2, -NH_2, -SO_2NH_2, halo substituted (C_1 to C_{12}) alkyl, or –O(halo substituted (C_1 to C_{12}) alkyl);

W is a protecting group;

comprising:

a) protecting 6-nitro indazole with a nitrogen protecting group W;

b) functionalizing the C-3 position of the indazole ring with an R^1 group; and

c) reducing the 6-nitro group to a 6-amino group.

6. The method of claim 5, wherein the protecting group W is a tetrahydropyran protecting group or is a trimethylsilylethoxymethyl protecting group.

7. The method of claim 5, wherein the C-3 position of the indazole ring is functionalized by:

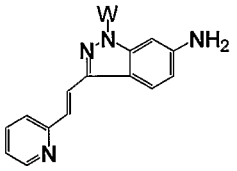
a) iodination with a metal halide to provide a N-1 protected (W) 3-iodo-6-nitro-indazole compound, and

b) coupling the N-1protected (W) 3-iodo-6-nitro-indazole compound with R^1 by a palladium catalyzed reaction.

8. The method of claim 5, wherein the metal halide is potassium iodide, and the palladium catalyzed reaction is a Heck reaction.

9. The method of claim 5, wherein R^1 is 2-vinyl pyridine.

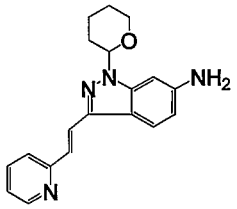
10. The method of claim 5, wherein the compound of formula II has formula IX:



IX

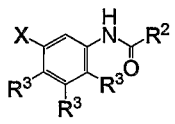
wherein W is a tetrahydropyran protecting group or is a trimethylsilylethoxymethyl protecting group.

11. The method of claim 5, wherein the compound of formula II has formula X:



X

12. A method for preparing a compound of formula III:



III

wherein:

R^2 is (C_1 to C_{12}) alkyl, (C_2 to C_{12}) alkenyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, (5 to 12-membered) heteroaryl, (C_1 to C_{12}) alkoxy, (C_6 to C_{12}) aryloxy, and R^2 is substituted with 0 to 4 R^5 groups;

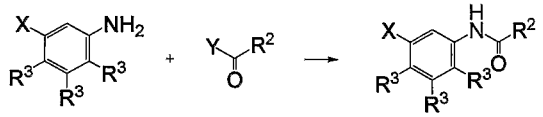
each R^3 is independently hydrogen, halogen, or (C_1 to C_8) alkyl, and the (C_1 to C_8) alkyl is substituted with 0 to 4 R^5 groups;

each R^5 is independently halogen, (C_1 to C_8) alkyl, (C_2 to C_8) alkenyl, (C_2 to C_8) alkynyl,

-OH, $-NO_2$, -CN, $-CO_2H$, -O(C_1 to C_8 alkyl), (C_6 to C_{12}) aryl, (C_6 to C_{12}) aryl (C_1 to C_8) alkyl, $-CO_2CH_3$, $-CONH_2$, $-OCH_2CONH_2$, $-NH_2$, $-SO_2NH_2$, halo substituted (C_1 to C_{12}) alkyl, or –O(halo substituted (C_1 to C_{12}) alkyl); and

X is an activated substituent group;

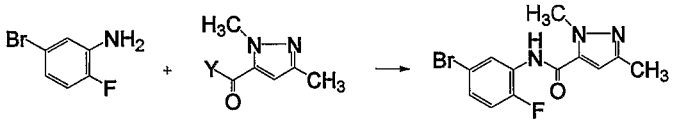
comprising, reacting a compound of formula XI with a compound of formula XII:



XI XII III

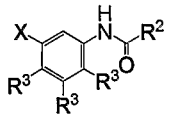
wherein Y is a leaving group, and X, R^2, and R^3 are as described above.

13. The method of claim 12, wherein the compound of formula XI has formula XIII, the compound of formula XII has formula XIV, and the compound of formula III has formula XV:



XIII XIV XV

14. The compound of formula III:



III

or pharmaceutically acceptable salt or solvate thereof, wherein:

R^2 is (C_1 to C_{12}) alkyl, (C_2 to C_{12}) alkenyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, (5 to 12-membered) heteroaryl, (C_1 to C_{12}) alkoxy, (C_6 to C_{12}) aryloxy, and R^2 is substituted with 0 to 4 R^5 groups;

each R^3 is independently hydrogen, halogen, or (C_1 to C_8) alkyl, and the (C_1 to C_8) alkyl is substituted with 0 to 4 R^5 groups;

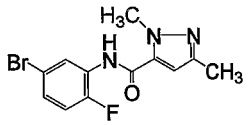
each R^5 is independently halogen, (C_1 to C_8) alkyl, (C_2 to C_8) alkenyl, (C_2 to C_8) alkynyl,

-OH, $-NO_2$, -CN, $-CO_2H$, -O(C_1 to C_8 alkyl), (C_6 to C_{12}) aryl, (C_6 to C_{12}) aryl (C_1 to C_8) alkyl,

$-CO_2CH_3$, $-CONH_2$, $-OCH_2CONH_2$, $-NH_2$, $-SO_2NH_2$, halo substituted (C_1 to C_{12}) alkyl, or –O(halo substituted (C_1 to C_{12}) alkyl); and

X is an activated substituent group.

15. The compound of claim 14 that has formula XV:



XV

or a pharmaceutically acceptable salt or solvate thereof.