METHODS FOR PREPARING INDAZOLE COMPOUNDS

Field of the Invention

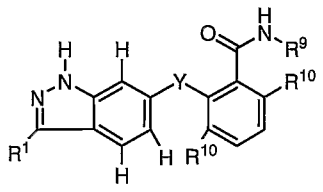
The present invention relates to methods for preparing indazole compounds, and intermediates thereof, which are useful as modulators and/or inhibitors of protein kinases.

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, each of 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 to C_8 alkyl);

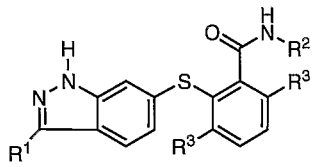
R^9 is a substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxyl, aryloxyl, cycloalkoxyl, -NH(C_1 to C_8 alkyl), -NH(aryl), -NH(heteroaryl), -N=CH(alkyl), $-NH(C=O)R^{11}$, or $-NH_2$, where R^{11} is independently selected from hydrogen, substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; and

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

In one aspect, the 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;

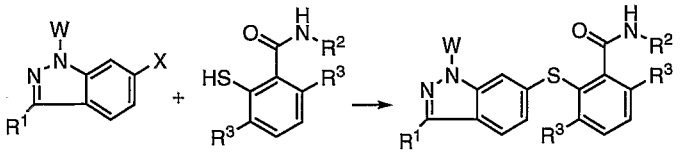
R^2 is (C_1 to C_{12}) alkyl, (C_3 to C_{12}) cycloalkyl, (5 to 12-membered) heterocycloalkyl, (C_6 to C_{12}) aryl, (5 to 12-membered) heteroaryl, (C_1 to C_{12}) alkoxy, (C_6 to C_{12}) aryloxy, (C_3 to C_{12}) cycloalkoxy, -NH(C_1 to C_8 alkyl), -NH(C_6 to C_{12} aryl), -NH(5 to 12-membered heteroaryl), -N=CH(C_1 to C_{12} alkyl), -NH(C=O)H, -NH(C=O)R^5, or $-NH_2$, 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; and R^1, R^2, and R^3 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 method 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 $Pd(dppf)Cl_2$-CH_2Cl_2.

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

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the base is cesium carbonate.

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, wherein the solvent is N, N-dimethyl formamide.

In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the reaction is carried out at about 80°C.

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

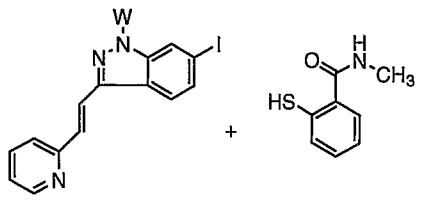
In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the activated substituent group X is chloride, bromide, or iodide.

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

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

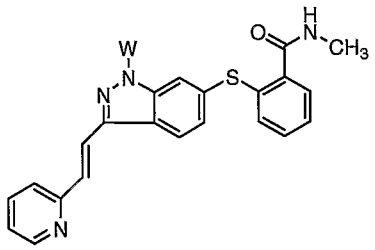
In another aspect, the invention relates to methods for preparing a compound of formula I, wherein the acid is methanesulfonic acid or is p-toluenesulfonic acid, and the alcoholic solvent is methanol, ethanol, n-propanol or isopropanol.

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:



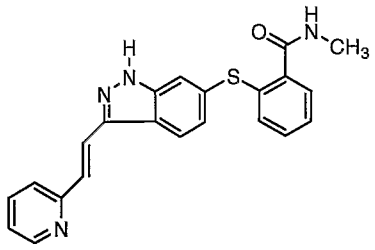
V VI

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



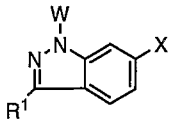
VII

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);

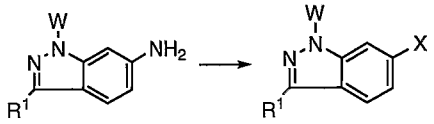
W is a protecting group; and

X is an activated substituent group;

comprising:

a) reacting a compound of formula IX with a diazotizing agent to form a diazonium salt; and

b) treating the diazonium salt with a metal halide,



IX II

wherein R^1, W and X are as described above.

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

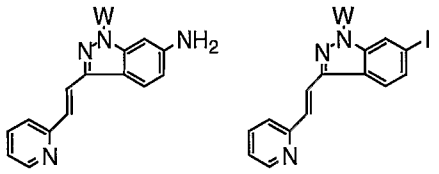
In another aspect, the invention relates to methods for preparing a compound of formula II, wherein the activated substituent group X is iodide.

In another aspect, the invention relates to methods for preparing a compound of formula II, wherein the diazotizing agent is sodium nitrite or t-butyl nitrite.

In another aspect, the invention relates to methods for preparing a compound of formula II, wherein the diazotizing agent is sodium nitrite, and the metal halide is potassium iodide.

In another aspect, the invention relates to methods for preparing a compound of formula II, further comprising a catalytic amount of iodine.

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



X V .

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. For example, 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. For example, 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." For example, 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, for example, in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3^{rd} 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. For example, 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, and can include 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. For example, 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. For example, in aryl iodides, the –I group is generally referred to as an activated

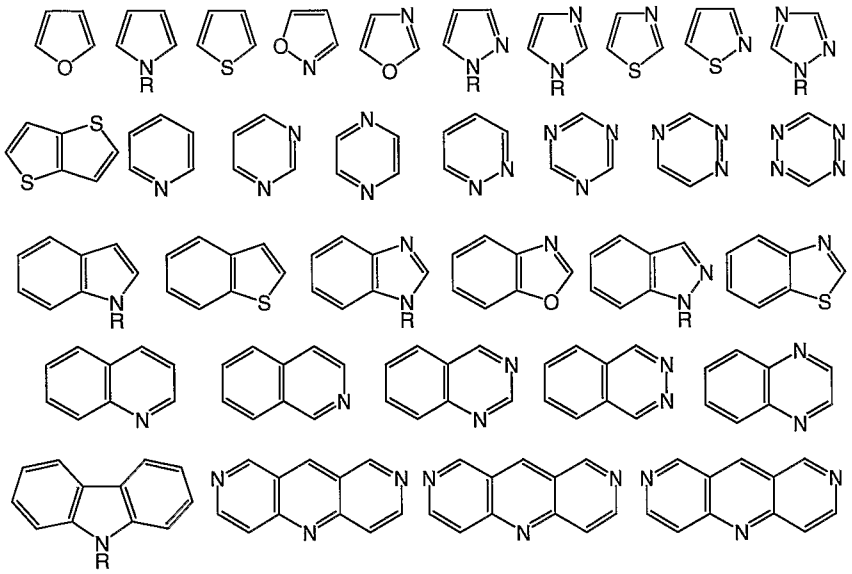
substituent group because it allows substitution reactions to take place at the aryl carbon. Suitable activated substituent groups are well known, and can include halides (chloride, bromide, iodide), activated hydroxyl groups (e.g., triflate, mesylate, and tosylate), and diazonium salts.

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.

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. For example, 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 (R)-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 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.

Detailed Description of the Invention

The 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 commonly 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. For example, the nucleophilic 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 de-protecting 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: tert-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: tert-butyldimethylsilyl), such groups may be applied and subsequently removed under known conditions. For example, such silyl protecting groups may be attached to nitrogen moieties and hydroxyl groups via their silyl chlorides (e.g., SEMCl: trimethylsilylethoxymethyl chloride, TBDMSCl: tert-butyldimethylsilyl chloride) in the presence of a suitable base (e.g., potassium carbonate), catalyst (e.g., 4-dimethylaminopyridine (DMAP)), and solvent (e.g, N,N-dimethyl formamide). 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. For example, 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. For example, 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. For example, such basic compounds include, but are not limited to, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium

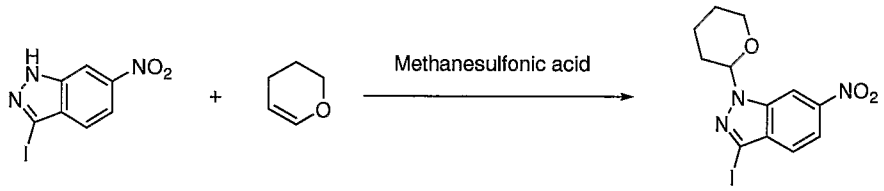
bicarbonate, sodium hydroxide, and potassium hydroxide. The cleavage of a silane protecting group may be conducted in an appropriate solvent that is compatible with the specific reaction conditions chosen and will not interfere with the desired transformation. Among such suitable solvents are, for example, 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. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, 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. For example, 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., dichloromethane). 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. 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 are, for example, 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. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, 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.



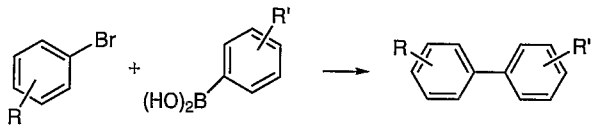
The various substituents contemplated for the compounds of formula I, and their intermediates, such as when R^1 is C_1-C_8 alkyl, -OH, -NO_2, -CN, -CO_2H, -O(C_1-C_8 alkyl), -aryl, -aryl(C_1-C_8 alkyl), -CO_2CH_3, -$CONH_2$, -OCH_2CONH_2, -NH_2, -SO_2NH_2, haloalkyl, or -O(haloalkyl), may require the 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 removal, is 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. For example, suitable solvents include, but are not limited to, ethyl acetate, isobutyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, dimethoxyethane, diisopropyl ether, chlorobenzene, 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.

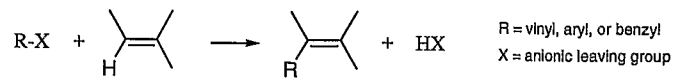
The Suzuki reaction is a palladium catalyzed coupling reaction in which the reaction of an optionally substituted aryl boronic acid or an optionally substituted heteroaryl boronic acid is coupled with a substituted aryl group or a substituted heteroaryl group, in which the substituents on the aryl group 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.

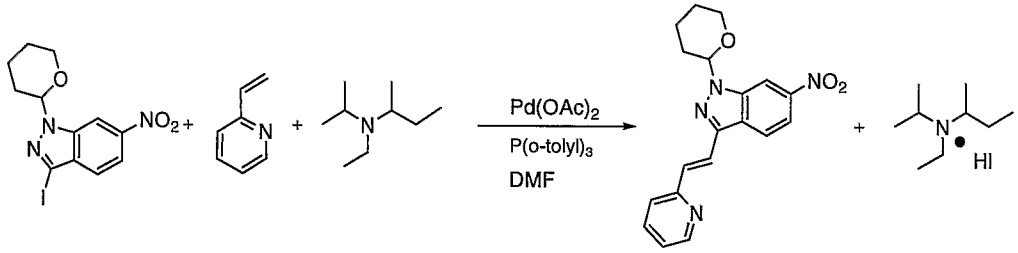


Palladium in the form of Pd(II) salts or complexes and Pd(0), with 1-5% mole concentration, is the most widely used metal catalyst for these types of reactions. A base such

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 $Ph_2P(CH_2)_{2-4}PPh_2$ 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.



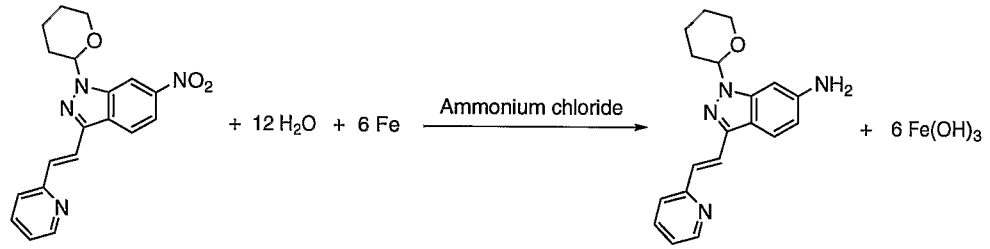
The compounds of formula I contain an indazole ring and phenyl ring that are bridged by a sulfide group. Such sulfide linked ring structures are obtained by coupling an indazole derivative which is substituted with an activated substituent group X (compound of formula II) with a thiophenol derivative (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.

Derivatization of the 6-nitroindazole ring compounds described above, with an activated substituent X group can be accomplished by reduction of the 6-nitro group to the 6-amino

indazole compound, followed by diazotization, and optionally, displacement of N_2 with a nucleophile such as a halide, water, or aqueous base.

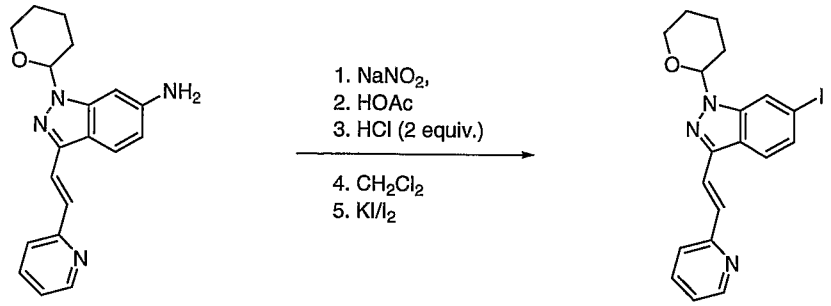
6-nitroindazole ring compounds can be converted to 6-amino indazole compounds by a reduction. The reduction of nitro groups to amino groups are well known. Metals, such as Fe (iron), Zn (zinc), Sn (tin) and In (indium) can be used with a H^+ source to reduce a nitro group to an amino group by a sequence 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.



Diazotizing reagents useful for converting an amino group to a diazonium salt include but are not limited to sodium nitrite and tert-butyl nitrite. These diazotizing reactions require the presence of a strong acid such as hydrochloric acid to convert the amino group into the diazonium salt. Alkali metal halides, such as lithium, sodium and potassium halides are a convenient source of nucleophilic halide anions. Hydroxyl groups are easily converted into triflate, mesylate and tosylate groups using standard procedures.

Treatment of 6-amino-3-(E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole with a diazotizing reagent, such as sodium nitrite in hydrochloric acid, provides the intermediate C-6 diazonium salt. Addition of a metal halide, such as potassium iodide (KI) and iodine (I_2) (I_2 is employed as a catalyst to facilitate the iodination process) provides 6-iodo-3-(E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole.



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 aryl sulfides to aryl compounds containing an activated substituent X are well known. For example, 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, for example: $Pd_2(dba)_3$ complexed to a phospine ligand such as 2-(tert-butyl$_2$-phosphino)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.

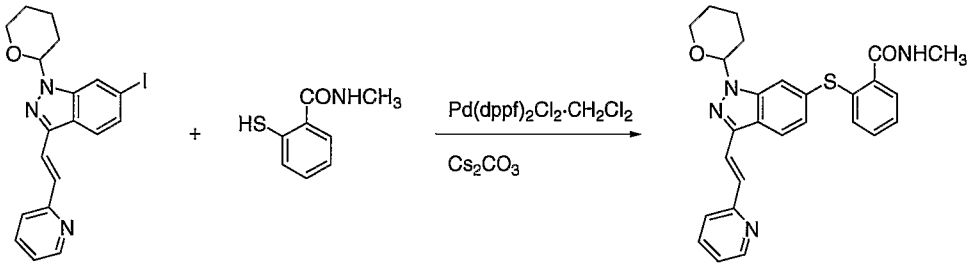
Bases which are useful in the above coupling reaction include but are not limited to potassium carbonate, sodium carbonate, cesium carbonate, sodium tert-butoxide, potassium tert-butoxide, potassium phenoxide, triethylamine, and the like, or mixtures thereof. Solvents may be used in such coupling reactions 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 known and may be found, for example, 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-iodo-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole is reacted with a catalytic amount of $Pd(dppf)Cl_2$-CH_2Cl_2 , cesium carbonate and 2-mercapto-N-methylbenzamide

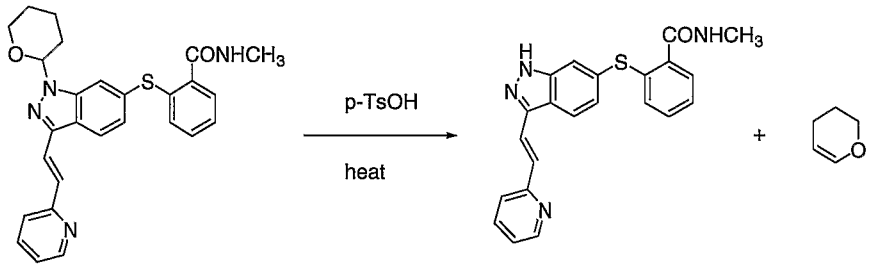
in DMF at 80 °C to provide 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole.



Other suitably functionalized indazole compounds that are substituted with an X group, especially an iodide group, would be expected to react similarly with a thiophenol 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.

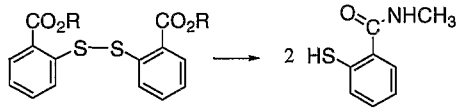
Deprotection of 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole using para-toluenesulfonic acid (p-TsOH) in methanol/water provides 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-H-indazole.



When a palladium catalyst is used in any of the above reaction steps, removal of residual palladium is an important objective. Such palladium removal can be accomplished using 10% cysteine-silica as discussed in a U.S. provisional patent application entitled Methods for the Removal of Heavy Metals, attorney docket number PC032215, filed on November 1, 2004, and is hereby incorporated by reference in its entirety. Palladium removal can also be combined with conditions that allow crystallization of the synthesized compounds in various polymorphic forms. For example, when a compound of formula I is prepared where R1 is 2-vinyl pyridine, R2 is methyl, and R3 are each hydrogen, the polymorphic form designated as Form IV can be produced by refluxing in tetrahydrofuran, N,N-dimethyl formamide, and methanol, followed by the addition of acetic acid and xylenes. The formation and characterization of Form IV, as well as

other polymorphs, is discussed in more detail in a U.S. provisional patent application entitled Polymorphic Forms of 6-[2-(methylcarboamoyl)phenylsulfanyl]-3-E-[2-(pyridine-2-yl)ethenyl]-indazole, attorney docket number PC019171, filed on November 1, 2004, and is hereby incorporated by reference in its entirety. This palladium removal process and polymorph control step is also described in greater detail in the Examples provided below.

2-mercapto-N-methylbenzamide can be prepared as follows. 2,2'-dithiosalicylic acid is treated with reagents such as thionyl chloride or oxalyl chloride in the presence of a suitable base such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, a trialkylamine, triethylamine for example, or a heteroaromatic base such as pyridine to provide the 2,2'-dithiosalicylic acid dichloride. Treatment of the dichloride compound with 2 M methylamine in THF provides 2,2'-dithio-N-methylbenzamide. Reduction of the disulfide linkage with sodium borohydride in ethanol provides 2 equivalents of 2-mercapto-N-methylbenzamide.



R = H
R = Cl
R = $NHCH_3$

The specific reaction conditions chosen will depend on the specific subject compound and reagents chosen. Other suitably functionalized thiophenol compounds may be generated using appropriately functionalized disulfides as starting materials. The resulting sulfides (compounds of formula III) should be protected from light to prevent disulfide formation. These sulfides may be isolated and further reacted with the compounds of formula II or they may be reacted with the compounds of formula II without isolation or further purification.

Another synthetic route to the compounds of formula I is provided in the Examples section below.

Examples

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 that are well known. Certain synthetic modifications may be done according to methods familiar to those of ordinary skill in the art.

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).

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

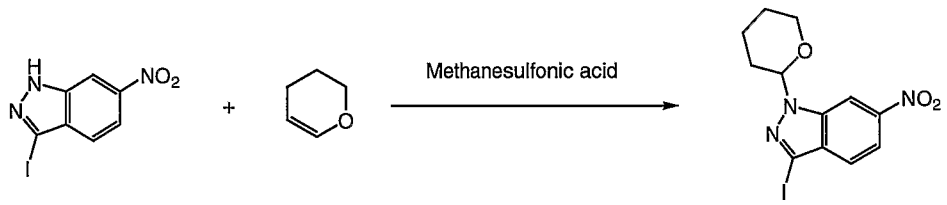
chloride, "H_3PO_4" means phosphoric acid, "CH_3SO_3H" means methanesulfonic acid, "Ac_2O" means acetic anhydride, "CH_3CN" means acetonitrile, "DHP" means 3,4-dihydro-2*H*-pyran.

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



6-Nitroindazole (45.08 Kg) is dissolved in DMF (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 DMF (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%).

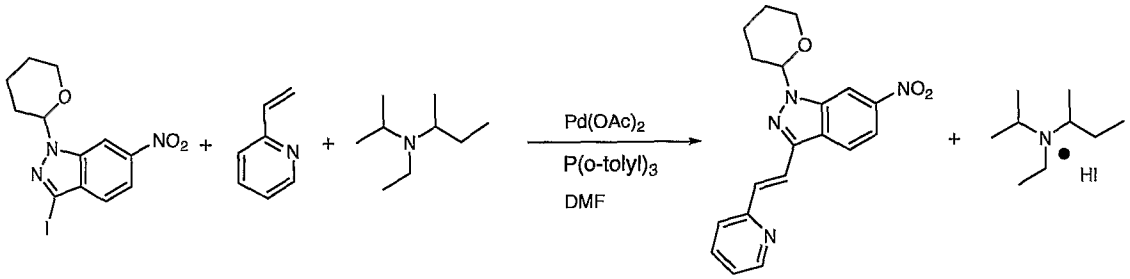
Example 2: Preparation of 3-iodo-6-nitro-1-(tetrahydropyran-2-yl)-1H-indazole



3-iodo-6-nitroindazole (74.6 Kg) is dissolved in methylene chloride (306 Kg) and THF (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

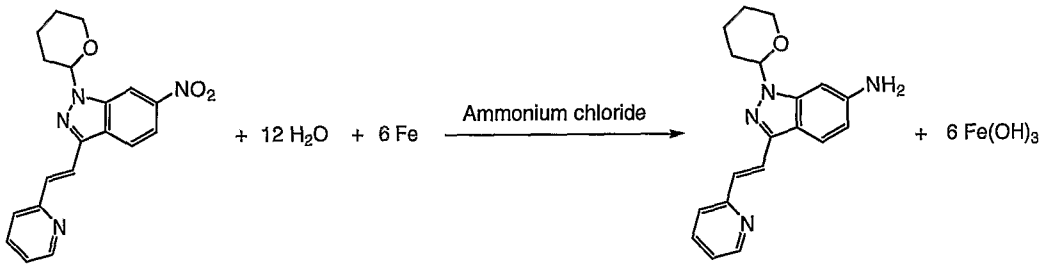
until the final volume is ca. 80 L. The resulting slurry is diluted with acetonitrile (60 Kg) and is agitated for 8 hours at -5°C. The slurry is filtered, and the solids are rinsed with cold acetonitrile (15 Kg). The solids are dried at room temperature under reduced pressure to provide 77.6 Kg of 3-iodo-6-nitro-1-(tetrahydropyran-2-yl)-1H-indazole (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 DMF (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).

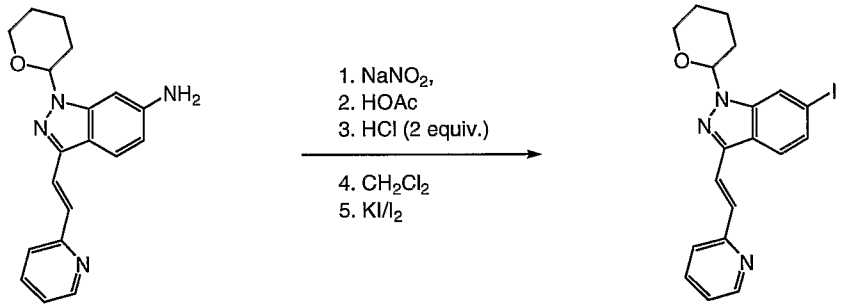
Example 4: Preparation of 6-amino-3-(E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole



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 THF (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 THF (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).

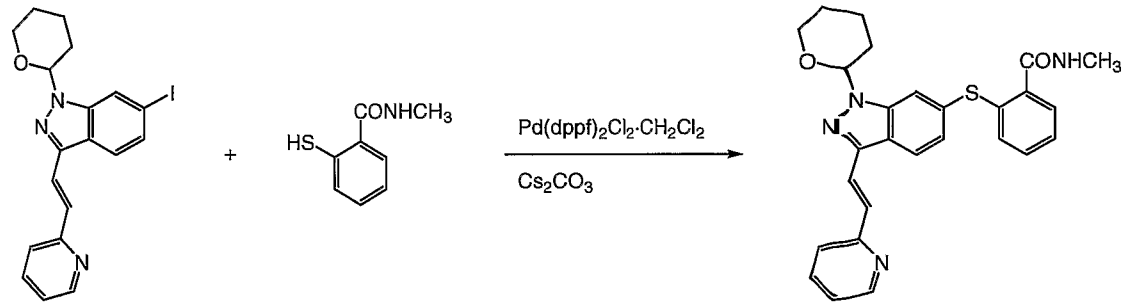
Example 5: Preparation of 6-iodo-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole



6-amino-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyran-2-yl)-1H-indazole (1 Kg) dissolved in acetic acid (6.5 L) is added over 1.5 hours to a solution of sodium nitrite (350 g) dissolved in water (3.0 L) at 0°C. The mixture is stirred for 1 hour at 0°C, and a solution of hydrochloric acid (560 mL diluted in 1 L of water) at 0°C is added over 15 minutes. The mixture is stirred for 1 hour at 0°C. The formation of the diazonium salt is monitored by HPLC. Methylene chloride (4 L) at 0°C is added over 10 minutes to the diazonium salt solution at 0°C, and a solution of potassium iodide (1.062 Kg) and iodine (396 g) dissolved in water (3 L) at 0°C is added over 1.5 hours. The reaction mixture is agitated for 3 hours at 0°C (until complete by HPLC). The mixture is then poured into a solution of 20% aqueous sodium hydrogen sulfite (2 Kg sodium thiosulfate in 10 L water) and methylene chloride (4 L) at 0°C, agitated, and the layers separated. The aqueous layer is extracted with methylene chloride (2 x 4 L) at 0°C and combined. A solution of 3 M aqueous sodium hydroxide (17 L) at 0°C is added over 40 minutes to the combined organic layers until the aqueous phase is basic (pH = 9 to 12). The phase separation is not clear due to the formation of an emulsion. A solution of 28% aqueous ammonium hydroxide (1 L) and water (2 L) is added, and the mixture is agitated for 30 minutes at 10°C, and allowed to settle for 24 hours to afford a clear phase separation. The layers are separated and the aqueous layer is extracted with methylene chloride (2 x 6 L). The combined organic layers (ca. 35 L) are loaded onto a glass fritted column (7 in. ID and 20 in. length) containing silica gel (4 Kg) and are eluted under nitrogen pressure with methylene chloride (8 L). The filtration is collected in three carboys and labeled as fractions 1, 2 and 3, respectively. The column is then eluted with 5% ethyl acetate in methylene chloride (32 L) and the filtration was collected in three carboys and labeled as

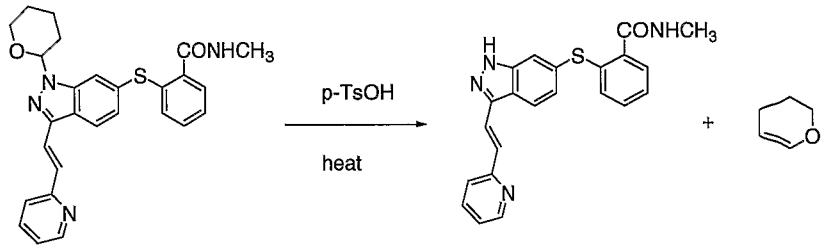
fractions 4, 5 and 6, respectively. The column is further eluted with 10% ethyl acetate in methylene chloride (24 L) and the filtration was collected in three carboys and labeled as fractions 7 and 8, respectively. Fractions 1 to 6 are combined, concentrated under reduced pressure, and dried in a vacuum oven for 24 to 48 hours (40°C and 25 mm Hg) to provide 1,110 g of 6-iodo-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole (75% yield with a purity of 97%).

Example 6: Preparation of 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole



6-iodo-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole (34.3 Kg) dissolved in DMF (162 Kg) is added to [1,1'-bis(diphenyl-phosphino)ferrocene]dichloro-palladium (II) complex with dichloromethane ($Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$) (2.9 Kg), and cesium carbonate (38.8 Kg). 2-mercapto-N-methylbenzamide (17.2 Kg) is added and the mixture is agitated for 4 to 16 hours at 80°C (until the reaction is complete by HPLC). The mixture is then cooled to 22°C and ethyl acetate (412 Kg) is added and the mixture is agitated for 1 hour at 22°C. Water (686 Kg) is added and the mixture is agitated at 22°C for 2 hours. The mixture is filtered and the solids are washed with ethyl acetate (62 Kg), water (137 Kg), and ethyl acetate (62 Kg). The solids are dissolved in THF (93.3 Kg) and methylene chloride (686 Kg), and the solution is eluted through a column containing sand (25 Kg, at the bottom of the column), Florisil (453 Kg, in the middle of the column) and sand (97.8 Kg, on the top of the column), with a solution of THF (15.4 Kg) and methylene chloride (113 Kg) 35°C, followed by five portions of THF (31 Kg) and methylene chloride (226 Kg) 35°C. The fractions containing the product are collected and concentrated under reduced pressure to a volume of ca. 103 L. Ethyl acetate (206 Kg) is added, and the solution is concentrated under reduced pressure to a volume of ca. 172 L. Water (69 g) is added and the solution is agitated for 2 hours at 22°C. The solids are filtered, washed with ethyl acetate (62 Kg), and dried in a vacuum oven for 24 to 48 hours (55°C and 25 mm Hg) to provide 20.2 Kg of 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole as a light brown solid (54% yield with a purity of 98%). The metal contents are 17.3 ppm for palladium and 42.5 ppm for iron. The product is light-sensitive and should be stored in the dark at 0°C.

Example 7: Preparation of 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-H-indazole



6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-(tetrahydropyroan-2-yl)-1H-indazole (20.2 Kg), p-toluene sulfonic acid monohydrate (40 Kg), methanol (111 Kg) and water (20 Kg) are combined and agitated for 1 to 5 hours at 64°C (until the deprotection is complete by HPLC analysis). The mixture is then cooled to 22°C and concentrated under reduced pressure to volume of ca. 90 L. Methanol (111 Kg) is added and the mixture is agitated for 1 hour at 64°C. Water (71 Kg) is added and the mixture is cooled to 22°C and concentrated under reduced pressure to a volume of ca. 100 L. The process is repeated to drive the reaction to completion by evaporation of the side-product (DHP) with water. Methanol (111 Kg) is added and the mixture is agitated for 1 hour at 64°C, diluted with water (71 Kg) and the mixture is agitated for 1 hour at 0°C. The mixture is filtered and the solids are washed with cold methanol (61 Kg). The solids are transferred to a reactor and ethyl acetate (61 Kg) is added. The mixture is agitated for 30 minutes at 65°C, cooled to 3°C, and the solids are filtered and washed with cold ethyl acetate (61 Kg). This sequence removes any residual methanol since trace amounts of methanol may prevent the formation of the desired polymorph form III during the neutralization step. The solids are transferred to a reactor, diluted with ethyl acetate (82 Kg), agitated for 3 minutes at 0°C, and neutralized by addition of 5% aqueous sodium bicarbonate solution (175 Kg) (aqueous phase pH ≥ 7). Caution: carbon dioxide is evolved. The slurry is agitated for 2 hours at 22°C and a sample is withdrawn (60 mL) to check the pH and to test for polymorph form. If the DSC indicates that the conversion of polymorph form VI to polymorph form III (~ ½ ethyl acetate solvate) is not complete, continue the agitation at 22°C and check DSC every 4 hours until the formation of polymorph form III is confirmed. A long period of agitation (ca. 16 hours) may be required for the complete polymorph conversion. Once the DSC indicates the formation of form III, the solids are filtered, washed with ethyl acetate (61 Kg), water (61 Kg), and ethyl acetate (61 Kg), and dried in a vacuum oven for 24 to 48 hours (40°C and 25 mm Hg) to provide 17.8 Kg of 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-H-indazole (98% yield with a purity of 98.8% by HPLC). The product is light sensitive and should be stored in the dark at 0°C.

Example 8: Polymorph Control of 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl) 1-H-indazole

If 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-H-indazole from Example 7 is an off-white solid (polymorph III), then proceed with Example 8a.

If 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-H-indazole from Example 7 is a pink solid (polymorph ??), then proceed with Example 8b.

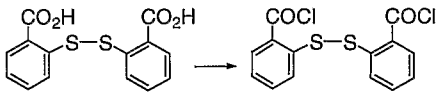
a. Conversion of Polymorph III to Polymorph IV

6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-H-indazole (polymorph III, 17.6 Kg) is added to acetic acid (115 Kg) and methanol (189.4 Kg) and the mixture is agitated for 1 hour at 68°C to dissolve the solids. The solution is filtered, diluted with xylenes (193 Kg), and concentrated at 68°C under reduced pressure to ca. 81 L. The addition of xylenes and subsequent concentration is repeated until the desired polymorph form IV is confirmed by an in-process DSC check. In some cases, additional agitation (ca. 16 hours) is needed for the complete conversion of polymorph form III to form IV. After conversion of polymorph form III to polymorph form IV, the solution is cooled to 50°C, the solids are filtered and rinsed with heptanes (44 Kg) and dried in a vacuum oven at 75°C for 24 hours to provide 13.4 Kg of 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-H-indazole polymorph form IV as an off-white solid (84% yield with a purity of 99% by HPLC). This product is light sensitive and should be stored in the dark at 0°C.

b. Color Removal and Polymorph Control

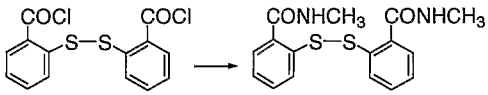
6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-H-indazole (pink tint, 2.423 Kg) is added to methanol (75 L) and the mixture is agitated for 1.5 hours at 15 to 25°C. The slurry is filtered, and the solids are washed with methanol (12.5 L) and dried in a vacuum oven at room temperature for 24 hours. The dried solids are added to a solution of acetic acid (100 L) at ca. 35°C, and the mixture is agitated for 45 minutes at ca. 35°C until a clear solution is obtained. The solution is cooled to room temperature and activated carbon (Darco G-60, 2.5 Kg) is added. The mixture is stirred at room temperature for 2 to 3 hours, filtered through Celite (3.0 Kg), and the filtrate is concentrated at 70°C under reduced pressure to a volume of 25 L. The solution is cooled to 25°C and xylenes (25 L) are added. The solution is heated to 70°C, and concentrated at 70°C under reduced pressure to a volume of 25 L. This procedure is repeated four times until solids appear. The slurry is cooled to room temperature, filtered, washed with xylenes (25 L) and heptanes (25 L), and the solids are dried in a vacuum oven for 24 hours (40 °C and 25 mm Hg) to provide 1.988 Kg of 6-(2-mercapto-N-methylbenzamide)-3-((E)-2-pyridin-2-yl-vinyl)-1-H-indazole as an off-white solid (79.5% yield with a purity of > 99% by HPLC).

Example 9: Preparation of 2,2' –dithiosalicylic acid dichloride



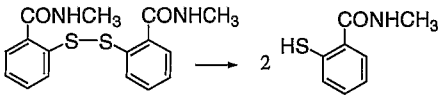
2,2'-dithiosalicylic acid (421 g) is dissolved in toluene (1.7 L) and thionyl chloride (212 mL) and DMF (7 mL) are added, and the mixture is agitated for 20 hours at 82°C. The mixture is then cooled to 70°C and hexanes (2 L) are added. Further cooling to 10°C provides a solid precipitate. The solids are filtered, washed with hexanes (2 x 250 mL), and dried in a vacuum oven for 24 hours (55°C and 25 mm Hg) to provide 390 g of 2.2' –dithiosalicylic acid dichloride (97% yield with a purity of 80% by ^{1}H NMR/DMSO).

Example 10: Preparation of 2,2'-dithio-N-methylbenzamide



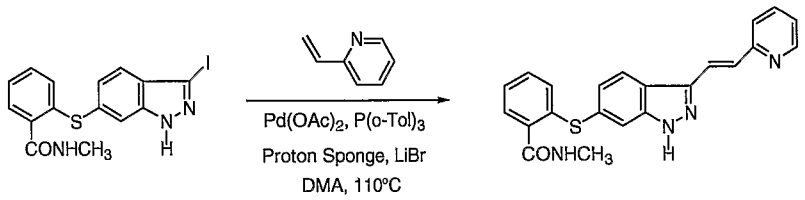
2,2'-dithiosalicylic acid dichloride (90 g) dissolved in THF (500 mL) is added to a solution of 2 M methyl amine in THF (655 mL) in over 40 minutes at 0 °C, and agitated at room temperature for 16 hours. The mixture is then diluted with water (200 mL) and the resulting slurry is filtered. The solids are washed with water (2x 50 mL), dried in a vacuum oven for 16 hours (55°C and 25 mm Hg) to provide 50 g of 2,2'-dithio-N-methylbenzamide (65% yield with a purity of 86% by HPLC).

Example 11: Preparation of 2-mercapto-N-methylbenzamide



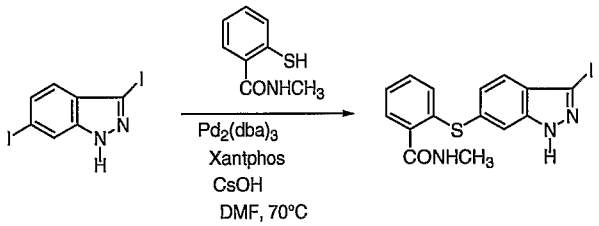
2,2'-dithio-N-methylbenzamide (967.2 g) is suspended in ethanol (9.0 L) and cooled to 0°C. Sodium borohydride (253 g) is added in portions over 4 hours, and the mixture is agitated for 5 hours at 0°C. 3 M hydrochloric acid (3.15 L) is then added to the mixture in over 15 minutes which adjusted the pH to 1.73. The mixture is concentrated under reduced pressure and 45°C to remove the ethanol. The concentrate is diluted with ethyl acetate (8 L) and water (4 L) and agitated for 20 minutes. The layers are allowed to separate (30 minutes), and the aqueous layer is removed. Solids and an emulsion remain in the organic layer. Water (1 L) is added to the organic layer and the mixture is agitated for 20 minutes. The aqueous layer is removed and a solution of saturated aqueous sodium chloride (3 L) is added to the organic layer. The mixture is agitated and the layers are separated. The organic layer is dried over sodium sulfate, filtered, and evaporated to a volume of ~4L before solids began to form. Heptanes (2 L) are added to the concentrate and the mixture is evaporated to provide 701.3 g of 2-mercapto-N-methylbenzamide (72% yield with a purity of 95% by HPLC). HPLC of this material showed only 1% of the disulfide present. Avoid exposure to air as this material readily forms the disulfide.

Example 12: Preparation of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-E-[2-(pyridine-2-yl)ethenyl]indazole



2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide (239.19 g), 2-vinylpyridine (75.7 mL, 702 Mmol), $Pd(OAc)_2$ (6.56 g), $P(o\text{-}Tol)_3$ (23.12 g), Proton Sponge (187.82 g), LiBr (314.59 g), and DMA (3.1L, 3.5 mL/g) were added to a 5 L 3-neck flask, equipped with a mechanical stirrer and a temperature probe. The mixture was degassed three times by alternately connecting to house vacuum and nitrogen. The mixture was then heated to 110 °C in one hour and the temperature was maintained at 110 °C for 24 hours, at which time all of the 2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide was consumed (HPLC). After cooling, the mixture was transferred to a 22 L extractor and followed by the addition of 5.5 L of CH_2Cl_2, 5.5 L of water and 275 mL of 37% aqueous HCl. After agitation and partitioning, the organic phase was extracted twice with 2.0 L of water and 100 mL of 37% HCl. At this stage, the organic phase (HPLC) did not contain any significant amount of the final product (HPLC), and was discarded. The combined aqueous layers were treated with 2.2 L of toluene, followed by the addition of 1.05 L of 28% NH_4OH over 45 minutes of time (via addition funnel). A thick precipitate formed at this stage. The resulting mixture was allowed to stir for approximately 48 hours. The mixture was then filtered and sucked dry. The cake was triturated with 3.5 L of toluene, stirred overnight, filtered and sucked dry. The cake was then transferred to a glass dish and dried at 50 °C under house vacuum overnight to afford 160.20 g of the final product.

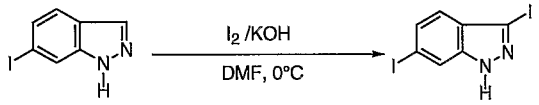
Example 13: Preparation of 2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide



3,6-diiodoindazole (250.00 g), 2-mercapto-N-methylbenzamide (118.48 g), $Pd_2(dba)_3$ (9.28 g), Xantphos (11.73 g), DMF (2.5 L, 10 mL/g), followed by CsOH were added sequentially to a 5 L four-neck flask equipped with a mechanical stirrer and a temperature probe. The reaction mixture was then stirred. The dark mixture was degassed three times by alternately connecting to house vacuum and then nitrogen. The mixture was heated to 70 °C over a period of 30 minutes and maintained at the same temperature for fours, at which time HPLC of the

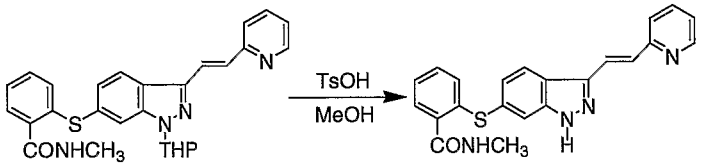
aliquot indicated that the 3,6-diiodoindazole was less than 3%. After cooling, the mixture was poured into a mixture of 7.5 L of water, 1.25 L of toluene and 1.25 L of CH_2Cl_2 in a 22 L extractor. The mixture was allowed to stir at ambient temperature overnight. A thick precipitate formed overnight. The mixture was filtered and the cake was sucked dry. The cake was further dried at 35 °C under house vacuum for six hours to afford 216 g of the final product. The mother liquor was then extracted with 1.5 L of EtOAc. After partitioning, the aqueous layer was discarded. The organic layer was washed twice each with 2 L of water and concentrated. The residue was treated with 250 mL of CH_2Cl_2 and stored overnight. A thick precipitate formed overnight. The mixture was filtered and the cake was sucked dry. The cake was dried at 35 °C under house vacuum overnight to afford 24.71 g of the final product. The combined yield was 241 g of the final product. The material showed satisfactory purity and was used in the next step without further purification. ^{1}H NMR 300MHz, DMSO ppm: 13.53 (s, 1H), 8.35 (q, J=4.7 Hz, 1H), 7.56 (s, 1H), 7.51-7.40 (m, 2H), 7.36-7.23 (m, 3H), 7.13 (dd, J=8.5, 1.3 Hz, 1H), 7.06-7.01 (m, 1H), 2.76 (d, J=4.7 Hz, 3H).

Example 14: Preparation of 3,6-diodoindazole



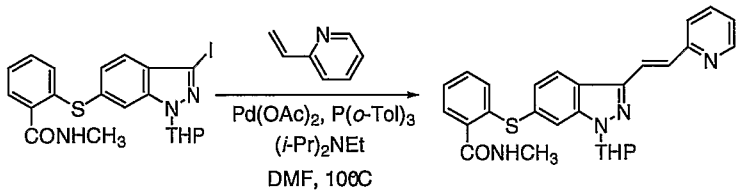
An aqueous solution of $NaHSO_3$ was prepared by adding 13.6 g of solid $NaHSO_3$ into 250 mL of DI water with strong stirring. 6-iodoindazole (30.0 g), followed by DMF (60 mL) were added to a 500 mL three-neck flask that was fitted with a mechanical stirrer, a temperature probe, and a 100 mL dropping funnel. After the stirring had begun, the flask was immersed in an ice/water bath. After 30 mintues, KOH was added in one portion, and the resulting mixture was stirred for an additional 30 minutes. A solution of 54.3g of I_2 in 55 mL of DMF (total volume was 71 mL) was added to the dropping funnel and the run-in started. After 30 minutes, 42 mL of the solution had been added to the reaction mixture. The addition was stopped and an aliquot sample was taken and analyzed with HPLC (TFASH method), which indicated that there was still 6-iodoindazole present. After an additional 10 mL of the iodine/DMF solution was added, the second aliquot sample showed that all the starting 6-iodoindazle was consumed. A solution of 13.6g of $NaHSO_3$ in DI water was added slowly to the reaction mixture. At this stage the dark solution became a yellow suspension. After stirring for one hour, the mixture was filtered and the cake was washed with 200 mL of water and 200 mL of hexanes. The cake was sucked dry and further dried in a vacuum oven (25 inch vacuum/60°C) for 18 hours to afford 38.60 g of the final product as a tan solid. ^{1}H NMR 300MHz, DMSO ppm: 7.96 (s, 1H), 7.46 (d, J=8.4 Hz, 1H), 7.24 (d, J=8.4 Hz, 1H), 3.33 (s, 1H).

Example 15: Final deprotection step to produce 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-E-[2-(pyridine-2-yl)ethenyl]indazole



N-1 THP 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-E-[2-(pyridine-2-yl)ethenyl]indazole (355 g) was suspended in 2,485 mL of methanol, after which p-toluenesulfonic acid monohydrate (718 g) was added. The mixture was then heated to 65 °C (hard reflux) for 4 hours under argon while the reaction was monitored by HPLC (gluco method). Heating continued until less than 1% of the N-1 THP protected starting material persisted. The heating was then removed and the reaction was cooled to room temperature. The solid was filtered and the wet cake was washed with methanol (2 volumes, 710 mL) then the solids were rinsed with ethyl acetate (2 volumes, 710 mL). The wet cake was transferred to a reactor containing sodium bicarbonate (126.84 g), deionized water (1800 mL), and ethyl acetate (975 mL), which was then stirred for 2 hours at 20°C. The solids were filtered and washed with 5 volumes of deionized water (1800 mL), then with 2 volumes of ethyl acetate (760 mL), and then dried in a vacuum oven at 40°C for 16 hours. The isolated yield for the reaction was 92.5% (274 g). The isolated material was identified as crystalline Form III free base (0.5 ethyl acetate solvate). ^{1}H NMR, 300 MHz, (DMSO-D6), ppm; 13.35 (1 H, s), 8.60 (1 H, d, J=3.8 Hz), 8.39 (1 H, m), 8.23 (1 H, d, J=8.5 Hz), 7.95 (1 H, d, J=16.4 Hz), 7.82 (1 H, ddd, J=7.7, 7.6, 1.8 Hz), 7.67 (1 H, d, J=7.8 Hz), 7.60 (a H, s), 7.57 (1 H, d, J=16.4 Hz), 7.49 (1 H, dd, J=7.1, 1.6 Hz), 7.35-7.26 (3 H, m), 7.19 (1 H, d, J=8.4 Hz), 7.04 (1 H, d, J=7.8 Hz), 2.77 (3 H, d, J=4.6 Hz). ^{13}C NMR, 75 MHz, (DMSO-D6) ppm: 168.23, 155.18, 149.81, 142.35, 142.22, 137.31, 136.00, 132.89, 130.64, 130.36, 129.51, 128.14, 126.50, 125.93, 124.08, 123.01, 122.85, 122.12, 120.642, 115.08, 26.45.

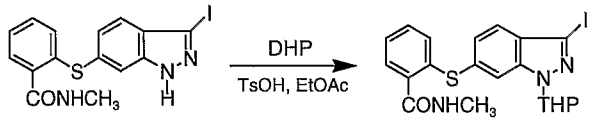
Example 16: Preparation of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-E-[2-(pyridine-2-yl)ethenyl]indazole using the tetrahydropyranyl protecting group



N-1 THP 2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide (21.77 g), 2-vinylpyridine (5.92 mL, 54.9 Mmol), $Pd(OAc)_2$ (0.96 g), $P(o\text{-}Tol)_3$ (3.42 g), $(i\text{-}Pr)_2NEt$ (11.3 mL, 64.9 Mmol), and N,N-dimethylformamide (550 mL) were added to a 1 L 3-neck flask, equipped with a mechanical stirrer and a temperature probe. The mixture was then degassed three times by alternately connecting to house vacuum and nitrogen. The mixture was heated to 100 °C and

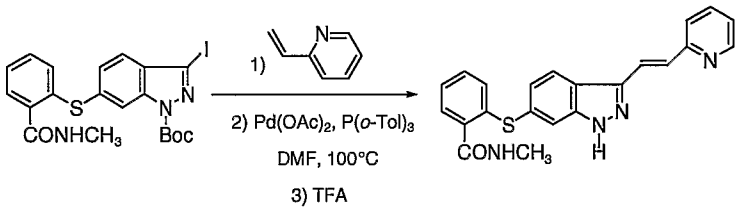
the temperature was maintained at 100 °C overnight, at which time all the starting material was consumed (HPLC). After cooling, the mixture was poured into 800 mL of saturated $NaHCO_3$ and 400 mL of EtOAc was added. The mixture was stirred for half an hour at which time a thick precipitate formed. The solid was filtered off and the filtrate was allowed to partition. After partitioning, the aqueous layer was extracted twice with 300 mL of EtOAc. The combined organic layers were washed twice with water, dried over $MgSO_4$ and concentrated. The residue crystallized on standing at room temperature. The solid was treated with 20 mL of EtOAc and filtered. The cake was allowed to air-dry overnight and afforded 17.66 g of the final product.

Example 17: Preparation of N-1 THP-protected 2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide



A mixture of 2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide (24.65 g), dihydropyran (5.50 mL, 60.3 Mmol), and $TsOH \cdot H_2O$ (1.146 g) in 600 mL of EtOAc was heated at 60 °C overnight. After cooling, the mixture was diluted with 500 mL of EtOAc, washed with $NaHCO_3$ (200 mL), dried over $MgSO_4$ and then concentrated *in vacuo*. The residue was pre-adsorbed onto silica gel and subjected to flash chromatography, using hexanes/EtOAc (2:1, 1:1, 1:2, 1:3) to yield 21.77 g of the final product.

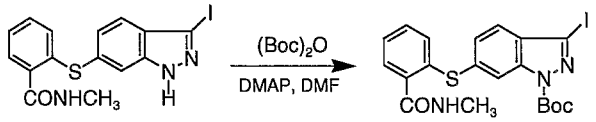
Example 18: Preparation of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-E-[2-(pyridine-2-yl)ethenyl]indazole using the *tert*-butoxycarbonyl protecting group



N-1 Boc 2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide (510 mg), and 2-vinylpyridine (0.14 mL, 1.3 Mmol) were added to a 100 mL 3-neck flask, equipped with a stirring bar and a temperature probe. The mixture was then degassed three times by alternately connecting to house vacuum and nitrogen. The mixture was allowed to stir for two hours, after which an aliquot indicated that only the starting material was present (HPLC). Initially, $Pd[P(t\text{-}Bu)_3]_2$ was used as a catalyst (9.28 g), along with 20 mL of DMF, and 124 mL of Cy_2NMe (711 Mmol) at room temperature for 2 hours, but the reaction did not work. Subsequently, it was found that when $Pd(OAc)_2$ was used as the catalyst, along with P(o-Tol)$_3$, the reaction worked. However, the role of the $Pd[P(t\text{-}Bu)_3]_2$ catalyst in the overall reaction could not be excluded. Accordingly, 22 mg of $Pd(OAc)_2$ and 91 mg of P(*o*-Tol)$_3$ were then added to the flask and the

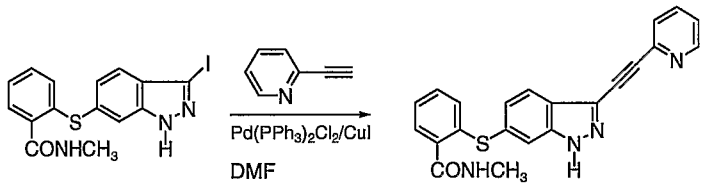
mixture was degassed again by alternately connecting to house vacuum and nitrogen three times. The mixture was heated to 100 °C and the temperature was maintained at 100 °C overnight, at which time all the starting material was consumed (HPLC). TFA (1.0 mL, 13.0 Mmol) was added to remove the Boc protecting group. After cooling, the mixture was poured into a mixture of 100 mL of water and 100 mL of EtOAc. After partitioning, the aqueous layer was extracted twice with 50 mL of EtOAc. The combined organic layers were washed twice with water, dried over $MgSO_4$ and concentrated. The residue was pre-adsorbed onto silica and subjected to gradient flash chromatography (Hexanes/EtOAc, 1:3, 1:4, EtOAc, EtOAc/MeOH, 100:1, 50/1) to yield 155 mg of the final product.

Example 19: Preparation of N-1 Boc 2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide



$(Boc)_2O$ (1.18 g) was added in small portions to a solution of 2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide (2.20 g), dimethylamino pyridine (66 mg), and N,N-dimethylformamide (22 mL), which was chilled in an ice-water bath. At the completion of the addition, HPLC of the aliquot indicated that all the 2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide was consumed. The reaction mixture was poured into a mixture of 100 mL of EtOAc and 100 mL of water. After partitioning, the aqueous layer was extracted two more times with 50 mL of EtOAc. The combined organic layers were washed twice with water, dried over $MgSO_4$ and concentrated. The residue was chromatographed using Hexanes/EtOAc (1:1, 1:2, 1:4, 0:1) to afford 1.35 g of the final product.

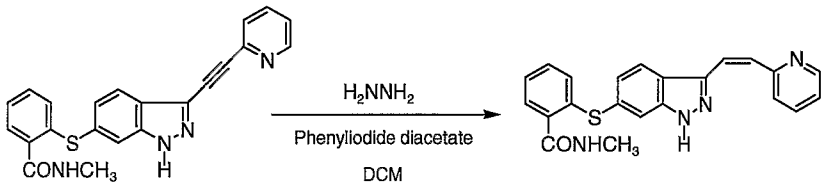
Example 20: Preparation of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-[2-(pyridine-2-yl)ethynyl]indazole



2-(3-Iodo-1H-indazol-6-ylsulfanyl)-N-methyl-benzamide (2.30 g), 2-ethynylpyridine (0.25 mL), $Pd(PPh_3)_2Cl_2$ (128 mg), CuI (64 mg), $(i\text{-}Pr)_2NEt$ (0.50 mL), and N,N-dimethylformamide (15 mL) were added to a 50 mL 3-neck flask, equipped with a stirring bar and a temperature probe. The mixture was degassed by alternately connecting to house vacuum and nitrogen three times, and heated at 66 °C for one hour. To the warm mixture was added 0.16 mL of 2-ethynylpyridine and 0.30 mL of $(i\text{-}Pr)_2NEt$. The resulting mixture was allowed to stir at 66 °C overnight, at which time HPLC indicated that all the starting material was consumed. After cooling, the mixture was diluted with 100 mL of dichloromethane and washed with water. To the organic layer was added

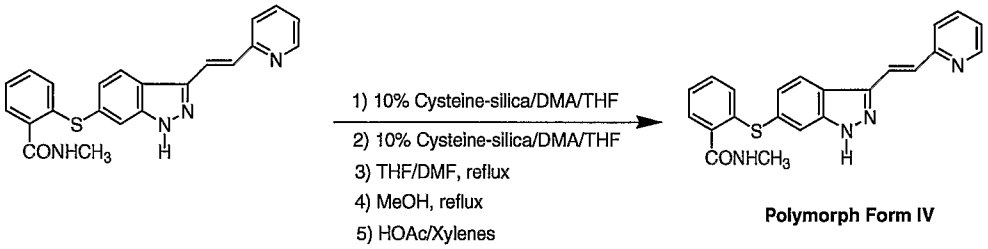
10 g of silica and agitated vigorously. The mixture was then filtered and the filtrate was discarded. The silica was then washed with tetrahydrofuran/dichloromethane (discarded) and followed by pure tetrahydrofuran. The tetrahydrofuran solution was concentrated *in vacuo* to yield 0.95 g of the final product.

Example 21: Preparation of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-Z-[2-(pyridine-2-yl)ethenyl]indazole



To a 100 mL 3-neck flask containing a solution of 0.95 g of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-[2-(pyridine-2-yl)ethynyl]indazole was added 2.5 g of phenyliodide diacetate followed by 1.0 mL of $H_2NNH_2 \cdot H_2O$. After the bubbling had settled, more phenyliodide diacetate and $H_2NNH_2 \cdot H_2O$ were added in small portions, until LC/MS indicated the disappearance of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-[2-(pyridine-2-yl)ethynyl]indazole and the formation of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-Z-[2-(pyridine-2-yl)ethenyl]indazole.

Example 22: Palladium removal and polymorph control of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-E-[2-(pyridine-2-yl)ethenyl]indazole



To a 12 L 3-neck flask, equipped with a mechanical stirrer, was added 160.20 g of 6-[2-(methylcarbamoyl)phenylsulfanyl]-3-E-[2-(pyridine-2-yl)ethenyl]indazole and 1.6 L of DMA and 1.6 L of THF. After stirring for 20 minutes, the mixture became homogeneous. To the clear solution was added 800.99 g of 10% cysteine-silica and the resulting mixture was allowed to stir at room temperature overnight.

The mixture was filtered through a medium sintered glass fritted funnel, and the cake was washed with a solution of 500 mL of DMA and 500 mL of THF. The cake was further washed with 2.0 L of THF and the filtrate was collected into a separate flask. The volatile parts in the latter filtrate were removed *in vacuo* and the residue was combined with the main filtrate. The combined filtrate was recharged back into the 12 L flask, followed by 800 g of 10% cysteine-silica. The flask was equipped with a mechanical stirrer and stirred over the weekend at room temperature.

The mixture was then filtered through a medium sintered glass fritted funnel and the silica was washed with a mixture of solvents of 500 mL of DMA and 500 mL of THF, followed by 3.0 L of THF. The volatile parts in the filtrate were removed *in vacuo* and the remaining solution was transferred to a 22 L 3-neck flask and treated with 12 L of water (added over a 20 minute period of time), a thick precipitate formed at this stage. After stirring overnight, the mixture was filtered and the cake was washed with 2.0 L of water and sucked dry.

The cake was charged to a 5 L 3-neck flask, followed by 1.6 L of THF and 160 mL of DMF. The flask was equipped with a mechanical stirrer, a reflux condenser and the mixture was heated at reflux for 8 hours. After cooling overnight, the mixture was filtered through sharkskin filter paper and sucked dry.

The cake was charged to a 5 L 3-neck flask and 1.6 L of MeOH was added. The flask was equipped with a mechanical stirrer, a water condenser and the contents were heated at reflux for 6 hours. After cooling overnight, the mixture was filtered through sharkskin filter paper and sucked dry.

The cake was dissolved into 1.6 L of HOAc with the assistance of gentle heating in the water bath of a rotary evaporator. The solution was filtered through #3 filter paper and the total volume of the filtrate was reduced to ~500 mL in volume on the rotary evaporator at 60 °C/60 mmHg. At this stage, the bulk of the mixture remained a yellow solution and a small amount of precipitate formed. To the flask was charged 500 mL of xylenes (precipitate formed) and the total volume was reduced to ~500 mL in volume on the rotary evaporator at 60°C/60 mmHg. The process was repeated two more times. After cooling, the mixture was filtered, the cake was washed with 500 mL of xylenes and sucked dry. The cake was transferred to a glass dish and further dried at 80°C/27 inch vacuum overnight.

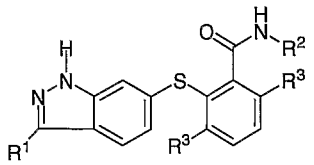
The cake was off-white in color and weighed 108.38g. X-ray powder diffraction analysis indicated that a crystalline form was present, which was characterized as Form IV by a powder X-ray diffraction pattern comprising peaks at the following approximate diffraction angles (2θ): 8.9, 12.0, 14.6, 15.2, 15.7, 17.8, 19.2, 20.5, 21.6, 23.2, 24.2, 24.8, 26.2, and 27.5.

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_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, (C_3 to C_{12}) cycloalkoxy, -NH(C_1 to C_8 alkyl), -NH(C_6 to C_{12} aryl), -NH(5 to 12-membered heteroaryl), -N=CH(C_1 to C_{12} alkyl), -NH(C=O)H, -NH(C=O)R^5, or -NH_2, and R^2 is substituted with 0 to 4 R^5 groups;

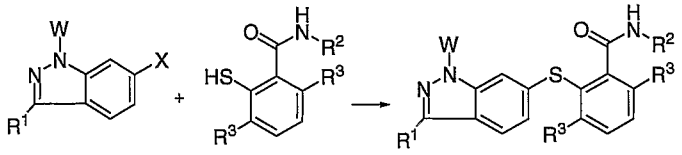
each R^3 is independently hydrogen, halogen, or (C_1 to C_8) alkyl, and the (C_1 to C_8) alkyl is substituted with 0 to 4 R^5 groups;

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; and R^1, R^2, and R^3 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, wherein the catalyst is a palladium catalyst.

3. The method of claim 2, wherein the catalyst is $Pd(dppf)Cl_2$-CH_2Cl_2.

4. The method of claim 1, wherein the base is selected from the group consisting of potassium carbonate, sodium carbonate, cesium carbonate, sodium t-butoxide, potassium t-butoxide, triethylamine, and mixtures thereof.

5. The method of claim 4, wherein the base is cesium carbonate.

6. The method of claim 1, further comprising a solvent in the reaction between the compound of formula II and the compound of formula III.

7. The method of claim 6, wherein the solvent is N, N-dimethyl formamide.

8. The method of claim 1, wherein the reaction is carried out at about 80°C.

9. The method of claim 1, wherein W is a tetrahydropyran protecting group or a trimethylsilylethoxymethyl protecting group.

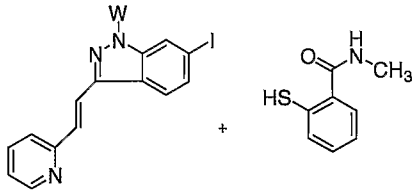
10. The method of claim 1, wherein the activated substituent group X is chloride, bromide, or iodide.

11. The method of claim 10, wherein the activated substituent group X is iodide.

12. The method of claim 1, wherein the protecting group W is tetrahydropyran, and the process of deprotecting comprises reacting the compound of formula IV with an acid in an alcoholic solvent.

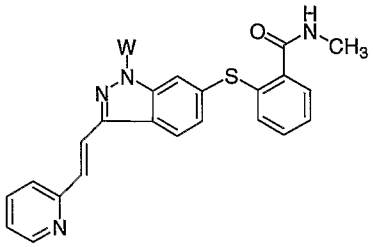
13. The process of claim 12, wherein the acid is methanesulfonic acid or is p-toluenesulfonic acid, and the alcoholic solvent is methanol, ethanol, n-propanol or isopropanol.

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



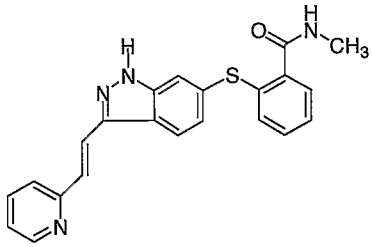
V VI

15. The method of claim 1, wherein the compound of formula IV has formula VII:



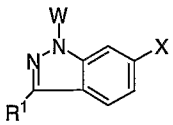
VII

16. The method of claim 1, wherein the compound of formula I has formula VIII:



VIII

17. 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);

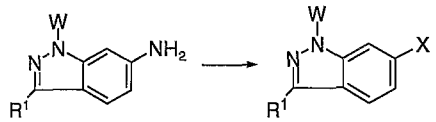
W is a protecting group; and

X is an activated substituent group;

comprising:

a) reacting a compound of formula IX with a diazotizing agent to form a diazonium salt; and

b) treating the diazonium salt with a metal halide,



IX II

wherein R^1, W and X are as described above.

18. The method of claim 17, wherein the activated substituent group X is chloride, bromide, or iodide.

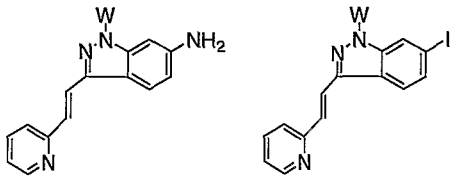
19. The method of claim 18, wherein the activated substituent group X is iodide.

20. The method of claim 17, wherein the diazotizing agent is sodium nitrite or t-butyl nitrite.

21. The method of claim 20, wherein the diazotizing agent is sodium nitrite, and the metal halide is potassium iodide.

22. The method of claim 21, further comprising a catalytic amount of iodine.

23. The method of claim 17, wherein the compound of formula IX has formula X, and the compound of formula II has formula V:



X V