

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 January 2010 (28.01.2010)

PCT

(10) International Publication Number
WO 2010/011538 A1

(51) International Patent Classification:

C07D 401/12 (2006.01) **C07O 405/14 (2006.01)**
C07D 401/14' (2006.01) **A61K 31/4412 (2006.01)**
C07D 403/12 (2006.01) **A61P 35/00 (2006.01)**
C07D 403/14' (2006.01)

(21) International Application Number:

PCT/US2009/050640

(22) International Filing Date:

15 July 2009 (15.07.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/083,294 24 July 2008 (24.07.2008) US
61/085,082 31 July 2008 (31.07.2008) US
61/108,659 27 October 2008 (27.10.2008) US

(71) Applicant (for all designated States except US): **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LI, Tiechao** [US/US]; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285 (US). **POBANZ, Mark, Andrew** [US/US]; 4293 Sedge Court, Zionsville, Indiana 46077 (US). **SHIH, Chuan** [US/US]; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285 (US). **WU, Zhipei** [US/US]; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285 (US). **YANG, Wei Jennifer** [US/US]; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285 (US). **ZHONG, Boyu** [US/US]; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285 (US).

(74) Agents: CLEVELAND, John, A. Jr. et al; Eli Lilly and Company, Patent Division, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

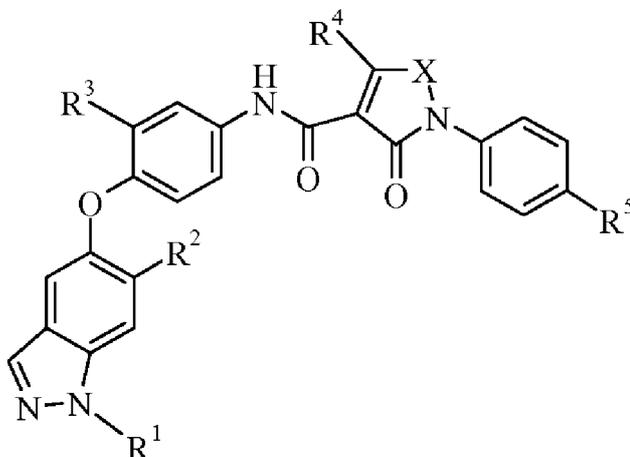
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hi))

Published:

- with international search report (Art. 21(3))

(54) Title: AMIDOPHENOXINDAZOLES USEFUL AS INHIBITORS OF C-MET



(I)

(57) Abstract: The present invention provides amidophenoxyindazole compounds useful in the treatment of cancer.

WO 2010/011538 A1

-1-

AMIDOPHENOXYINDAZOLES USEFUL AS INHIBITORS OF C-MET

5 c-Met is a member of the tyrosine kinase growth factor receptor family. c-Met expression occurs in endothelial, epithelial, and mesenchymal cells. Binding to c-Met of the endogenous ligand, hepatocyte growth factor (HGF), promotes cell migration, proliferation, and invasion.

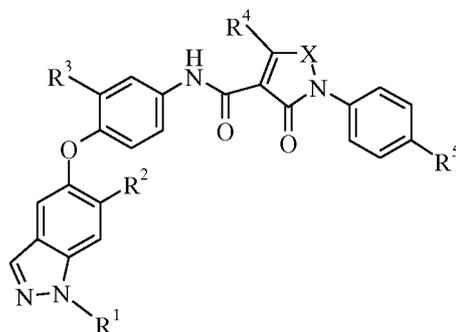
c-Met is implicated in the progression of certain tumors. c-Met overexpression
10 has been shown in numerous tumor types including colon, breast, renal, lung, hemangiomas, squamous cell myeloid leukemia, melanomas, glioblastomas, and astrocytomas. Activation of tumor cell c-Met receptors enhances tumor cell proliferation, invasion/metastasis, and resistance to apoptosis and cytotoxic therapies.

Various amidophenoxyheteroaryl c-Met inhibitors have been reported. See for
15 example, US2005/0288290, US2006/021 1695, US2006/0004006, and WO 2007103308.

However, there is still a need for further compounds that inhibit c-Met. The present invention provides novel amidophenoxyindazole compounds believed to have clinical use for treatment of cancer through inhibiting c-Met. Preferred compounds of the present invention are also believed to provide an improvement in potency over certain
20 other c-Met inhibitor compounds found in the art.

The present invention provides compounds of Formula I:

A compound of the formula:



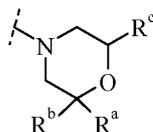
Formula I

25 wherein:

-2-

R¹ is H or methyl;

R² is amino, dimethylamino, fluoro, cyclopropyl, pyridyl optionally substituted with an amino substituent or 1-2 methyl substituents, pyrazolyl optionally substituted with two methyl substituents, 2-methoxy-pyrimidin-5-yl, 4-methylsulfonylphenyl, tetrahydro-2H-pyran-4-ylamino, (tetrahydro-2H-pyran-4-yl)amino carbonyl, or a morpholin-4-yl substituent:



where R^a, R^b and R^c are independently selected from H or methyl;

R³ is H or F;

R⁴ is H, methyl, piperidin-1-ylmethyl, morpholin-4-ylmethyl, or pyrazol-1-ylmethyl;

R⁵ is H or F; and

X is CH=N, CH=CH, CH=C(CH₃), C(CH₃)=CH, C(CH₃)=N, N(CH₃), or C(morpholin-4-ylmethyl)=CH;

or a pharmaceutically acceptable salt thereof.

The present invention provides a method of treating cancer selected from the group consisting of lung cancer, breast cancer, colorectal cancer, renal cancer, pancreatic cancer, head cancer, neck cancer, hereditary papillary renal cell carcinoma, childhood hepatocellular carcinoma, and gastric cancer in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

The present invention also provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

This invention also provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use as a medicament. Additionally, this invention provides use of a compound of Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer. In particular these cancers are selected from the group consisting of lung cancer, breast cancer, colorectal cancer, renal cancer,

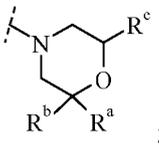
-3-

pancreatic cancer, head cancer, neck cancer, hereditary papillary renal cell carcinoma, childhood hepatocellular carcinoma, and gastric cancer. Furthermore, this invention provides a pharmaceutical composition for treating cancer selected from the group consisting of lung cancer, breast cancer, colorectal cancer, renal cancer, pancreatic
 5 cancer, head cancer, neck cancer, hereditary papillary renal cell carcinoma, childhood hepatocellular carcinoma, and gastric cancer comprising a compound of Formula I or a pharmaceutically acceptable salt thereof as an active ingredient.

It will be understood by the skilled reader that most or all of the compounds of the present invention are capable of forming salts. The compounds of the present invention
 10 are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Such pharmaceutically acceptable acid addition salts and common methodology for preparing them are well known in the art. *See, e.g., P. Stahl, et al, HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION AND USE, (VCHA/Wiley-VCH, 2002); L.D. Bighley, S.M. Berge, D.C. Monkhouse, in "Encyclopedia of Pharmaceutical Technology". Eds. J. Swarbrick and J.C. Boylan, Vol. 13, Marcel Dekker, Inc., New York, Basel, Hong Kong 1995, pp. 453-499; S.M. Berge, et al, "Pharmaceutical Salts, " Journal of Pharmaceutical Sciences, Vol 66, No. 1, January 1977. Preferred pharmaceutically acceptable salts of the compounds of the present invention are the methanesulfonate salts.*

20 Preferred are compounds of Formula I wherein:

- (a) R¹ is H;
- (b) R¹ is methyl;
- (c) R² is amino, dimethylamino, cyclopropyl, 6-methyl-pyridin-3-yl, pyrazol-

4-yl, or a morpholin-4-yl of the formula:  ;

- 25 (d) R² is amino, dimethylamino, pyrazol-4-yl, or morpholin-4-yl;
- (e) R² is pyrazo-4-yl;
- (f) R¹ is methyl and R² is pyrazol-4-yl;
- (g) R³ is F;
- (h) R¹ is methyl, R² is pyrazol-4-yl, and R³ is F;

-4-

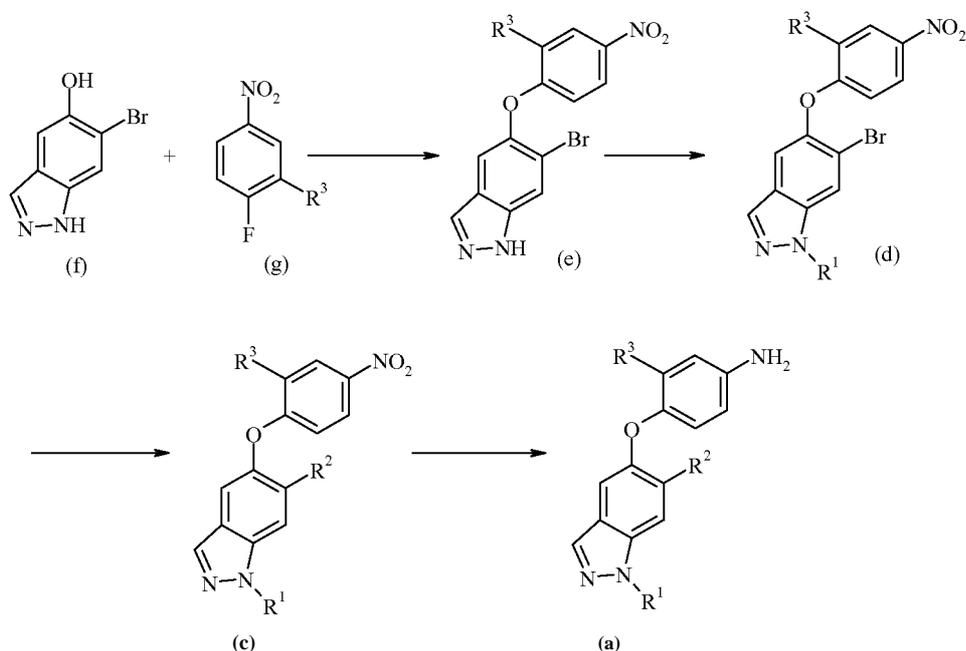
- (i) R^4 is H, methyl, or morpholin-4-ylmethyl;
- (j) R^4 is H;
- (k) R^1 is methyl, R^2 is pyrazol-4-yl, R^3 is F, and R^4 is H;
- (l) R^5 is H;
- 5 (m) R^5 is F;
- (n) R^1 is methyl, R^2 is pyrazol-4-yl, R^3 is F, R^4 is H, and R^5 is H;
- (o) R^1 is methyl, R^2 is pyrazol-4-yl, R^3 is F, R^4 is H, and R^5 is F;
- (p) X is CH=CH or CH=C(CH₃);
- (q) R^1 is methyl, R^2 is pyrazol-4-yl, R^3 is F, R^4 is H, R^5 is H, and X is CH=CH
- 10 or CH=C(CH₃);
- (r) R^1 is methyl, R^2 is pyrazol-4-yl, R^3 is F, R^4 is H, R^5 is F, and X is CH=CH or CH=C(CH₃);
- (s) R^1 is methyl, R^2 is pyrazol-4-yl, R^3 is F, R^4 is H, R^5 is H or F, and X is CH=C(CH₃);
- 15 (t) R^1 is methyl, R^2 is pyrazol-4-yl, R^3 is F, R^4 is H, R^5 is H, and X is CH=C(CH₃); and
- (u) R^1 is methyl, R^2 is pyrazol-4-yl, R^3 is F, R^4 is H, R^5 is F, and X is CH=C(CH₃).

20 The compounds of the present invention can be prepared according to the following synthetic schemes by methods well known and appreciated in the art. Suitable reaction conditions for the steps of these schemes are well known in the art and appropriate substitutions of solvents and co-reagents are within the skill of the art. Likewise, it will be appreciated by those skilled in the art that synthetic intermediates

25 may be isolated and/or purified by various well known techniques as needed or desired, and that frequently, it will be possible to use various intermediates directly in subsequent synthetic steps with little or no purification. Furthermore, the skilled artisan will appreciate that in some circumstances, the order in which moieties are introduced is not critical. The particular order of steps required to produce the compounds of the present

30 invention is dependent upon the particular compound being synthesized, the starting compound, and the relative liability of the substituted moieties, as is well appreciated by

-6-



The compound of formula (a) can be prepared as illustrated in Scheme II, where R¹, R², and R³ are as previously defined.

The compound of formula (f) can react with a properly substituted compound of formula (g) at elevated temperature, in the presence of a suitable base such as sodium bicarbonate in a proper solvent such as DMF to provide the compound of formula (e).
 The compound of formula (e) can be methylated with a proper methylation reagent such as methyl iodide in a suitable solvent such as THF with a suitable base such as potassium tert-butoxide to provide the compound of formula (d), where R¹ is a methyl.
 The compound of formula (e) can also be protected with a suitable protecting reagent such as 2,3-dihydropyran (DHP) in a appropriate solvent such as THF, in the presence of an acid such as CH₃SO₃H to provide the compound of formula (d), where R¹ is a protecting group such as 2-tetrahydropyranyl. [Methods for introducing or removing protecting groups are well known in the art; see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons, New York, (1999)].

The compound of formula (d) can react under various transition-metal facilitated coupling conditions to provide the desired compound of formula (c) with a properly substituted R² as previously defined. More specifically, if it is a carbon-carbon coupling, the compound of formula (c) can be made under coupling conditions such as a Suzuki

-7-

coupling with a suitable boronic acid, an appropriate catalyst such as 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride (PdC[^]Cdppf)), and a proper base such as CsF in a suitable solvent such as 1,4-dioxane at elevated temperature. If it is a carbon-nitrogen coupling, the compound of formula (c) can be made under coupling
5 conditions such as a Buchwald-Hartwig coupling with a proper nitrogen-containing reactant such as morpholine, a suitable ligand such as 2-di-tert-butylphosphino-2'-methylbiphenyl, a base such as KOH, and a catalyst such as tris(dibenzylideneacetone)-dipalladium (0) (Pd₂(dba)₃), in an appropriate solvent such as tert-butanol at elevated
10 temperature. The coupling reaction can be carried out under conventional heating conditions or under microwave reaction conditions well known to the skilled artisan.

The compound of formula (c) can be reduced to an amino compound under various reduction conditions well known to the skilled artisan. More specifically, the compound of formula (c) can react with stannous chloride in a suitable solvent such as ethyl acetate (EtOAc)/ethanol (EtOH) at an elevated temperature to give the desired
15 compound of formula (a). If R¹ is a nitrogen-protecting group such as 2-tetrahydropyranyl, the protecting group will be cleaved. R¹ will be a proton after the reduction.

The compound of formula (c) can also be reduced by reacting with *N,N*-dimethylhydrazine and FeCl₃ in a proper solvent such as methanol (MeOH), or
20 H₂/palladium on carbon (Pd/C) in proper solvent such as EtOH. Both reduction conditions will only reduce the nitro group to an amino group, and will leave the nitrogen-protecting group, R¹, untouched.

It is well known to the skilled artisan that reactions on nitrogen of some nitrogen-containing heterocycles such as indazole compounds could generate tautomers. The ratio
25 of tautomers depends essentially on the mode of performing reactions and different conditions. Intermediates disclosed in this invention with nitrogen protecting groups such as THP may exist as regioisomers. In the compounds of the present invention, when R¹ is a proton, it may exist as a pair of fast exchanging tautomers as illustrated in Scheme III.

30

Scheme III.

-8-



The following preparations and examples are named using ChemDraw® Ultra version 10.0.

5

Preparation 1

N-(4-Methoxy-2-methylphenyl) acetamide

To a solution of 4-methoxy-2-methylaniline (120 g, 0.88 mol) in DCM (400 mL) is added acetic acid anhydride (120 mL, 1.2 mol) dropwise. The reaction mixture is stirred at room temperature (RT) for 3 hours. After petroleum ether (PE) (1.6 L) is added, the slurry is stirred for another one hour. The precipitate is collected by filtration and is washed with PE to give the product as a pink solid (130 g, 82% yield). MS (*m/z*): 180.0 (M+H).

15

Preparation 2

N-(5-Bromo-4-methoxy-2-methylphenyl)acetamide

To a solution of *N*-(4-methoxy-2-methylphenyl)acetamide (130 g, 0.73 mol) in acetic acid (800 mL) is added bromine (42 mL, 0.8 mol) dropwise at 0 °C. After addition, the resulting mixture is stirred at RT overnight. Saturated aqueous NaHSO₃ is added until a clear solution is obtained, and then a large amount of water (2.0 L) is added forming a precipitate. The precipitated solid is collected and washed with water to give the crude product (thin layer chromatography (TLC) solvent: DCM:EtOAc=10:1). The solid is dissolved in minimum amount of refluxing DCM, and then PE (about 10-20% volume of DCM used) is added. The resulting solution is cooled to RT. After 2 hours, the precipitated solid is collected and washed with PE to give a white product (108 g, 57% yield). MS (*m/z*): 260.0 (M+H).

25

-9-

Preparation 3

5-Bromo-4-methoxy-2-methylaniline

To a solution of *N*-(5-bromo-4-methoxy-2-methylphenyl)acetamide (108 g, 0.42 mol) in MeOH (400 mL) is added concentrated HCl (160 mL, 2 mol). After being heated at reflux overnight, the mixture is neutralized with aqueous NaHCO₃, and extracted with EtOAc (1200 mL). The organic phase is dried and concentrated to afford the product (76 g, 84% yield). MS (*m/z*): 216.0 (M+H).

10

Preparation 4

1-(5-Bromo-4-methoxy-2-methylphenyl)diazonium tetrafluoroborate

To a solution of 5-bromo-4-methoxy-2-methylaniline (76 g, 0.35 mol) in HBF₄ (48% wt, 140 mL) and H₂O (280 mL) is added a solution of NaNO₂ (27.6 g, 0.4 mol) in H₂O (60 mL) at 0 °C. After the addition is completed, the reaction mixture is stirred at 0 °C for 30 minutes (min). The precipitate is filtered, washed with a small amount of ice water several times and dried to give the product (110 g, 99% yield). MS (*m/z*): 229.0 (M+H).

20

Preparation 5

6-Bromo-5-methoxy-7 *H*-indazole

1-(5-Bromo-4-methoxy-2-methylphenyl)diazonium tetrafluoroborate (110 g, 0.35 mol) is added in one portion to a stirred mixture of KOAc (140.5 g, 1.43 mol) and 18-crown-6-ether (9.3 g, 0.035 mol) in CHCl₃ (800 mL) and stirred at RT overnight. The mixture is filtered and the solid is washed with DCM. The combined filtrate is concentrated and the residue is purified by silica gel column chromatography (DCM:MeOH = 50:1) to give the product (10 g). The cake is added to THF (1600 mL) and the mixture is stirred at RT for one hour. The mixture is filtered and the filtrate is concentrated to give 10 g of the crude product (total yield 88%). MS (*m/z*): 229.0 (M+H).

30

Preparation 6

6-Bromo-5-hydroxy-7 *H*-indazole

-10-

To a solution of 6-bromo-5-methoxy-1 *H*-indazole (60 g, 0.265 mol) in DCM (1300 mL) is added a solution of BBr_3 (105 g, 0.42 mol) in DCM (200 mL) at 0 °C. The reaction mixture is warmed to RT and stirred overnight. Then the reaction solution is quenched with MeOH at 0 °C. The solvent is removed *in vacuo* and the residue is neutralized with NaHCO_3 solid. The mixture is partitioned by water (1500 mL) and EtOAc (1500 mL). The aqueous layer is extracted with EtOAc (1500 mL) two times. The combined organic layers are dried and concentrated to give crude product, which is purified by silica gel column chromatography (PE:THF = 2:1) to give the desired product (42.5 g, 75% yield). MS (*m/z*): 215.0 (M+H).

10

Preparation 7

6-Bromo-5-(2-fluoro-4-nitrophenoxy)-1 *H*-indazole

A mixture of 6-bromo-5-hydroxy-7 *H*-indazole (7.0 g, 33.0 mmol), 3,4-difluoronitrobenzene (4.98 mg, 31.0 mmol), NaHCO_3 (2.5 g, 31.0 mmol) in DMF (100 mL) is stirred at 80 °C for 4 hours. Then LiCl (10% aqueous solution) is added and the solution is extracted with EtOAc. The organic phase is dried over anhydrous MgSO_4 , filtered and concentrated. The residue is purified by silica gel column chromatography eluting with PE:DCM (1:1) to give the desired product (5.5 g, 46.6% yield). MS (*m/z*): 354.0 (M+H)..

20

The following compound is prepared essentially by the method of Preparation 7:

Prep. No.	Chemical name	Physical data MS (<i>m/z</i>) (M+H)
8	6-Bromo-5-(4-nitrophenoxy)-1 <i>H</i> -indazole	336

Preparation 9

6-Bromo-5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole

To a solution of 6-bromo-5-(2-fluoro-4-nitrophenoxy)-1 *H*-indazole (5.0 g, 14.2 mmol) in THF (50 mL) is added DHP (2.4 g, 28.5 mmol) and $\text{CH}_3\text{SO}_3\text{H}$ (1.0 g, 10.4 mmol). The resulting mixture is stirred at RT for 1 hour. Then EtOAc and aqueous NaHCO_3 solutions are added. The organic phase is separated, dried over anhydrous MgSO_4 , filtered and concentrated. The residue is purified by silica gel column

25

-11-

chromatography eluting with PE:EtOAc (5:1) to give the desired product (5.5 g, 89.0% yield). MS (m/z): 436.0 (M+H).

The following compound is prepared essentially by the method of Preparation 9:

Prep. No.	Chemical name	Physical data MS (m/z)(M+H)
10	6-Bromo-5-(4-nitrophenoxy)-1-(tetrahydro-2H-pyran-2-yl)-1 <i>H</i> -indazole	418.0

5

Preparation 11

6-Bromo-1-methyl-5-(4-nitrophenoxy)-1 *H*-indazole

To a mixture of 6-bromo-5-(4-nitrophenoxy)-1 *H*-indazole (2.68 g, 8.02 mmol) and KOH (600 mg, 10.69 mmol) in acetone (100 mL) cooled with an ice-water bath is added dropwise methyl iodide (0.55 mL, 8.83 mmol). After the reaction mixture is stirred at 0 °C for 2 hours, it is stirred at RT overnight. The solvent is removed, and the residue is purified by silica gel column chromatography eluting with PE:EtOAc (3: 1) to give the product (1.50 g, 53.7% yield). MS (m/z): 348.0 (M+H).

15 The following compound is prepared essentially by the method of Preparation 11:

Prep. No.	Chemical name	Physical data MS(m/z)(M+H)
12	6-Bromo-5-(2-fluoro-4-nitrophenoxy)-1-methyl-1 <i>H</i> -indazole	365.9

Alternatively, 6-bromo-5-(2-fluoro-4-nitrophenoxy)- 1-methyl-1*H*-indazole (Preparation 12) may also be prepared in the following 3 step process:

2,4-Dibromo-5-hydroxy-benzaldehyde (50 g, 178.6 mmol), 1,2-difluoro-4-nitrobenzene (28.4 g, 178.6 mmol) and potassium carbonate (49.0 g, 357.2 mmol) are stirred in DMF (500 mL) at 60 °C for 2 hours. The reaction is quenched with water (1000 mL) and extracted with methyl tert-butylether (MTBE) (2 x 500 mL). The organic layer is washed with saturated sodium chloride aqueous solution (2 x 500 mL), dried with anhydrous sodium sulfate, and concentrated to obtain a yellow solid. The crude solid is

20

-12-

recrystallized in EtOAc/PE (1:5) to give 2,4-dibromo-5-(2-fluoro-4-nitrophenoxy)benzaldehyde as a yellow solid (52.8 g, 70.6% yield).

2,4-Dibromo-5-(2-fluoro-4-nitrophenoxy)benzaldehyde (13.0 g, 31.0 mmol) is refluxed with methylhydrazine (4.3 g, 93 mmol) in THF (130 mL) for 2 hours. The reaction is quenched with water (150 mL) and extracted with MTBE (2 x 150 mL). The organic layer is washed with saturated sodium chloride aqueous solution (2 x 150 mL), dried with anhydrous sodium sulfate, and concentrated to obtain a solid. The crude solid is recrystallized in EtOAc/hexane to obtain 1-(2,4-dibromo-5-(2-fluoro-4-nitrophenoxy)benzylidene)-2-methylhydrazine as a yellow solid (10.6 g, 76.7% yield).

MS (*m/z*): 447.9 (M+H).

1-(2,4-Dibromo-5-(2-fluoro-4-nitrophenoxy)benzylidene)-2-methylhydrazine (1.0 g, 2.2 mmol), cuprous chloride (22 mg, 0.2 mmol), potassium carbonate (0.638 g, 7.2 mmol), DMF (10 mL), and a stir bar are combined in a pressure tube under nitrogen. The cap is sealed and the tube is placed in an oil bath with stirring. The bath is heated to 100 °C over 30 min and held at 100 °C for 6 hours and then cooled to RT. The reaction mixture is poured into a separatory funnel containing MTBE (10mL) and water (10 mL). The layers are separated and the aqueous layer is extracted with an additional portion of MTBE (10 mL). The organic layers are combined, and washed with water followed by saturated sodium chloride aqueous solution. The organic layer is dried over magnesium sulfate and concentrated to yield 0.70 g of crude product. The crude solid is dissolved in DCM and heptane, and then concentrated to remove DCM resulting in the formation of a slurry. The product is collected by filtration and dried under vacuum to give 6-bromo-5-(2-fluoro-4-nitrophenoxy)-1-methyl-1*H*-indazole as a solid (0.65 g, 79% yield). MS (*m/z*): 367.8 (M+H).

25

Preparation 13

6-Bromo-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-indazol-5-ol

To a solution of 6-bromo-5-hydroxy-7*H*-indazole (725.0 g, 3.4 mol) in THF (10.2 L) is added DHP (336.5 mL, 3.57 mol) and CH₃SO₃H (65.4 g, 0.68 mol) at RT. The resulting mixture is stirred at RT for 22 hours. The reaction mixture is quenched with distilled water (6 L) and extracted with EtOAc (6 L). Saturated aqueous NaHCO₃

30

-13-

solution (1100 mL) is added to adjust the pH to 8. After phase separation, the organic phase is washed with water (4 L) and then saturated aqueous sodium chloride (3 L), dried over anhydrous Na₂SO₄, filtered, and concentrated to give the product as a solid (1.64 kg, 99.3% yield). MS (*m/z*): 299.0 (M+H).

5

Preparation 14

6-Bromo-5-(2-fluoro-4-nitrophenoxy)-2-(tetrahydro-2 *H*-pyran-2-yl)-2 *H*-indazole

To a solution of 6-bromo-2-(tetrahydro-2 *H*-pyran-2-yl)-2 *H*-indazol-5-ol (1.475 kg, 4.96 mol) in DMF (5.3 L) is added 3,4-difluoronitrobenzene (1.18 kg, 7.45 mol) and
10 NaHCO₃ (625.5 g, 7.45 mol) at RT. The reaction mixture is heated at 70 °C for 10 hours and then cooled to less than 20 °C. Deionized (DI) water (7.9 L) is slowly added to the solution and the resulting slurry is stirred at 15 °C for one hour. The solid is collected by vacuum filtration, and the solid cake is washed with water (8 L). It is then air dried under vacuum on filter and is triturated with methyl MTBE (18.6 L) at reflux conditions for two
15 hours. The slurry is then cooled to RT and the solid is collected by vacuum filtration. The solid cake is washed with MTBE (4 L X 2) and dried in a vacuum oven at 35 °C to give the desired product (1.405 kg, 64.9% yield). MS (*m/z*): 436.0 (M+H).

Preparation 15

20 5-(2-Fluoro-4-nitrophenoxy)-6-(pyridine-4-yl)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole

A mixture of 6-bromo-5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole (5.0 g, 11.5 mmol), 4-pyridineboronic acid (3.0 g, 24.3 mmol), PdCl₂(dppf) (1.8 g, 2.25 mmol) and CsF (5.0 g, 33.0 mmol) in 1,4-dioxane (100 mL) is stirred at 110 °C overnight. Then, aqueous NH₄Cl and EtOAc are added. The organic phase is
25 separated, dried over anhydrous MgSO₄ and concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (3:1) to give the desired product (2.8 g, 56% yield). MS (*m/z*): 435.1 (M+H).

The following compounds are prepared essentially by the method of Preparation 15:

Prep. No.	Chemical name	Physical data MS (<i>m/z</i>) (M+H)
16	5-(2-Fluoro-4-nitrophenoxy)-6-(4-(methylsulfonyl)phenyl)-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)-1 <i>H</i> -indazole	512.1
17	<i>tert</i> -Butyl 4-(5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)-1 <i>H</i> -indazol-6-yl)-1 <i>H</i> -pyrazole-1-carboxylate	524.1
	5-(2-Fluoro-4-nitrophenoxy)-6-(1 <i>H</i> -pyrazol-4-yl)-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)-1 <i>H</i> -indazole	424.1
18	5-(2-Fluoro-4-nitrophenoxy)-6-(pyridin-3-yl)-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)-1 <i>H</i> -indazole	435.1
19	6-(1,3-Dimethyl-1 <i>H</i> -pyrazol-5-yl)-5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydropyran-2-yl)-1 <i>H</i> -indazole	452.1
20	5-(2-Fluoro-4-nitrophenoxy)-6-(2-methoxypyrimidin-5-yl)-1-(tetrahydropyran-2-yl)-1 <i>H</i> -indazole	466.1
21	5-(2-Fluoro-4-nitrophenoxy)-6-(2-methylpyridin-4-yl)-1-(tetrahydropyran-2-yl)-1 <i>H</i> -indazole	449.1
22 *	6-Cyclopropyl-5-(2-fluoro-4-nitrophenoxy)-2-(tetrahydro-2 <i>H</i> -pyran-2-yl)-2 <i>H</i> -indazole	398
23	<i>tert</i> -Butyl 4-(1-methyl-5-(4-nitrophenoxy)-1 <i>H</i> -indazol-6-yl)-1 <i>H</i> -pyrazole-1-carboxylate	436.0
	1-Methyl-5-(4-nitrophenoxy)-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazole	336.0
24	5-(2-Fluoro-4-nitrophenoxy)-1-methyl-6-(2-methylpyridin-4-yl)-1 <i>H</i> -indazole	379.1
25	5-(2-Fluoro-4-nitrophenoxy)-1-methyl-6-(pyridin-3-yl)-1 <i>H</i> -indazole	365.1
26	<i>tert</i> -Butyl 4-(5-(2-fluoro-4-nitrophenoxy)-1-methyl-1 <i>H</i> -indazol-6-yl)-1 <i>H</i> -pyrazole-1-carboxylate	454.0
27	<i>tert</i> -Butyl 4-(5-(2-fluoro-4-nitrophenoxy)-1-methyl-1 <i>H</i> -indazol-6-yl)-1 <i>H</i> -pyrazole-1-carboxylate	454.1
	5-(2-Fluoro-4-nitrophenoxy)-1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazole	354.1

*: Reaction is carried out under microwave conditions at 95 °C for about 90 min.

-15-

6-(2,6-Dimethylpyridin-4-yl)-5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydropyran-2-yl)-1 *H*-indazole

To a solution of 6-bromo-5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydropyran-2-yl)-1*H*-indazole (1.31 g, 3.0 mmol) in 1,4-dioxane (20 mL) is added bis(pinacolato)diboron (0.91 g, 3.6 mmol), Pd₂(dba)₃ (0.14 g, 0.2 mmol), tricyclohexylphosphine (0.1 g, 0.4 mmol), potassium acetate (KOAc) (0.59 g, 6.0 mmol) under N₂. After the reaction mixture is heated to reflux for 3 hours under N₂, it is cooled to RT. 4-Bromo-2,6-dimethylpyridine hydrobromide (0.8 g, 3.0 mmol), PdCl₂(dppf) (0.16 g, 0.2 mmol), CsF (1.38 g, 9.0 mmol) are added under N₂. The resulting mixture is heated at reflux overnight under N₂. The solid is filtered off and the filtrate is concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (from 5:1 to 1:1) to give the product (0.67 g, 48.3% yield). MS (*m/z*): 463.1 (M+H).

Preparation 29

4-(5-(2-Fluoro-4-nitrophenoxy)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-yl)morpholine

To a solution of 6-bromo-5-(2-fluoro-4-nitro-phenoxy)-1-(tetrahydropyran-2-yl)-1*H*-indazole (8.0 g, 18 mmol) in tert-butanol (150 mL) and H₂O (3.2 mL) is added Pd₂(dba)₃ (320 mg, 0.35 mmol), 2-di-tert-butylphosphino-2'-methylbiphenyl (480 mg, 1.54 mmol), KOH (3.2 g, 57 mmol) and morpholine (3.2 g, 36.7 mmol) under N₂. After the mixture is stirred at 70 °C for 2 hours under a N₂ atmosphere, it is filtered and the filtrate is concentrated. The residue is partitioned with EtOAc (100 mL) and saturated aqueous NH₄Cl (30 mL). The organic layer is separated, dried over MgSO₄, and concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (3:1) to give the product (4.5 g, 56.5% yield). MS (*m/z*): 443.1 (M+H).

The following compounds are prepared essentially by the method of Preparation 29:

Prep. No.	Chemical name	Physical data MS (<i>m/z</i>)(M+H)
30	5-(2-Fluoro-4-nitrophenoxy)- <i>N,N</i> -dimethyl-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)-1 <i>H</i> -indazol-6-amine	401.2
31	<i>N,N</i> -Dimethyl-5-(4-nitrophenoxy)-1-(tetrahydro-2 <i>H</i> -pyran-2-	383.1

	yl)-1 <i>H</i> -indazol-6-amine	
--	---------------------------------	--

Preparation 32

4-(5-(2-Fluoro-4-nitrophenoxy)-2-(tetrahydro-2 *H*-pyran-2-yl)-2*H* -indazol-6-yl)-2-methylmorpholine (racemic)

5 To a 25 mL microwave vial is added 6-bromo-5-(2-fluoro-4-nitrophenoxy)-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-indazole (0.8 g, 1.8 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (98 mg, 165 μ mol) and Pd₂(dba)₃ (50 mg, 55 μ mol). The mixture is suspended in toluene (12 mL, 113 mmol) and then 2-methylmorpholine hydrochloride (278 mg, 2.02 mmol) and sodium tert-butoxide (454 mg, 4.58 mmol) are added. The
10 reaction mixture is heated at 150 °C for 25 min in a microwave reactor. The reaction mixture is then concentrated and the residue is purified on a silica gel column eluting with hexanes (A) and EtOAc (B), gradient from 90% (A):10%(B) to 60%(A):40%(B) over 60 min then to 50%(A):50%(B) for 20 min to give an orange solid as the desired product (410 mg, 39% yield). MS (*m/z*): 457 (M+H).

15

The following compounds are prepared essentially by the method of Preparation 32:

Prep. No.	Chemical name	Physical data MS (<i>m/z</i>)(M+H)
33	(2 <i>R</i>)-4-(5-(2-Fluoro-4-nitrophenoxy)-2-(tetrahydro-2 <i>H</i> -pyran-2-yl)-2 <i>H</i> -indazol-6-yl)-2-methylmorpholine	456.8
34	(2 <i>S</i> ,6 <i>R</i>)-4-(5-(2-Fluoro-4-nitrophenoxy)-2-(tetrahydro-2 <i>H</i> -pyran-2-yl)-2 <i>H</i> -indazol-6-yl)-2,6-dimethylmorpholine	470.8

Preparation 35

4-(5-(2-Fluoro-4-nitrophenoxy)-2-(tetrahydro-2 *H*-pyran-2-yl)-2*H*-indazol-6-yl)-2,2-dimethylmorpholine

20

6-Bromo-5-(2-fluoro-4-nitrophenoxy)-2-(tetrahydro-2 *H*-pyran-2-yl)-2*H*-indazole (1.5 g, 3.4 mmol) is added to a 50 mL Genevac Carousel® tube and is suspended into the amylene hydrate (10 mL, 91.4 mmol) and N₂ is bubbled in suspension. To the mixture is added 2-(di-tert-butylphosphino)-2'-methylbiphenyl (97.7 mg, 309 μ mol), Pd₂(dba)₃ (94.5
25 mg, 103 μ mol) and DI water (0.3 mL), and N₂ bubbling is continued for 10 min. To this mixture is added 2,2-dimethylmorpholine hydrochloride (1.04 g, 6.9 mmol) and a

-17-

solution of KOH (617 mg, 11.0 mmol) dissolved in 0.3 mL of distilled water. The reaction mixture is heated at 80 °C for 2 hours and then cooled to RT. The mixture is then poured into EtOAc (300 mL), washed with distilled water (1 x 100 mL) and then saturated aqueous sodium chloride (100 mL). The combined aqueous layers are extracted with EtOAc (100 mL). The combined organic solution is dried with Na₂SO₄, filtered, and concentrated to dryness to give a gold solid. The solid is purified on a silica gel column eluting with hexanes (A) and EtOAc (B), gradient from 95%(A):5%(B) to 75%(A):25%(B) over 70 min to give a light yellow solid as the desired product (410 mg, 25% yield). MS (*m/z*): 470.8 (M+H).

10

Preparation 36

5-(2-Fluoro-4-nitrophenoxy)-6-(pyridine-4-yl)-1 *H*-indazole

To a solution of 5-(2-fluoro-4-nitrophenoxy)-6-(pyridine-4-yl)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole (2.8 g, 6.45 mmol) in EtOH (30 mL) is added HCl (concentrated 5.0 mL). The mixture is stirred at 80 °C for 2 hours. Then aqueous NaHCO₃ and EtOAc are added. The organic phase is dried over anhydrous MgSO₄ and concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (3:1) to give the desired product (1.95 g, 86.0% yield). MS (*m/z*): 351.0 (M+H).

20

Preparation 37

3-Fluoro-4-(6-(pyridine-4-yl)-1 *H*-indazole-5-yloxy)aniline

A mixture of 5-(2-fluoro-4-nitrophenoxy)-6-(pyridine-4-yl)-1 *H*-indazole (1.95 g, 4.5 mmol) and SnCl₂·2H₂O (10.2 g, 45.3 mmol) in EtOAc/EtOH (200 mL/10 mL) is stirred at 80 °C for 2 hours. Then aqueous NaHCO₃ and EtOAc are added. The organic phase is dried over anhydrous MgSO₄ and concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (2:1) to give the desired product (1.10 g, 61.0% yield). MS (*m/z*): 321.0 (M+H).

30

Preparation 38

3-Fluoro-4-(6-(4-(methylsulfonyl)phenyl)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-5-yloxy)aniline

-18-

To a solution of 5-(2-fluoro-4-nitrophenoxy)-6-(4-(methylsulfonyl)phenyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (320 mg, 0.63 mmol) in EtOAc (50 mL) is added Pd/C (10%, 100 mg). The resulting mixture is degassed by evacuation and backfilled with H₂ three times. It is stirred under an atmosphere of H₂ at RT overnight. The solid is removed by filtration and the filtrate is concentrated. The residue is purified by silica gel column chromatography eluting with DCM:MeOH (20:1) to give the desired product (250 mg, 83% yield). MS (*m/z*): 482.1 (M+H).

The following compounds are prepared essentially by the method of Preparation 38:

Prep. No.	Chemical name	Physical data MS (<i>m/z</i>)(M+H)
39	3-Fluoro-4-(1-methyl-6-(2-methylpyridin-4-yl)-1 <i>H</i> -indazol-5-yloxy)aniline	349.1
40	<i>tert</i> -Butyl 4-(5-(4-amino-2-fluorophenoxy)-1-methyl-1 <i>H</i> -indazol-6-yl)-1 <i>H</i> -pyrazole-1-carboxylate	424

10

Preparation 41

4-(6-(1*H*-Pyrazol-4-yl)-1*H*-indazol-5-yloxy)-3-fluoroaniline

To a solution of 5-(2-fluoro-4-nitrophenoxy)-6-(1*H*-pyrazol-4-yl)-1-(tetrahydropyran-2-yl)-1*H*-indazole (900 mg, 2.13 mmol) and 4-[5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydropyran-2-yl)-1*H*-indazol-6-yl]-pyrazole-1-carboxylic acid *tert*-butyl ester (3.1 g, 5.92 mmol) in EtOAc/EtOH (75 mL/75 mL) is added stannous chloride dihydrate (10 g, 52.74 mmol). The reaction mixture is stirred at reflux overnight. After it is cooled and basified with saturated aqueous NaHCO₃ to pH 8-9, the mixture is extracted with EtOAc (100 mL). The organic phase is separated, dried over MgSO₄, and concentrated. The residue is purified by silica gel column chromatography eluting first with PE:EtOAc (1:1) and then with EtOAc to give the product (1.75 g, 71.0% yield). MS (*m/z*): 310.0 (M+H).

15
20

The following compounds are prepared essentially by the method of Preparation 41:

Prep. No.	Chemical name	Physical data MS (<i>m/z</i>)(M+H)
42	3-Fluoro-4-(6-(pyridin-3-yl)-1 <i>H</i> -indazol-5-yloxy)aniline	321.1

Prep. No.	Chemical name	Physical data MS (m/z)(M+H)
43	4-(6-(1,3-Dimethyl-1 <i>H</i> -pyrazol-5-yl)-1 <i>H</i> -indazol-5-yloxy)-3-fluoroaniline	338.1
44	3-Fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)aniline	329.1
45	4-[6-(2,6-Dimethylpyridin-4-yl)-1 <i>H</i> -indazol-5-yloxy]-3-fluoroaniline	349.1
46	3-Fluoro-4-[6-(2-methoxypyrimidin-5-yl)-1 <i>H</i> -indazol-5-yloxy]aniline	352.1
47	5-(4-Amino-2-fluorophenoxy)- <i>N,N</i> -dimethyl-1 <i>H</i> -indazol-6-amine	287.1
48	3-Fluoro-4-(6-(2-methylpyridin-4-yl)-1 <i>H</i> -indazol-5-yloxy)aniline	335.1
49	5-(4-Aminophenoxy)- <i>N,N</i> -dimethyl-1 <i>H</i> -indazol-6-amine	269.1
50	4-(1-Methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)aniline	306.0
51	3-Fluoro-4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)aniline	324.1
52	3-Fluoro-4-(1-methyl-6-(pyridin-3-yl)-1 <i>H</i> -indazol-5-yloxy)aniline	335.1

Preparation 53

4-(6-Cyclopropyl-2-(tetrahydro-2 *H*-pyran-2-yl)-2 *H*-indazol-5-yloxy)-3-fluoroaniline

To a 25 mL glass vial is added 6-cyclopropyl-5-(2-fluoro-4-nitrophenoxy)-2-(tetrahydro-2 *H*-pyran-2-yl)-2 *H*-indazole (395 mg, 994 μ mol) and MeOH (20 mL, 494 mmol). To the suspension is added *N,N*-dimethylhydrazine (756 μ L, 9.94 mmol) and FeCl₃ (163 mg, 994 μ mol). The vial is capped, and heated to 60 °C and stirred for 2 hours and then stirred at 50 °C overnight. The mixture is filtered over a Buchner funnel and the solid washed with MeOH (100 mL). The filtrate is collected and concentrated to give a brown/orange solid. The residue is purified on a silica gel column eluting with DCM (A) and a 10% MeOH in a DCM solution (B), gradient from 100% (A) to 85%(A):15%(B) over 50 min to give a yellow solid as the title compound (358 mg, 98% yield). MS (m/z): 368 (M+H).

15 The following compounds are prepared essentially by the method of Preparation 53:

Prep. No.	Chemical name	Physical data MS (m/z)(M+H)
-----------	---------------	-----------------------------

Prep. No.	Chemical name	Physical data MS (<i>m/z</i>)(M+H)
54	3-Fluoro-4-(6-(2-methylmorpholino)-2-(tetrahydro-2 <i>H</i> -pyran-2-yl)-2 <i>H</i> -indazol-5-yloxy)aniline	427
55	4-(6-(2,2-Dimethylmorpholino)-2-(tetrahydro-2 <i>H</i> -pyran-2-yl)-2 <i>H</i> -indazol-5-yloxy)-3-fluoroaniline	441
56	3-Fluoro-4-(6-((<i>R</i>)-2-methylmorpholino)-2-(tetrahydro-2 <i>H</i> -pyran-2-yl)-2 <i>H</i> -indazol-5-yloxy)aniline	427
57	4-(6-((<i>2S,6R</i>)-2,6-dimethylmorpholino)-2-(tetrahydro-2 <i>H</i> -pyran-2-yl)-2 <i>H</i> -indazol-5-yloxy)-3-fluoroaniline	441
58	3-Fluoro-4-(6-morpholino-2-(tetrahydro-2 <i>H</i> -pyran-2-yl)-2 <i>H</i> -indazol-5-yloxy)aniline	413

Preparation 59

N-(Diphenylmethylene)-5-(2-fluoro-4-nitrophenoxy)- 1-methyl- *1H*-indazol-6-amine

To a 10 mL microwave vial is added 6-bromo-5-(2-fluoro-4-nitrophenoxy)-1-
 5 methyl- *1H*-indazole (500 mg, 1.37 mmol), 4,5-bis(diphenylphosphino)-9,9-
 dimethylxanthene (73 mg, 123 μ mol) and Pd₂(dba)₃ (38 mg, 41 μ mol). The mixture is
 suspended in toluene (5 mL, 47 mmol) and benzophenone imine (272 mg, 1.5 mmol) and
 sodium tert-butoxide (203 mg, 2.05 mmol) are added. The mixture is heated at 150 °C
 for 20 min in a microwave reactor. After cooling, the reaction solution is concentrated to
 10 give a brown oil which is dissolved in DCM (150 mL) and washed with saturated
 aqueous sodium chloride (2 x 50 mL). The aqueous layers are combined and extracted
 with DCM (1 x 50 mL), dried with Na₂SO₄, filtered and concentrated to give a brown
 residue. The residue is purified on a silica gel column eluting with hexanes (A) and
 EtOAc (B), gradient from 85%(A):15%(B) to 50%(A):50%(B) over 50 min to give a
 15 yellow solid material as the title compound (574 mg, 90.1% yield). MS (*m/z*): 467.2
 (M+H).

Preparation 60

5-(4-Amino-2-fluorophenoxy)- *N*-benzhydryl- 1-methyl- *1H*-indazol-6-amine

20 To a 100 mL round bottom flask is added *N*-(diphenylmethylene)-5-(2-fluoro-4-
 nitrophenoxy)- 1-methyl- *1H*-indazol-6-amine (424 mg, 909 μ mol) and EtOH (35 mL,
 601 mmol). To the mixture is added ammonium formate (1000 mg, 15.9 mmol) followed

-21-

by the addition of 10% Pd/C (300 mg, 141 μ mol) and the reaction mixture is stirred at RT for 1 hour and heated at 45 $^{\circ}$ C for 15 min. The solvent is removed and the residue is dissolved in DCM (150 mL) and distilled water (100 mL). The organic layer is washed with distilled water (1 x 100 mL), and the combined aqueous layers are extracted with
5 DCM (1 x 50 mL). The combined organic solution is dried with Na₂SO₄, filtered, and concentrated. The crude is purified on a silica gel column eluting with hexanes (A) and EtOAc (B), gradient from 90%(A)10%(B) to 40%(A):60%(B) over 90 min to give an off-white solid material as the title compound (204 mg, 51% yield). MS (*m/z*): 438.8 (M+H).

10

Preparation 61

1-Acetyl-6-bromo-1 *H*-indazol-5-yl acetate

A mixture of 6-bromo-5-hydroxy-1 *H*-indazole (25 g, 117 mmol) in acetic acid anhydride (75 mL) is heated at 110 $^{\circ}$ C with stirring for 2 hours. After it is cooled, diethyl ether (100 mL) is added. The precipitate is collected by filtration, washed with diethyl
15 ether (30 mL), and dried under vacuum to afford the product (34 g, 98% yield). MS (*m/z*): 297.0 (M+H).

Preparation 62

Ethyl 5-hydroxy-1*H*-indazole-6-carboxylate

An autoclave is charged with 1-acetyl-6-bromo-1 *H*-indazol-5-yl acetate (25 g, 84 mmol), TEA (25 g, 252 mmol), dichloro bis (benzonitrile) palladium (Pd(PhCN)₂Cl₂) (1.6 g, 4.2 mmol), 1,1'-bis(diphenylphosphino)ferrocene (dppf) (4.7 g, 8.4 mmol) and EtOH (500 mL) is stirred at 130 $^{\circ}$ C under an atmosphere of CO for 8 hours. The reaction mixture is concentrated, and the residue is purified by silica gel column chromatography
25 to afford the product (15.5 g, 90% yield). MS (*m/z*): 207.0 (M+H).

Preparation 63

Ethyl 5-hydroxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-6-carboxylate

To a solution of ethyl 5-hydroxy-1 *H*-indazole-6-carboxylate (15.5 g, 75 mmol) in
30 DCM (100 mL) and THF (100 mL) containing methanesulfonic acid (721 mg, 7.5 mmol) is added a solution of 3,4-dihydro-2*H*-pyran (6.6 g, 79 mmol) in DCM (20 mL) dropwise

-22-

at RT. The resulting solution is stirred at RT overnight. After the solvent is removed, EtOAc (500 mL), saturated aqueous sodium chloride (500 mL) and NaHCO₃ (5 g) are added. The organic layer is separated, dried and concentrated. The residue is purified by silica gel column chromatography to afford the product (16.8 g, 77% yield). MS (*m/z*):

5 291.1 (M+H).

Preparation 64

Ethyl-5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2-*H*-pyran-2-yl)-1-*H*-indazole-6-carboxylate

10 A mixture of ethyl 5-hydroxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-6-carboxylate (10.8 g, 37 mmol), 1,2-difluoro-4-nitrobenzene (7.1 g, 44 mmol), NaHCCl₃ (7.4 g, 88 mmol) and DMF (100 mL) is stirred at 80 °C for 2 hours. After it is cooled to RT, water (400 mL) and PE (50 mL) are added and the mixture is stirred for 20 min. The precipitate is collected and dried under vacuum at 50 °C to afford the product (15 g, 95%

15 yield). MS (*m/z*): 430.1 (M+H).

Preparation 65

5-(2-Fluoro-4-nitrophenoxy)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-6-carboxylic acid

20 To a solution of ethyl-5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole-6-carboxylate (22 g, 51.2 mmol) in THF (60 mL) and MeOH (60 mL) and H₂O (10 mL) is added LiOH (3 g, 125 mmol). The resulting solution is stirred at RT for 1.5 hours and the organic solvents are removed. The aqueous residue is acidified with cold 6N HCl to pH 2, and extracted with EtOAc (150 mL). The organic phase is

25 separated, dried, and concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc:acetic acid (100:100:1) to afford the product (19.5 g, 95% yield). MS (*m/z*): 402.1 (M+H).

Preparation 66

30 *tert*-Butyl 5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2-*H*-pyran-2-yl)-1-*H*-indazol-6-ylcarbamate

-23-

A mixture of 5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole-6-carboxylic acid (590 mg, 1.47 mmol), diphenylphosphoryl azide (485 mg, 1.76 mmol), TEA (179 mg, 1.76 mmol), 4 Å molecular sieves (3 g) in tert-butanol (40 mL) is stirred at 80 °C overnight. The mixture is filtered and the filtrate is concentrated. The residue is purified by silica gel column chromatography eluting with PE/EtOAc (10:1) to give the desired product (400 mg, 65% yield). MS (*m/z*): 473.1 (M+H).

Preparation 67

tert-Butyl 5-(4-amino-2-fluorophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-6-ylcarbamate

To a solution of *tert-butyl* 5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-6-ylcarbamate (400 mg, 0.85 mmol) in EtOAc (50 mL) is added Pd/C (10%, 50 mg). The resulting mixture is degassed by evacuation and backfilled with H₂ three times. The mixture is stirred under an atmosphere of H₂ at RT overnight. The solid is removed by filtration and the filtrate is concentrated. The residue is purified by silica gel column chromatography eluting with DCM:MeOH (10:1) to give the desired product (300 mg, 80% yield). MS (*m/z*): 443.2 (M+H).

Preparation 68

5-(2-Fluoro-4-nitrophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-*N*-(tetrahydro-2 *H*-pyran-4-yl)-1 *H*-indazole-6-carboxamide

The solution of 5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole-6-carboxylic acid (0.5 g, 1.25 mmol), tetrahydropyran-4-ylamine (0.13 g, 1.25 mmol), EDCI (0.24 g, 1.25 mmol), HOBt (0.17 g, 1.25 mmol), *N*-methylmorpholine (0.5 mL) in DMF (5 mL) is stirred at RT overnight. Then the reaction mixture is partitioned with saturated aqueous NH₄Cl (20 mL) and EtOAc (50 mL). The organic phase is separated, dried over MgSO₄, and concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (1:1) to provide the product (0.49 g, 81.2% yield). MS (*m/z*): 485.1 (M+H).

Preparation 69

-24-

5-(4-Amino-2-fluorophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-*N*-(tetrahydro-2 *H*-pyran-4-yl)-1 *H*-indazole-6-carboxamide

To a solution of 5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-*N*-(tetrahydro-2 *H*-pyran-4-yl)-1 *H*-indazole-6-carboxamide (0.49 g, 1.0 mmol) in MeOH (50 mL) is added Pd/C (100 mg, 10% wt) under N₂. The resulting mixture is degassed by evacuation and backfilled with nitrogen. Then the reaction mixture is stirred at RT under H₂ atmosphere overnight. The solid is removed by filtration and the filtrate is concentrated to give a crude product (0.42 g, 91.4% yield). MS (*m/z*): 455.1 (M+H).

10

Preparation 70

5-(Benzyloxy)-6-bromo-1 *H*-indazole

To a solution of 6-bromo-5-hydroxy-*1H*-indazole (5 g, 23.5 mmol) in THF (50 mL) is added benzyl alcohol (3.05 g, 28.2 mmol), PPh₃ (7.39 g, 28.2 mmol) and diethylazodicarboxylate (4.46 mL, 28.2 mmol). After the reaction mixture is stirred at RT overnight, EtOAc (50 mL) and saturated aqueous NH₄Cl (30 mL) are added. The organic phase is separated, dried over MgSO₄, and concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (4: 1) to provide the product (5.0 g, 70.2% yield). MS (*m/z*): 303.0 (M+H).

20

Preparation 71

5-(Benzyloxy)-6-bromo- 1-(tetrahydro-2 *H*-pyran-2-yl)- 1*H*-indazole

To a solution of 5-(benzyloxy)-6-bromo-1 *H*-indazole (5 g, 16.5 mmol) in THF (30 mL) and DCM (30 mL) is added 3,4-dihydro-2 *H*-pyran (3 mL, 32.8 mmol) and methanesulfonic acid (1 mL, 15.3 mmol). After the reaction mixture is stirred at RT for 2 hours, EtOAc (50 mL) and saturated aqueous NaHCO₃ are added. The organic phase is separated, dried over MgSO₄, and concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (4:1) to give the desired product (2.7 g, 42.2% yield). MS (*m/z*): 387.0 (M+H).

30

Preparation 72

-25-

5-(Benzyloxy)-1-(tetrahydro-2*H*-pyran-2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazol-6-amine

To a solution of 5-(benzyloxy)-6-bromo-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole (2 g, 5.16 mmol) in toluene (30 mL) is added tetrahydropyran-4-ylamine (800 mg, 7.91 mmol), palladium acetate (60 mg, 267 μ mol), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (200 mg, 508 μ mol) and sodium tert-butoxide (700 mg, 7.28 mmol) under N₂. After the reaction is stirred at 100 °C under N₂ for 1 hour, EtOAc (30 mL) is added and the reaction mixture is filtered. The filtrate is concentrated and the residue is purified by silica gel column chromatography eluting first with EtOAc:PE (1/1) and then EtOAc to give the desired product (1.87 g, 88.8% yield). MS (*m/z*): 408.2 (M+H).

Preparation 73

15 *N*-(5-(Benzyloxy)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)acetamide

To a solution of 5-(benzyloxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1 *H*-indazol-6-amine (1.87 g, 4.59 mmol) in THF (30 mL) is added acetyl chloride (0.39 mL, 5.48 mmol) and K₂CO₃ (760 mg, 5.50 mmol). After the reaction mixture is heated to reflux for 30 min, H₂O (20 mL) and EtOAc (30 mL) are added. The organic phase is separated, washed with saturated aqueous NH₄Cl, dried and concentrated to give the product (1.7 g, 82.4% yield). MS (*m/z*): 450.2 (M+H).

Preparation 74

25 *N*-(5-Hydroxy-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-6-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)acetamide

To a solution of *N*-(5-(benzyloxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-6-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)acetamide (1.7 g, 3.78 mmol) in EtOH (100 mL) and EtOAc (100 mL) is added Pd/C (1 g, 10% wt). After the reaction mixture is stirred at RT under H₂ overnight, it is filtered and the filtrate is concentrated. The residue is purified by silica gel column chromatography eluting first with PE:EtOAc (1:1) and then EtOAc to give the product (1.2 g, 88.2% yield). MS (*m/z*): 360.2 (M+H).

-26-

Preparation 75

N-(5-(2-Fluoro-4-nitrophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-1*H*-indazol-6-yl)-*N*-(tetrahydro-2 *H*-pyran-4-yl)acetamide

- 5 To a solution of *N*-(5-hydroxy-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-6-yl)-*N*-(tetrahydro-2 *H*-pyran-4-yl)acetamide (1.2 g, 3.34 mmol) in DMF (30 mL) is added 1,2-difluoro-4-nitrobenzene (0.64 g, 4.02 mmol) and Cs₂CO₃ (1.63 g, 5.00 mmol). After the reaction mixture is stirred at 100 °C for 2 hours, EtOAc (60 mL) and saturated aqueous NH₄Cl are added. The organic phase is separated, dried over MgSO₄ and concentrated.
- 10 The residue is purified by silica gel column chromatography eluting first with PE:EtOAc (1:1) and then EtOAc to give the product (1.44 g, 86.5% yield). MS (*m/z*): 499.2 (M+H).

Preparation 76

5-(4-Amino-2-fluorophenoxy)-*N*-(tetrahydro-2 *H*-pyran-4-yl)-1 *H*-indazol-6-amine

- 15 The title compound is prepared essentially by the method of Preparation 4 1. MS (*m/z*): 343.1 (M+H).

Preparation 77

5-(Benzyloxy)-6-(6-methylpyridin-3 -yl)-1-(tetrahydro-2 *H*-pyran-2-yl)-1*H*-indazole

- 20 To a solution of 5-(benzyloxy)-6-bromo-1-(tetrahydro-2 *H*-pyran-2-yl)-1*H*-indazole (4 g, 10.3 mmol) in 1,4-dioxane (25 mL) is added bis(pinacolato)diboron (3 g, 11.8 mmol), dppf (0.3 g, 541 μmol), PdCl₂(dppf) (0.42 g, 514 μmol) and KOAc (2 g, 20.4 mmol) under N₂. After the reaction mixture is stirred at reflux for 5 hours, 5-bromo-2-methylpyridine (2.1 g, 12.2 mmol), tetrakis(triphenylphosphine)palladium (Pd(PPh₃)₄) (0.6 g, 519 μmol) and Cs₂CO₃ (4 g, 12.3 mmol) are added and the mixture is stirred at
- 25 reflux overnight. The reaction mixture is cooled and filtered, the filtrate is concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (2:1) to give the product (1.9 g, 46.0% yield). MS (*m/z*): 400.1 (M+H).

30

Preparation 78

6-(6-Methylpyridin-3-yl)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-5-ol

-27-

To a solution of 5-(benzyloxy)-6-(6-methylpyridin-3-yl)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole (1.44 g, 3.60 mmol) in EtOH (50 mL) and EtOAc (50 mL) is added Pd/C (500 mg, 10 % wt) under N₂. The resulting mixture is degassed by evacuation and backfilled with nitrogen. Then the reaction mixture is stirred at RT under H₂ atmosphere overnight. The reaction mixture is filtered. The filtrate is concentrated to give the product (982 mg, 88.0% yield). MS (*m/z*): 310.1 (M+H).

Preparation 79

5-(2-Fluoro-4-nitrophenoxy)-6-(6-methylpyridin-3-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole

The title compound is essentially made by the same method of Preparation 75. MS (*m/z*): 449.2 (M+H).

Preparation 80

3-Fluoro-4-(6-(6-methylpyridin-3-yl)-1 *H*-indazol-5-yloxy)aniline

The title compound is prepared essentially by the method of Preparation 41. MS (*m/z*): 335.1 (M+H).

Preparation 81

1-(4-Bromo-2-fluorophenoxy)-2-fluoro-5-methyl-4-nitrobenzene

The title compound is prepared essentially by the same method of Preparation 75. ¹H NMR (d₆-dimethylsulfoxide (DMSO)) δ 8.20 (d, 1H), 7.80 (d, 1H), 7.42 (d, 1H), 7.30(d, 1H), 7.10(d, 1H).

Preparation 82

4-(4-Bromo-2-fluorophenoxy)-5-fluoro-2-methylaniline

The title compound is prepared essentially by the method of Preparation 53. MS (*m/z*): 315.8 (M+H).

Preparation 83

5-(4-Bromo-2-fluorophenoxy)-6-fluoro-1 *H*-indazole

-28-

To a suspension of 4-(4-bromo-2-fluorophenoxy)-5-fluoro-2-methylaniline (5.2 g, 16.6 mmol) in water (100 mL) is added fluoroboric acid (6.06 g, 33.1 mmol) at RT. The solution is cooled to 0 °C and NaNO₂ (1.71 g, 24.8 mmol) in water (2 mL) is added. The reaction is stirred at 0 °C for 40 min. CHCl₃ (200 mL) is added. The organic phase is separated, dried over Na₂SO₄, and filtered. To the filtrate is added KOAc (7.31 g, 74.5 mmol) and 18-crown-6-ether (0.218 g, 0.82 mmol). The reaction is stirred at RT for 1 hour. The reaction mixture is washed with saturated aqueous sodium chloride, dried over Na₂SO₄, filtered and evaporated. The residue is washed with DCM and filtered to offer the desired product as a light yellow solid. The filtrate is purified by chromatography eluting with DCM then EtOAc:hexane (1:1) to give additional desired product. Both portions of the solid are combined to offer the desired product (3.2 g, 59% yield). MS (*m/z*): 324.8 (M+H).

Preparation 84

15 5-(4-Bromo-2-fluorophenoxy)-6-fluoro-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole

The title compound is prepared essentially by the method of Preparation 9.

MS (*m/z*): 410.8 (M+H).

Preparation 85

20 N-(Diphenylmethylene)-3-fluoro-4-(6-fluoro-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-5-yloxy)aniline

The mixture of 5-(4-bromo-2-fluorophenoxy)-6-fluoro-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole (0.97 g, 2.37 mmol), benzophenone imine (0.64 g, 3.56 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.10 g, 0.075 mol), Cs₂CO₃ (1.16 g, 3.56 mmol), Pd₂(dba)₃ (0.11 g, 0.12 mmol) in 1,4-dioxane (20 mL) is purged with nitrogen, heated to 100 °C and stirred overnight. The reaction mixture is cooled to RT, extracted with EtOAc, washed with saturated aqueous sodium chloride, dried over Na₂SO₄, filtered and concentrated (1.45 g). MS (*m/z*): 510 (M+H).

-29-

Preparation 86

3-Fluoro-4-(6-fluoro-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-5-yloxy)aniline

To a solution of *N*-(diphenylmethylene)-3-fluoro-4-(6-fluoro-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-5-yloxy)aniline (1.45 g, 2.85 mmol) in THF (30 mL) and water (5 mL) is added IN aqueous HCl (5.69 mL, 5.69 mmol). The reaction is stirred at RT for 2 hours. EtOAc is added and the mixture is washed with saturated aqueous NaHCO₃ solution, saturated aqueous sodium chloride, dried over Na₂SO₄, filtered and evaporated. The residue is purified by chromatography eluting with DCM then EtOAc:hexane (1:1) to offer the desired product as a pale gel (0.53 g, 54% yield). MS (*m/z*): 346 (M+H).

10

Preparation 87

Ethyl 5-(2-fluoro-4-nitrophenoxy)- 1-(tetrahydro-2*H*-pyran-2-yl)- 1*H*-indazole-6-carboxylate

The title compound is essentially made by the same method of Preparation 75. MS (*m/z*): 430.1 (M+H).

15

Preparation 88

Ethyl 5-(2-fluoro-4-nitrophenoxy)- 1*H*-indazole-6-carboxylate

To a solution of ethyl 5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-1*H*-indazole-6-carboxylate (15 g, 35 mmol) in DCM (300 mL) is added trifluoroacetic acid (TFA) (30 mL), and stirred at RT overnight. DCM is evaporated. The residue is partitioned between EtOAc (800 mL) and 5% aqueous NaHCO₃ (400 mL). The organic layer is washed with saturated aqueous sodium chloride, dried over MgSO₄, and concentrated. The residue is purified by silica gel column chromatography eluting with PE:acetone (5: 1) to afford the product (10.4 g, 86% yield). MS (*m/z*): 346. 1 (M+H).

25

Preparation 89

Ethyl 5-(2-fluoro-4-nitrophenoxy)-1-methyl-1 *H*-indazole-6-carboxylate

The title compound is prepared essentially by the method of Preparation 11: MS (*m/z*): 360.1 (M+H).

30

-30-

Preparation 90

5-(2-Fluoro-4-nitrophenoxy)-1-methyl-1*H*-indazole-6-carboxylic acid

To a solution of ethyl 5-(2-fluoro-4-nitrophenoxy)-1-methyl-1*H*-indazole-6-carboxylate (1.19 g, 3.5 mmol) in THF/H₂O (15 mL/5 mL) is added LiOH (0.2 g, 8.3 mmol). After the reaction is stirred at RT for 2 hours, the solvents are removed. The residue is acidified with 2N HCl to pH 5, and extracted with EtOAc (50 mL). The organic phase is washed with saturated aqueous sodium chloride, dried and concentrated to give the product (1.1 g, 100% yield). MS (*m/z*): 332.0 (M+H).

10

Preparation 91

tert-Butyl 5-(2-fluoro-4-nitrophenoxy)-1-methyl-1*H*-indazol-6-ylcarbamate

The suspension of 5-(2-fluoro-4-nitrophenoxy)-1-methyl-1*H*-indazole-6-carboxylic acid (1.1 g, 3.3 mmol), diphenyl phosphoryl azide (0.91 g, 3.3 mmol), TEA (0.33 g, 3.3 mmol) and 4A molecular sieve (2.5 g) in *tert*-butanol (50 mL) is heated at reflux overnight. Then the solid is filtered off and the filtrate is concentrated. The residue is partitioned between saturated aqueous sodium chloride (40 mL) and EtOAc (100 mL). The organic phase is separated, dried and concentrated and the residue is purified by silica gel column chromatography eluting with PE:acetone (4: 1) to give the product (0.64 g, 47.9% yield). MS (*m/z*): 403. 1 (M+H).

20

Preparation 92

tert-Butyl 5-(4-amino-2-fluorophenoxy)-1-methyl-1*H*-indazol-6-ylcarbamate

The title compound is prepared essentially by the method of Preparation 38. MS (*m/z*): 373.1 (M+H).

25

Preparation 93

5-(5-(Benzyloxy)-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazol-6-yl)pyridin-2-amine

To a solution of 5-(benzyloxy)-6-bromo-1-(tetrahydro-2 *H*-pyran-2-yl)-1 *H*-indazole (1.5 g, 3.87 mmol) in 1,4-dioxane (50 mL) is added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (1 g, 4.54 mmol), Pd(PPh₃)₄ (200 mg, 173

30

-31-

μmol) and CS_2CO_3 (5 g, 10.6 mmol). After the reaction mixture is stirred at reflux overnight, it is partitioned between EtOAc (100 mL) and saturated aqueous NH_4Cl (50 mL). The organic phase is separated, dried and concentrated. The residue is purified by silica gel column chromatography eluting with DCM:MeOH (15: 1) to give the product
5 (0.80 g, 51.5% yield). MS (m/z): 401.1 (M+H).

Preparation 94

tert-Butyl 5-(5-(benzyloxy)-1-(tetrahydro-2 H-pyran-2-yl)-1 H-indazol-6-yl)pyridin-2-ylcarbamate

10 To a solution of 5-(5-(benzyloxy)-1-(tetrahydro-2 H-pyran-2-yl)-1 H-indazol-6-yl)pyridin-2-amine (310 mg, 774 μmol) in THF (20 mL) is added di-*tert*-butyldicarbonate (250 mg, 1.13 mmol) and TEA (1 mL, 7.17 mmol). After the reaction mixture is stirred at RT for 3 hours, it is partitioned between EtOAc (50 mL) and saturated aqueous NH_4Cl (20 mL). The organic phase is separated, dried and concentrated. The residue is purified
15 by silica gel column chromatography eluting with PE:EtOAc (3:1) to give the product (260 mg, 67.1% yield). MS (m/z): 501.2 (M+H).

Preparation 95

tert-Butyl 5-(5-hydroxy-1-(tetrahydro-2 H-pyran-2-yl)-1 H-indazol-6-yl)pyridin-2-ylcarbamate

20 To a solution of *tert-butyl 5-(5-(benzyloxy)-1-(tetrahydro-2 H-pyran-2-yl)-1 H-indazol-6-yl)pyridin-2-ylcarbamate* (260 mg, 519 μmol) in EtOH (25 mL) and EtOAc (25 mL) is added Pd/C (100 mg, 10% wt) under N_2 . The resulting mixture is degassed by evacuation and backfilled with nitrogen. Then the reaction mixture is stirred at RT under
25 H_2 atmosphere for 6 hours. The reaction mixture is filtered. The filtrate is concentrated to give the product (200 mg, 93.8% yield). MS (m/z): 411.1 (M+H).

Preparation 96

tert-Butyl 5-(5-(2-fluoro-4-nitrophenoxy)-1-(tetrahydro-2 H-pyran-2-yl)-1 H-indazol-6-yl)pyridin-2-ylcarbamate

30 The title compound is essentially made by the same method of Preparation 75.

-32-

MS (*m/z*): 550.2 (M+H).

Preparation 97

5 *tert-Butyl* 5-(5-(4-amino-2-fluorophenoxy)- 1-(tetrahydro-2*H*-pyran-2-yl)- 1*H*-indazol-6-yl)pyridin-2-ylcarbamate

The title compound is prepared essentially by the method of Preparation 38.

MS (*m/z*): 520.2 (M+H).

Preparation 98

10 *tert-Butyl* 4-(5-(2-fluoro-4-nitrophenoxy)- 1-methyl- 1*H*-indazol-6-yl)- 1*H*-pyrazole- 1-carboxylate

5-(2-Fluoro-4-nitrophenoxy)-1-methyl-6-(1 *H*-pyrazol-4-yl)-1 *H*-indazole (1.56 g, 4.42 mmol) in DCM (15.6 mL) is added di-*tert*-butyldicarbonate (1.09 mL, 4.83 mmol). The mixture is stirred for 30 min. HPLC shows the reaction is complete. The solvent is removed under reduced pressure. Then MTBE (5 mL) is added. The solution is cooled with ice water bath and stirred for 15 min, then filtered to give the title compound as a solid (0.764 g, 48.9 %).

Preparation 99

20 6-Bromo-5-(2-fluoro-4-nitrophenoxy)- 1*H*-indazole

To a 3000 mL flask is added 6-bromo-5-(2-fluoro-4-nitrophenoxy)-2-(tetrahydro-2*H*-pyran-2-yl)-2 *H*-indazole (250 g, 573.1 mmol) followed by MeOH (1000 mL) and MeSO₃H (112.71 mL, 1.72 mol) and heated to 50 °C for 14 hours. Solid crystallizes out of solution. The mixture is then cooled to RT. The reaction mixture is concentrated under vacuum at 45 °C to dryness to get solid. The solid is diluted with DCM (2000 mL) and treated with water (1000 mL) and 5N NaOH (about 350 mL) until the pH is 8-9. The organic layer is separated and the solvent is removed followed by azeotrope with toluene to give 195.6 g of the yellow solid material. MS (*m/z*): 354.0 (M+H).

30 Preparation 100

6-Bromo-5-(2-fluoro-4-nitrophenoxy)- 1-methyl- 1*H*-indazole

-33-

To a 4000 mL flask is added 6-bromo-5-(2-fluoro-4-nitrophenoxy)-1H-indazole (230 g, 653.2 mmol), DMF (3000 mL), and K_2CO_3 (135.41 g, 979.78 mmol). The reaction mixture is cooled to 4.5 oC with an ice bath. To the mixture is added methyl iodide (92.71 g, 653.19 mmol) and the reaction is allowed to stir for 20 min at the same temperature. The reaction is allowed to warm to RT and stir for 13 hours. The reaction mixture is monitored by liquid chromatography mass spectrometry. Additional methyl iodide (50 g) and $NaHCO_3$ (33 g) are added and the reaction mixture is stirred at RT until the reaction is completed. The reaction mixture is divided into two portions labeled (A) and (B), and each one is quenched with water (1 L) followed by extraction with EtOAc (1 L) causing some solids to form. The combined solids from (A) and (B) are collected by vacuum filtration to give 70 g of crude weight having about 90% 6-bromo-5-(2-fluoro-4-nitrophenoxy)-1-methyl-1H-indazole (which is the desired isomer) and 8% 6-bromo-5-(2-fluoro-4-nitrophenoxy)-2-methyl-2H-indazole isomers. This solid is then triturated with 1000 mL of DCM and 750 mL of MeOH overnight (about 14 hours). The solid is collected by filtration and rinsed with fresh DCM (100 mL) to give 55.5 g of desired material labeled (C). The mother liquor is concentrated and labeled (D). The organic layer from (A) and (B) are separated and concentrated. The residues from (A) and (B) are combined to give 185 g of crude as an orange solid labeled (E).

The crude compound (E) is dissolved in MeOH and DCM, and then the solution is divided into 3 portions. 600 g of silica gel is mixed with each portion of solution, and then the silica gel mixture is loaded into seven 270 g size empty cartridges. Seven 1.5 kg ISCO® columns are used with solvent system starting with 25% EtOAc in hexanes, then it is switched to 50% EtOAc in hexanes to give 62 g of the desired compound as a yellow powder labeled (F). After 7 runs, there are some mixed fractions of 6-bromo-5-(2-fluoro-4-nitrophenoxy)-1-methyl-1H-indazole and 6-bromo-5-(2-fluoro-4-nitrophenoxy)-2-methyl-2H-indazole isomers. The fractions are combined and combined with mother liquor (D) from the procedure described above to give 17 g of the mixture. The mixture is dissolved in MeOH and DCM, mixed with 170 g of silica into the solution, and run on a 1.5 kg column to give 10 g of a yellow powder as the desired product labeled (G). Total yield (55.5 g (C), 62 g (F), and 10 g (G)) is 127.5 g.

-34-

Preparation 101

tert-Butyl 4-(5-(2-fluoro-4-nitrophenoxy)-1-methyl-1*H*-indazol-6-yl)-1*H*-pyrazole-1-carboxylate

To a 12 L round bottom flask equipped with overhead agitation, a thermocouple, heating mantle, condenser, and subsurface nitrogen sparge is added 1,4-dioxane (7.44 L) and water (1.67 L). The solution is purged with N₂ (inlet tube). Next 6-bromo-5-(2-fluoro-4-nitrophenoxy)-1-methyl-1*H*-indazole (595 g, 1.63 mol) is added and the solution is purged with N₂ again. *tert-Butyl* 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate (717.02 g, 2.44 mol), potassium phosphate tribasic *N*-hydrate (689.8 g, 3.25 mol), and 1,1'-Bis(di-*tert*-butylphosphino)ferrocene (7.71 g, 16.25 mmol) are added. Finally, Pd₂(dba)₃ (7.44 g, 8.13 mmol) is added. The solution is purged for 15 min and then heated at 60 °C for 12 hours. The reaction is not complete and more Pd₂(dba)₃ (7.44 g, 8.13 mmol) is added. The solution is again heated at 60 °C for 3 additional hours and the reaction is complete. 1,4-Dioxane is then removed (Buchi® bath temp 60 °C) and the residue is re-dissolved in 10 volumes (6 L) of DCM. Water (3 L) is added and then the layers are separated. The organic solution is dried over Na₂SO₄, filtered and concentrated to a dark oil (835 g). The material is not purified and is forward processed to the next step. The material is about 60% desired product and about 40% 5-(2-fluoro-4-nitrophenoxy)-1-methyl-6-(1*H*-pyrazol-4-yl)-1*H*-indazole. The crude obtained is protected in the next step. It is assumed that 50% of the crude product is the 5-(2-fluoro-4-nitrophenoxy)-1-methyl-6-(1*H*-pyrazol-4-yl)-1*H*-indazole.

To a 22 L round bottom flask with overhead agitation, thermocouple, 1 L addition funnel, N₂ purge, and cooling bath is added a solution of crude 5-(2-fluoro-4-nitrophenoxy)-1-methyl-6-(1*H*-pyrazol-4-yl)-1*H*-indazole (835 g, 1.18 mol) in DCM (6 L) of di-*tert*-butyldicarbonate (283.69 g, 1.30 mol) dissolved in DCM (350 mL) of is added to an addition funnel. The solution is added dropwise over 48 min. After the reaction is complete, DCM is removed by rotary evaporation to give a dark oil. To the dark oil is added MTBE (2.5 L) and the oily solution is cooled to about 0-5 °C. The solution is seeded with material obtained in Preparation 98. After seeding, crystallization is observed and the resulting slurry is stirred for 30-40 min. The pale yellow slurry is filtered over a polypropylene pad and the cake is washed with cold (0-5 °C) MTBE (1.5

-35-

L). The solids are dried in a 40 °C vacuum oven overnight to give the desired product (443 g, 60% crude yield). MS (*m/z*): 354.0 (M+H). The material is shown to be about 93-95% pure by HPLC and is therefore forward processed.

5

Preparation 102

tert-Butyl 4-(5-(4-amino-2-fluorophenoxy)-1-methyl-1*H*-indazol-6-yl)-1*H*-pyrazole-1-carboxylate

To a 3 gallon tank is added *tert-bvXyl* 4-(5-(2-fluoro-4-nitrophenoxy)-1-methyl-1*H*-indazol-6-yl)-1*H*-pyrazole-1-carboxylate (433.0 g, 952.8 mmol) followed by THF (6.5 L) and Pd/C (21.65 g, 10% Pd/C and 21.65 g, 5% Pd/C). The mixture is heated to 35 °C under hydrogen gas for 2 hours. The reaction is then cooled to RT and allowed to stir under hydrogen gas overnight, then is heated to 40 °C under hydrogen gas for seven hours. An additional 2 g Pd/C (1 g, 10% Pd/C and 1 g, 5% Pd/C) is added and stirred under hydrogen gas for another hour and cooled to RT. The mixture is again stirred under hydrogen gas overnight and the reaction is completed. The mixture is filtered over a combination of GFF® and Watman® paper. The filtrate is concentrated to a slightly yellow solid (446 g, 110% recovery).

20

Preparation 103

Methyl 2-oxo-1,2-dihydropyridine-3-carboxylate

To a flask is added 2-hydroxynicotinic acid (10 g, 72 mmol), concentrated H₂SO₄ (2 mL) and MeOH (400 mL), followed by toluene (80 mL). The reaction mixture is heated to reflux overnight with a Dean-Stark trap. After cooling to RT, the mixture is filtered and the filtrate is concentrated. The residue is dissolved in DCM (200 mL), neutralized with saturated aqueous NaHCO₃ to pH 7 and extracted with DCM (200 mL) for three times. The combined organic phases are dried and concentrated to give the desired product (8.2 g, 74% yield). MS (*m/z*): 153.9 (M+H).

30

Preparation 104

Methyl 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

To a mixture of methyl 2-oxo-1,2-dihydropyridine-3-carboxylate

-36-

(6.0 g, 39 mmol), 4-fluorophenylboronic acid (16.3 g, 116 mmol), cupric acetate (14 g, 78 mmol) and pyridine (12 g, 0.156 mol) in DCM (300 mL) is added 4 Å molecular sieves (5 g). The reaction mixture is stirred at RT overnight open to air. After the solids are filtered and washed with water, the filtrate is extracted with DCM (100 mL). The organic layer is dried over MgSO₄ and concentrated. The residue is purified by silica gel column chromatography eluting with PE:DCM (2:1 to 0:1) to give the product (9.6 g, 100% yield). MS (*m/z*): 248.0 (M+H).

Preparation 105

10 Ethyl 2-(4-fluorophenyl)hydrazinecarboxylate

To a solution of 4-fluorophenylhydrazine hydrochloride (2 g, 12.05 mmol) in THF (60 mL) is added DIPEA (6 mL, 34.40 mmol), ethyl chloroformate (1.2 mL, 12.55 mmol) and 4-dimethylaminopyridine (0.16 g, 1.31 mmol). The mixture is stirred at RT for 4 hours. The reaction is diluted with water and extracted with EtOAc, the organic phase is washed with saturated aqueous sodium chloride, dried over Na₂SO₄ and concentrated. The residue is purified by column chromatography on silica gel, eluting with DCM then DCM:MeOH (80:1) to afford the title compound (1.92 g, 80.5% yield). MS (*m/z*): 199 (M+H).

20 Preparation 106

1-(4-Fluorophenyl)-2-methylhydrazine

To a mixture of LiAlH₄ (1.1 g) in THF (15 mL) is added a solution of ethyl 2-(4-fluorophenyl)hydrazinecarboxylate (1.9 g, 9.59 mmol) in THF (10 mL) dropwise under nitrogen in an ice-salt bath. After the addition, the ice bath is removed and the mixture is heated to 60 °C overnight. The reaction is cooled and quenched with water. The precipitate is filtered and washed with EtOAc. The organic phase is separated, dried over Na₂SO₄, and concentrated. The residue is purified by flash chromatography, eluting with PE:EtOAc (80:1 to 60:1) to afford the title compound (1 g, 74% yield). MS (*m/z*): 141 (M+H).

30 Preparation 107

Ethyl 2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1 *H*-pyrazole-4-carboxylate

-37-

A mixture of 1-(4-fluorophenyl)-2-methylhydrazine (0.6 g, 4.28 mmol), diethyl 2-acetylmalonate (0.96 g, 4.75 mmol), and acetic acid (0.51 g, 8.49 mmol) in water (15 mL) is heated at 115 °C for 3 hours. The reaction is cooled and extracted with EtOAc twice. The organic phase is washed with saturated aqueous sodium chloride, dried over Na₂SO₄ and concentrated. The residue is purified by column chromatography on silica gel, eluting with DCMMcOH (from 150:1 to 60:1) to afford the title compound (0.59 g, 49.5% yield). MS (*m/z*): 279 (M+H).

Preparation 108

(E)-2-(2-(4-Fluorophenyl)hydrazono)acetaldehyde

A solution of 4-fluorophenylhydrazine hydrochloride (1 g, 6 mmol) in THF (20 mL) is treated with DIPEA (3 mL, 18 mmol). Then oxalaldehyde (40% in water, 0.89 g, 6.0 mmol) in THF (10 mL) is added dropwise in an ice-bath. After the addition, the mixture is stirred at RT for 30 min, quenched with water, and extracted with EtOAc. The organic phase is washed with saturated aqueous sodium chloride, dried over Na₂SO₄ and concentrated to afford the crude title compound (0.97 g, 97% yield). MS (*m/z*): 167 (M+H).

Preparation 109

Ethyl 2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxylate

Crude (E)-2-(2-(4-fluorophenyl)hydrazono)acetaldehyde (0.97 g, 5.8 mmol) is dissolved in EtOH (50 mL), and diethyl malonate (0.93 g, 5.8 mmol) and piperidine (0.2 mL, 2.0 mmol) are added. The mixture is heated at reflux overnight. The reaction mixture is then cooled and concentrated. The residue is diluted with water and extracted with EtOAc twice. The combined organic extracts are dried over Na₂SO₄ and concentrated. The residue is purified by column chromatography on silica gel, eluting with PE:EtOAc (from 3:1 to 1:1), to afford title compound (0.26 g, 17 % yield of two steps) MS (*m/z*): 263 (M+H).

Preparation 110

Methyl 3-(4-fluorophenylamino)-3-oxopropanoate

-38-

To a solution of 4-fluoroaniline (4.4 mL, 45 mmol) in acetone is added TEA (8.5 mL, 67 mmol) and methyl malonyl chloride (7.2 mL, 67 mmol). The mixture is stirred at RT for 5 hours and then concentrated. After water (20 mL) is added, the residue is acidified with concentrated HCl to pH 3. The precipitate is collected by filtration and washed with PE to give the product (14.1 g, 100% yield). MS (*m/z*): 212.1 (M+H).

The following compounds are prepared essentially by the method of Preparation 110:

Prep. No.	Chemical name	Physical data MS (<i>m/z</i>)(M+H)
111	Ethyl 3-oxo-3-(phenylamino)propanoate	208
112	Ethyl 3-(4-fluorophenylamino)-3-oxopropanoate	226.1

Preparation 113

10 Ethyl 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate

To a solution of methyl 3-(4-fluorophenylamino)-3-oxopropanoate (10.1 g, 48 mmol) in EtOH (100 mL) is added *trans*-4-methoxy-3-buten-2-one (5.7 g, 57 mmol) and CH₃ONa (3.1 g, 57 mmol). The mixture is heated at reflux overnight and then concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (from 5:1 to 2:1) to give the product (2.1 g, 16% yield). MS (*m/z*): 276.1 (M+H).

The following compounds are prepared essentially by the method of Preparation 113:

Prep. No.	Chemical name	Physical data MS(<i>m/z</i>) (M+H)
114	Ethyl 1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	276.1
115	Ethyl 5-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate	258.1

20

Preparation 116

(Z)-4-Aminopent-3-en-2-one

To a solution of 2,4-pentanedione (20.0 g, 0.2 mol) in water (20 mL) is added 25% aqueous ammonia (13.2 mL, 0.2 mol) dropwise at RT. The mixture is stirred at RT

-39-

for 2 hours. Then the solvent is removed to give the product (20.0 g, 100% yield) as a solid. ¹H NMR (Acetone-d₆, 300 MHz): 1.88 (s, 3H), 1.88 (s, 3H), 2.8 (br s, 1H), 6.54 (br s, 1H), 9.7 (br s, 1H).

5

Preparation 117

Ethyl 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate

A solution of (Z)-4-aminopent-3-en-2-one (20.0 g, 0.2 mol) in dry THF (20 mL) is added to a solution of ethyl cyanoacetate (22.6 g, 0.2 mol) and TEA (20.2 g, 0.2 mol) in dry THF (200 mL). The reaction mixture is heated at reflux for 56 hours and then
10 concentrated. The residue is kept standing at RT for 5 hours and the precipitate is filtered and washed with EtOAc to afford the title compound (7.3 g, 19.9% yield). MS (*m/z*): 196.0 (M+H).

Preparation 118

15

Ethyl 1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate

A suspension of ethyl 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (5.0 g, 0.025 mol), 4-fluorophenylboronic acid (10.7 g, 0.077 mol), cupric acetate (1.33 g, 0.007 mol), pyridine (6.86 mL), and 4 Å molecular sieves (5.0 g) in 1,4-dioxane (80 mL) is heated at 80 °C for 68 hours. The solids are filtered off and the filtrate is
20 concentrated. The residue is partitioned with EtOAc (50 mL) and 2N HCl (70 mL). The precipitated solid is collected by filtration and washed with EtOAc to give the title product (1.2 g). The EtOAc filtrate is separated, dried and concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc:MeOH (40:20:1) to give another portion of product (0.12 g), (1.32 g total, 17.8 % yield). MS (*m/z*): 290.1
25 (M+H).

Preparation 119

Ethyl 4,6-dimethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylate

A suspension of ethyl 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (7.5
30 g, 0.038 mol), phenylboronic acid (14.1 g, 0.115 mol), cupric acetate (1.38 g, 0.008 mol), pyridine (7.5 mL) in 1,4-dioxane (80 mL) is heated at 80 °C for 96 hours. The solid is

-40-

filtered off and the filtrate is concentrated. The residue is partitioned with EtOAc (50 mL) and 2N HCl (70 mL), and the precipitate is collected by filtration and washed with EtOAc to give the title product (2.95 g). The EtOAc solution is separated, dried and concentrated. The residue is purified by silica gel column chromatography eluting with PE:acetone (2:1) to give another portion of (0.3 g). (3.25 g, 31.2% yield). MS (*m/z*): 272.0 (M+H).

Preparation 120

10 Ethyl 5-(bromomethyl)-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1 *H*-pyrazole-4-carboxylate

To a solution of ethyl 2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1 *H*-pyrazole-4-carboxylate (1.2 g, 4.3 mmol) and azobisisobutyronitrile (AIBN) (0.09 g, 0.06 mmol) in DCM is added N-bromosuccinimide (NBS) (0.9 g, 4.3 mmol) in three portions at RT. The resulting reaction mixture is stirred at RT overnight. The mixture is concentrated and the residue is purified by silica gel column chromatography eluting with PE:EtOAc (4: 1) to give the product as a white solid (1.3 g, 84% yield). MS (*m/z*) 357.0 (M+H).

Preparation 121

20 Ethyl 5-((1*H*-pyrazol-1-yl)methyl)-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-pyrazole-4-carboxylate

To a solution of ethyl 5-(bromomethyl)-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1 *H*-pyrazole-4-carboxylate (1.3 g, 3.6 mmol) and 1*H*-pyrazole (0.25 g, 3.6 mmol) in THF (50 mL) and H₂O (1 mL) cooled in an ice-water bath is added solid KOH (0.2 g, 3.6 mmol) in three portions. After the reaction mixture is stirred at RT overnight, the solvent is removed. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (4:1) to give the product (0.87 g, 70% yield). MS (*m/z*): 345.1 (M+H).

30 The following compounds are prepared essentially by the method of Preparation 121 :

Prep.	Chemical name	Physical data
-------	---------------	---------------

No.		MS(<i>m/z</i>)(M+H)
122	Ethyl 2-(4-fluorophenyl)-1-methyl-5-(morpholinomethyl)-3-oxo-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxylate	364.1
123	Ethyl 2-(4-fluorophenyl)-1-methyl-3-oxo-5-(piperidin-1-ylmethyl)-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxylate	362.1

Preparation 124

Ethyl 1-(4-fluorophenyl)-5-(morpholinomethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

A mixture of ethyl 1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (0.275 g, 1 mmol), NBS (0.2 g, 1.1 mmol), AIBN (40 mg, 0.2 mmol) in CCl₄ (20 mL) is heated at reflux for 3 hours. After the reaction is cooled down, morpholine (0.088 mL, 1 mmol) and K₂CO₃ (0.14 g, 1 mmol) are added. The reaction is stirred at RT for another 2 hours. The solvent is removed, and the residue is diluted with water (10 mL) and extracted with EtOAc (20 mL) twice. The combined organic phases are washed with saturated aqueous sodium chloride, dried, and concentrated. The residue is purified by silica gel column chromatography eluting with DCM:MeOH (from 100:1 to 50:1, containing 0.5% 2 N NH₃ in MeOH), to afford the title compound (0.17 g, 47% yield). MS (*m/z*): 361.1 (M+H).

15

Preparation 125

Ethyl 2-(4-fluorophenylcarbamoyl)-3-methylbut-2-enoate

To a solution of 4-fluoroaniline (2 g, 18 mmol) in diethyl isopropylidene malonate (10 g, 50 mmol) is added 1*H*-imidazole (0.25 g, 3.67 mmol). The reaction mixture is stirred at 200 °C under N₂ for 3 hours. After the reaction is cooled, silica gel is added. The mixture is loaded onto a silica gel column, and eluted first with PE and then PE:EtOAc (3:1) to give the product (1.85 g, 39% yield). MS (*m/z*): 266.1 (M+H).

20

Preparation 126

Ethyl 1-(4-fluorophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate

25

A mixture of ethyl 2-(4-fluorophenylcarbamoyl)-3-methylbut-2-enoate (1.85 g, 6.97 mmol) and *N,N*-dimethylformamide dimethyl acetal (5 mL, 37.45 mmol) is stirred at 90 °C for 90 min. After the reaction is cooled, EtOAc (30 mL) and saturated

-42-

NH₄Cl solution (20 mL) are added. The organic phase is separated, dried and concentrated. The residue is purified by silica gel column chromatography eluting with DCM:MeOH (10:1). The fractions containing product are concentrated, and the residue is mixed with ether to give 1.2 g of yellow solid which is filtered and discarded. The filtrate is concentrated and purified again by silica gel column chromatography eluting with DCMMeOH (20:1) to give the product (500 mg, 26% yield). MS (*m/z*): 276.1 (M+H).

Preparation 127

10 Ethyl 2-(4-fluorophenyl)-6-methyl-3-oxo-2,3-dihydropyridazine-4-carboxylate

To a suspension of 1-triphenylphosphoranylidene-2-propanone (3.18 g, 9.99 mmol) in THF (50 mL) is added diethyl ketomalonate (1.74 g, 9.99 mmol). The resulting mixture is stirred at RT for 30 min to give a clear solution. Then this solution is added to a solution of 4-fluorophenylhydrazine hydrochloride (1.62 g, 9.96 mmol) in EtOH:H₂O (30 mL:30 mL). After the resulting mixture is refluxed for 1 hour, TEA (3 mL) is added and the mixture is stirred at reflux for another 1 hour. Then it is concentrated and the residue is partitioned with saturated aqueous NH₄Cl (30 mL) and EtOAc (30 mL). The organic phase is separated, dried and concentrated. The residue is purified by silica gel column chromatography eluting with PE:EtOAc (3:1) to give the product (1.20 g, 43% yield). MS (*m/z*): 211.1 (M+H).

Preparation 128

1-(4-Fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

To a solution of methyl 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (10.0 g, 0.04 mol) in MeOH (150 mL) and water (50 mL) is added LiOH (1.9 g, 0.08 mol). The resulting reaction mixture is stirred at RT for 0.5 hour. After most of the MeOH is removed, the mixture is acidified with concentrated aqueous HCl until a white solid precipitates. The solid is collected by filtration and washed with water (5 mL) to give the desired product (8.7 g, 93% yield). MS (*m/z*): 234.0 (M+H).

30

The following compounds are prepared essentially by the method of Preparation 128:

Prep. No.	Chemical name	Physical data MS(m/z)(M+H)
129	2-(4-Fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid	251
130	2-(4-Fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxylic acid	235
131	1-(4-Fluorophenyl)-6-methyl-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid	248.1
132	1-(4-Fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid	
133	4,6-Dimethyl-2-oxo-1-phenyl-1,2-dihydro-pyridine-3-carboxylic acid	244.0
134*	5-((1H-Pyrazol-1-yl)methyl)-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid	
135**	2-(4-Fluorophenyl)-1-methyl-5-(morpholinomethyl)-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylic acid	336.1
136	2-(4-Fluorophenyl)-1-methyl-3-oxo-5-(piperidin-1-ylmethyl)-2,3-dihydro-1H-pyrazole-4-carboxylic acid	334.1
137	1-(4-Fluorophenyl)-5-methyl-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid	248.0
138	5-Methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid	230.1
139	1-(4-Fluorophenyl)-5-(morpholinomethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	333.1
140**	1-(4-Fluorophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	248.1
141	2-(4-Fluorophenyl)-6-methyl-3-oxo-2,3-dihydropyridazine-4-carboxylic acid	249.0

*: KOH is used as the base.

** : NaOH is used as the base.

Preparation 142

5 6-Methyl-2-oxo- 1-phenyl- 1,2-dihydro-pyridine-3 -carboxylic acid

To a solution of sodium ethoxide in EtOH (prepared from sodium (0.5 g, 21.75 mmol) dissolved in EtOH (40 mL)) is added ethyl 3-oxo-3-(phenylamino)propanoate (4 g, 19.30 mmol) and *trans*-4-methoxy-3-buten-2-one (2 g, 19.98 mmol). After the reaction is stirred at reflux overnight, the mixture is concentrated. The residue is

10 partitioned between H₂O (50 mL) and EtOAc (50 mL). The aqueous layer is acidified with concentrated HCl to a pH 3~4 and then it is extracted with EtOAc. The organic

-44-

extracts are dried and concentrated. The residue is purified by silica gel column chromatography eluting with DCM:MeOH (25:1) to give the product (1.20 g, 27% yield). MS (*m/z*): 230.0 (M+H).

5

Preparation 143

1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1 *H*-pyrazole-4-carboxylic acid

To a mixture of 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1 *H*-pyrazole-4-carbaldehyde (2 g, 9.25 mmol) in water (100 mL) at 75 °C is added a solution of KMnO_4 (1.5 g, 9.49 mmol) in water (200 mL) slowly. After the addition is complete, the reaction mixture is stirred at 75 °C for another 1 hour. Solid KOH is added to make the solution alkaline and the mixture is filtered while it is hot. To the filtrate is added EtOH (10 mL) and EtOAc (50 mL). The organic phase is separated and discarded. The aqueous phase is acidified with concentrated HCl to pH 5 and extracted with EtOAc (60 mL) and DCM (60 mL). The organic phases are combined, dried, and concentrated to give the title product (1.9 g, 88.46% yield). MS (*m/z*): 233.1 (M+H).

15

Preparation 144

Ethyl 3-(4-fluorophenylamino)-3-oxopropanoate

To a 4-necked 10 L round bottom flask, is added DCM (5000 mL), 4-fluoroaniline (111 g, 1.0 mol) and TEA (166 mL, 1.2 mol). Ethyl malonyl chloride (196 g, 1.3 mol) in DCM (500 mL) is added dropwise under N_2 at 0-5 °C (under ice bath) during 4 hours. After addition, the mixture is stirred for 30 min at this temperature. Water (2 L) is added into the mixture with stirring at this temperature. The organic phase is washed with saturated NaHCO_3 , saturated aqueous sodium chloride and dried over anhydrous Na_2SO_4 . The aqueous phase is extracted with EtOAc (2 x 1 L). The organic phase is washed with saturated aqueous sodium chloride and dried over anhydrous Na_2SO_4 . After filtration, the combined organic solution is concentrated to dryness under reduced pressure. The residue is washed with PE (1 L) to give ethyl 3-(4-fluorophenylamino)-3-oxopropanoate (230 g, crude yield 102%) as a yellow solid. MS (*m/z*): 226.1 (M+H).

30

Preparation 145

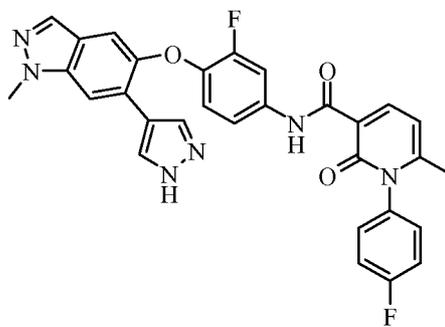
-45-

1-(4-Fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

To a 4-necked 3 L round bottom flask, is added EtOH (1500 mL), ethyl 3-(4-fluorophenylamino)-3-oxopropanoate (139 g, 617 mmol), sodium ethoxide (65.6 g, 925 mmol) and 4-methoxy-3-buten-2-one (103 g, 925 mmol). The mixture is refluxed for 3 hours. After the solution is cooled to RT, the reaction mixture is concentrated under reduced pressure to remove the EtOH. The residue is diluted with DCM (700 mL) and 1 M HCl (1500 mL). The aqueous phase is extracted with DCM (3 x 500 mL). The combined organic extracts are washed with saturated aqueous sodium chloride (1000 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue is triturated with EtOAc (150 mL) at RT (10-15 °C) for 1 hour. After filtration and washing with EtOAc (50 mL), 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid is obtained as a yellow solid (85.3 g, 56% yield). MS (*m/z*): 248 (M+H).

Example 1

15 *N*-(3-Fluoro-4-(1-methyl-6-(1*H*-pyrazol-4-yl)-1*H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide



To a 100 mL round bottom flask is added *tert-butyl* 4-(5-(4-amino-2-fluorophenoxy)-1-methyl-1*H*-indazol-6-yl)-1*H*-pyrazole-1-carboxylate (1.43 g, 3.38 mmol), 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (1.25 g, 5.07 mmol), EDCI (1.48 g, 7.6 mmol) and HOBt (776 mg, 5.07 mmol) followed by DMF (15 mL, 193.99 mmol) and then DIPEA (1.47 mL, 8.44 mmol). The mixture is allowed to stir at RT overnight. The reaction mixture is diluted into EtOAc (300 mL) and washed with saturated aqueous sodium chloride (5 x 100 mL). The combined aqueous solution is extracted with EtOAc (1 x 100 mL) and then the combined organic solutions

-46-

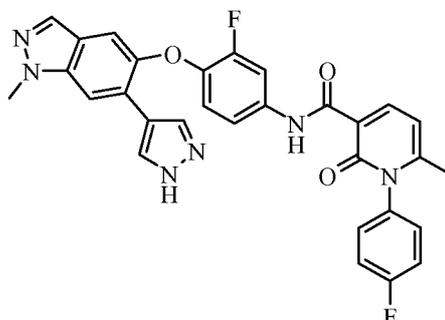
are dried over Na₂SO₄, filtered, and concentrated to dryness. The solid is purified on a silica gel column eluting with DCM (A) and a 10% MeOH in a DCM solution (B), gradient from 100% (A) to 80% (A):20% (B) over 70 min to give *tert-butyl* 4-(5-(2-fluoro-4-(1-(4-fluorophenyl)-6-methyl-1,2-dihydropyridine-3-carboxamido)phenoxy)-1-methyl-1*H*-indazol-6-yl)-1*H*-pyrazole-1-carboxylate as a gold solid (2.20 g, 87% yield). MS (*m/z*): 653. (M+H), 675 (M+Na).

To a round bottom flask is added *tert-butyl* 4-(5-(2-fluoro-4-(1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)-1-methyl-1*H*-indazol-6-yl)-1*H*-pyrazole-1-carboxylate (1.92 g, 2.94 mmol) and DCM (50 mL) followed by triethylsilane (1.88 mL, 11.77 mmol) and TFA (17.8 mL, 235.35 mmol). The reaction mixture is allowed to stir at RT for 1.5 hours. The solvent is removed and diluted into DCM (150 mL) and washed with saturated aqueous NaHCO₃ solution (2 x 100 mL). The organic solution is dried with Na₂SO₄, and concentrated under reduced pressure to give a solid material. The solid is purified on a silica gel column eluting with DCM (A) and a 10% MeOH in DCM solution (B), gradient from 100% (A) to 75%(A):25%(B) over 70 min, held at this 75:25 ratio for 15 min to give the title compound as an off-white solid. The solid is dissolved in hot EtOH (50 mL) followed by a portion-wise addition of distilled water (250 mL) causing a white solid to precipitate. The solid is filtered over a Buchner funnel and washed with distilled water (3 x 15 mL), air dried, and vacuum dried at 60 °C for 15 hours to give the title compound as an off-white solid (1.27 g, 78% yield). MS (*m/z*): 552.8 (M+H).

Example 2

N-(3-Fluoro-4-(1-methyl-6-(1*H*-pyrazol-4-yl)-1*H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide

-47-



A 12 L round bottom flask is equipped with overhead agitation, a thermocouple, and a N₂ purge. *tert-Butyl* 4-(5-(4-amino-2-fluorophenoxy)-1-methyl-1*H*-indazol-6-yl)-1*H*-pyrazole-1-carboxylate (404 g, 954.08 mmol) is dissolved in DMF (2 L) and charged to the flask. DMF (1 L) is used to rinse the flask. 1-(4-Fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (259.46 g, 1.05 mol) and EDCI (228.63 g, 1.19 mol) are added and it is rinse in with DMF (500 mL). Then HOBt (189.94 g, 1.24 mol) is added and it is again rinsed in with DMF (500 mL). Finally, DIPEA is slowly added (184.97 g, 1.43 mol). The dark solution is then stirred at RT over the weekend. To a 20 L bottom outlet flask is added DI water (3 L) and DCM (5 L). The reaction mixture is poured in and it is rinsed in with DCM (1 L). The organic layer is separated, washed with DI water (3 X 3 L), dried over Na₂SO₄, filtered, rinsed solids with DCM and concentrated the filtrate. EtOAc (2 L) is added to the residue and the solution is stirred for 1 hour. The product crystallizes out. The mixture is concentrated. Another portion of EtOAc (2 L) is added and concentrated to remove all of the DCM. EtOAc (650 mL) and MTBE (3 L) are added to the residue and the solution is stirred in an ice bath for 1 hour. The tan slurry is filtered using a polypropylene pad. The cake is rinsed with MTBE (2 x 500 mL). The light tan solid is dried overnight in the vacuum oven at 40 °C to give the crude product (553 g). The crude product is purified by silica gel column chromatography eluting with (50% EtOAc (50%):35% DCM (35%): n-heptane (15%)) to give the pure desired product *tert-butyl* 4-(5-(2-fluoro-4-(1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)-1-methyl-1*H*-indazol-6-yl)-1*H*-pyrazole-1-carboxylate (424 g, 68%). MS (*m/z*): 651.0 (M-H).

tert-Butyl 4-(5-(2-fluoro-4-(1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)-1-methyl-1*H*-indazol-6-yl)-1*H*-pyrazole-1-

-48-

carboxylate (423.9 g, 649.50 mmol) is dissolved in DCM (4.24 L). HCl in MeOH (5.74 N, 799.99 mL, 4.59 mol) is added and the solution is heated at 30 °C for 1 hour. Then the reaction mixture is heated to 45 °C and DCM (1.5 L) is added. After two hours, the solution is heated to 50 °C and DCM (2 L) is added. After 3 hours, DCM (2 L) is added followed by HCl in MeOH (4.5 N, 721.67 mL, 3.25 mol). After another 45 min, DCM (1 L), HCl in MeOH (4.5 N, 288.67 mL, 1.30 mol), and MeOH (1.5 L) are added. The reaction solution is then heated to 60 °C. After 4 hours, MeOH (2 L) is added and 10 min later DCM (1 L) is added followed by HCl in MeOH (4.5 N, 200 mL). After 5 hours, the reaction is complete. The reaction mixture is concentrated to about 1/3 volume. MeOH (2 L) is added and the solution is concentrated to a thick slurry. Again, MeOH (2 L) is added and the mixture is concentrated to a thick slurry. The slurry is cooled to about 10-15 °C and then filtered. The solids are washed with MeOH. The solids are placed in a 55 °C vacuum oven for 2 days to give the desired product *N*-(3-fluoro-4-(1-methyl-6-(1-*H*-pyrazol-4-yl)-1-*H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide hydrochloride (377 g, 92.8%). MS (*m/z*): 551.0 (M-H).

To a 22 L round bottom flask equipped with mechanical stirring under nitrogen is added *N*-(3-fluoro-4-(1-methyl-6-(1-*H*-pyrazol-4-yl)-1-*H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide hydrochloride (367 g, 0.62 mol) followed by DCM (7.34 L) and water (7.34 L). Na₂CO₃ (181.6 g, 1.71 mol) is added and the mixture is stirred at RT for 30 min. The pH is checked and found to be about 9.4. The mixture is filtered over polypropylene. The solids are collected and placed into a 5 L round bottom flask. A 20% water/MeOH solution (2.6 L) is added and the slurry is stirred for 30 min. The slurry is filtered and the solids are washed with 20% water/MeOH (600 mL). The solids are placed in a vacuum oven at 35 °C overnight. The first weighing indicates 394 g (theoretical yield 324.8 g, about 121% mass recovery). TGA (Thermogravimetric analysis)/DSC (differential scanning calorimetry) shows about 17 wt % free water and 10-11 wt% volatile loss at the melt. The solids are dried at 55 °C in a vacuum oven with a N₂ sweep for 3.5 hours (354.7 g, about 109% mass recovery, NMR shows about 9.3 wt % DCM). No free water is present according to TGA/DSC. The material is sent for milling.

-49-

The jet mill (AIjet™ 0101) in a glove bag is assembled inside a walk in hood and hooked up to N₂ to a 100 lb header. The inlet pusher nozzle is adjusted for maximum draw and max nitrogen flow is introduced into the mill. Pressure readings are noted as 90 psi on pusher nozzle and 85 psi on both grind nozzles. The starting material (353.4 g) is slowly fed to the mill inlet, stopping to empty the receiver sock as needed. The total milling time is 22 min and 25 second. The calculated feed rate is 15.8 g/min (353.4 grams divided by 22.42 min). The milled material (335.7 g, 95%) is obtained with 17.7 g loss. Particle size analysis result of the milled material is d90 of 4.6 microns.

TGA/DSC indicates about 11.4 wt % volatiles at the melt and NMR (DMSO) shows about 9.3 wt % DCM. ¹H NMR (DMSO) δ 12.94 (br s, 1 H), 11.88 (s, 1H), 8.44 (d, *J* = 7.47 Hz, 1 H), 8.12 (br s, 1 H), 8.00 (br s, 1 H), 7.96 (s, 1 H), 7.94 (d, *J* = 2.2 Hz, 1 H), 7.91 (d, *J* = 2.6 Hz, 1 H), 7.87 (s, 1H), 7.47-7.37 (m, 5 H), 6.82 (t, *J* = 9.26 Hz, 8.82 Hz, 1 H), 6.65 (d, *J* = 7.49 Hz, 1 H), 4.04 (s, 3 H), 2.03 (s, 3 H). LC/MS: (M + H) 553.1.

Anhydrous Crystal Form Preparation

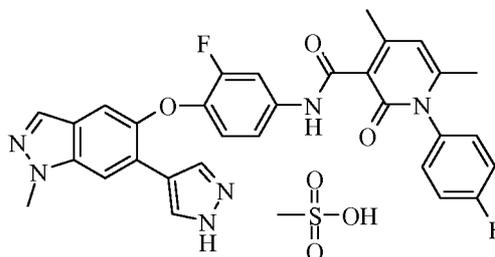
To 10 mL of EtOH is added 120 mg of the above compound into a 20 mL vial. The sample is heated to 70 °C with stirring. Initially the solids start to dissolve and then a suspension forms followed by a white precipitate. The sample is cooled to RT while being stirred. A small sample of the slurry is taken by pipette and allowed to air dry. This material is highly crystalline and proves to be an ethanol solvate by TGA. To the remaining suspension, 10 mL of heptane is added and then heated to boiling. The measured temperature is monitored at 70.8 °C until the volume has been reduced to 10 mL. When the temperature starts to rise, the heat is removed and the slurry stirred at RT overnight. The solid is isolated by vacuum filtration and dried in a vacuum oven at 45 °C for 3 hours, resulting in 77% recovery. The crystalline form shows a weight loss of 0.17% from 25-238 °C by TGA. The form's onset of melting is 247.8 °C.

Example 3

N-(3-Fluoro-4-(1-methyl-6-(1*H*-pyrazol-4-yl)-1*H*-indazol-5-yloxy) phenyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate

30

-50-



To a solution of 3-fluoro-4-(1-methyl-6-(1 *H*-pyrazol-4-yl)-1 *H*-indazol-5-yloxy)aniline (300 mg, 927.8 μmol) and 1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (300 mg, 1.15 mmol) in DMF (5 mL) is added HOBt (130 mg, 0.962 mmol), EDCI (180 mg, 0.939 mmol) and *N*-methylmorpholine (0.5 mL). After the reaction mixture is stirred at 60 $^{\circ}\text{C}$ overnight, it is partitioned between EtOAc (50 mL) and saturated aqueous NH_4Cl (30 mL). The organic phase is separated, dried and concentrated. The residue is triturated with EtOAc (5 mL) and the solids are collected by filtration to give *N*-(3-fluoro-4-(1-methyl-6-(1 *H*-pyrazol-4-yl)-1 *H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide as the desired product (230 mg, 43.7% yield.) MS (m/z): 567.2 (M+H).

To a solution of *N*-(3-fluoro-4-(1-methyl-6-(1 *H*-pyrazol-4-yl)-1 *H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide (230 mg, 0.406 mmol) in acetone (10 mL) is added MeSO_3H (39 mg, 0.406 mmol). After the reaction is stirred at RT for 0.5 hour, it is concentrated. The residue is washed with ether and dried to give *N*-(3-fluoro-4-(1-methyl-6-(1 *H*-pyrazol-4-yl)-1 *H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate (250 mg, 92.9% yield.) MS (m/z): 567.2 (M+H).

20

The following compounds are prepared essentially by the method of Example 3 with the exception that in certain cases the freebase is generated and not the salt:

Ex. No.	Chemical name	Structure	Physical data MS(m/z)(M+H)
---------	---------------	-----------	-----------------------------------

Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(M+H)
4	1-(4-Fluorophenyl)-6-methyl- <i>N</i> -(4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		535.2
5	<i>N</i> -(3-Fluoro-4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate		535.1
6	<i>N</i> -(3-Fluoro-4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-4,6-dimethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate		549.1
7	<i>N</i> -(3-Fluoro-4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide methanesulfonate		556.2
8	<i>N</i> -(3-Fluoro-4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide methanesulfonate		540.2
9	<i>N</i> -(3-Fluoro-4-(1-methyl-6-(2-methylpyridin-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		578.1

Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(M+H)
10	6-Methyl- <i>N</i> -(4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate		517.2
11	5-((1 <i>H</i> -Pyrazol-1-yl)methyl)- <i>N</i> -(3-fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide		627.2
12	<i>N</i> -(3-Fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide		558.1
13	<i>N</i> -(4-(6-(Dimethylamino)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate		498.2
14	<i>N</i> -(3-Fluoro-4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-5-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		553.1
15	<i>N</i> -(3-Fluoro-4-(6-(pyridin-3-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide		550.2

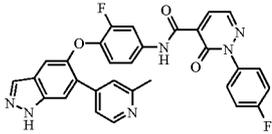
Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(M+H)
16	5-((1 <i>H</i> -Pyrazol-1-yl)methyl)- <i>N</i> -(4-(6-(dimethylamino)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-1-methyl-3-oxo-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide methanesulfonate		585.1
17	1-(4-Fluorophenyl)-4,6-dimethyl- <i>N</i> -(4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		549.2
18	<i>N</i> -(3-Fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		544.2
19	<i>N</i> -(3-Fluoro-4-(6-(tetrahydro-2 <i>H</i> -pyran-4-ylamino)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		586.1
20	<i>N</i> -(4-(6-(Dimethylamino)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide		503.1
21	<i>N</i> -(4-(6-(Dimethylamino)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide		530.2

Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(M+H)
22	<i>N</i> -(4-(6-(Dimethylamino)-1 <i>H</i> -indazol-5-yloxy)phenyl)-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate		480.2
23	<i>N</i> -(3-Fluoro-4-(6-(6-methylpyridin-3-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide		564.1
24	4,6-Dimethyl- <i>N</i> -(4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate		531.2
25	<i>N</i> -(3-Fluoro-4-(1-methyl-6-(pyridin-3-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide methanesulfonate		567.1
26	<i>N</i> -(3-Fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide		544.1
27	5-Methyl- <i>N</i> -(4-(1-methyl-6-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate		517.1

Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(M+H)
28	<i>N</i> -(3-Fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-1-methyl-5-(morpholinomethyl)-3-oxo-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide methanesulfonate		646.2
29	<i>N</i> -(3-Fluoro-4-(6-(pyridin-3-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide		535.5
30	<i>N</i> -(3-Fluoro-4-(6-(pyridin-3-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-1-methyl-5-(morpholinomethyl)-3-oxo-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide		638.2
31	<i>N</i> -(3-Fluoro-4-(6-(pyridin-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide methanesulfonate		537.1
32	<i>N</i> -(3-Fluoro-4-(6-(pyridin-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide methanesulfonate		553.2
33	<i>N</i> -(3-Fluoro-4-(6-(pyridin-3-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide methanesulfonate		553.1

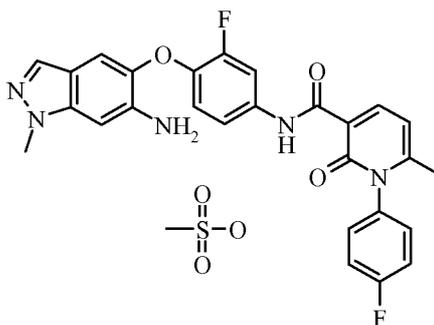
Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(M+H)
34	<i>N</i> -(4-(6-(1 <i>H</i> -Pyrazol-4-yl)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-6-methyl-3-oxo-2,3-dihydropyridazine-4-carboxamide methanesulfonate		540.1
35	<i>N</i> -(4-(6-(Dimethylamino)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide		516.2
36	<i>N</i> -(3-Fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-5-(morpholinomethyl)-2-oxo-1,2-dihydropyridine-3-carboxamide		643.2
37	<i>N</i> -(3-Fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		558.1
38	<i>N</i> -(3-Fluoro-4-(6-(6-methylpyridin-3-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		578.1
39	<i>N</i> -(3-Fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-6-methyl-3-oxo-2,3-dihydropyridazine-4-carboxamide		559.2

Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(M+H)
40	<i>N</i> -(4-(6-(1,3-Dimethyl-1 <i>H</i> -pyrazol-5-yl)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide		554.2
41	<i>N</i> -(3-Fluoro-4-(6-(pyridin-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide methanesulfonate		535.2
42	<i>N</i> -(3-Fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide		545.1
43	<i>N</i> -(4-(6-(1,3-Dimethyl-1 <i>H</i> -pyrazol-5-yl)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		581.1
44	<i>N</i> -(4-(6-(2,6-Dimethylpyridin-4-yl)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-1,5-dimethyl-3-oxo-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide methanesulfonate		581.2
45	<i>N</i> -(3-Fluoro-4-(6-(2-methylpyridin-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-1-methyl-3-oxo-5-(piperidin-1-ylmethyl)-2,3-dihydro-1 <i>H</i> -pyrazole-4-carboxamide		650.1
46	<i>N</i> -(3-Fluoro-4-(6-(2-methoxypyrimidin-5-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-		567.2

Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(M+H)
	carboxamide		
47	<i>N</i> -(3-Fluoro-4-(6-(2-methylpyridin-4-yl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide		551.2

Example 48

N-(4-(6-Amino-1-methyl-1*H*-indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate



5

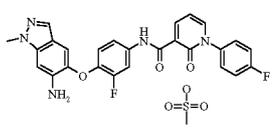
To a 10 mL screw-cap vial is added 5-(4-amino-2-fluorophenoxy)-*N*-benzhydryl-1-methyl-1*H*-indazol-6-amine (91 mg, 208 μ mol), 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (66.7 mg, 269.78 μ mol), EDCI (90.9 mg, 466.9 μ mol) and HOBt (47.7 mg, 311.3 μ mol) followed by DMF (2 mL, 25.9 mmol). To the mixture is added DIPEA (90.5 μ L, 518.8 μ mol) and the mixture is stirred at RT for 12 hours. Additional EDCI (50 mg), HOBt (25 mg), DIPEA (0.02 mL), and 1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (40 mg) are added and the mixture is stirred for an additional 24 hours. The reaction is diluted into EtOAc (100 mL) and washed with saturated aqueous sodium chloride (3 x 25 mL). The combined aqueous solution is extracted with EtOAc (1 x 25 mL). The combined organic solution is dried over Na₂SO₄, filtered, and concentrated to dryness. The residue is purified on a silica gel column eluting with DCM (A) and a 10% MeOH in DCM solution (B), gradient from 100% (A) to 90%(A):10%(B) over 60 min to give a clear wax material as the desired product (114 mg, 82% yield). MS (*m/z*) 667.8 (M+H).

-59-

To a 25 mL round bottom flask is added *N*-(4-(6-(benzhydrylamino)-1-methyl-1*H*-indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (100 mg, 149.7 μ mol) and DCM (15 mL, 15.6 mmol) followed by the addition of triethylsilane (0.3 mL, 1.8 mmol) and TFA (2 mL, 26.9 mmol). The reaction mixture is stirred at RT for 3 hours. The solvent is removed and then the residue is diluted in DCM (50 mL) and washed with a saturated NaHCO₃ solution (1 x 25 mL). The aqueous layer is extracted with DCM (1 x 25 mL) and the combined organic solution is dried with Na₂SO₄, filtered and concentrated. The residue is purified on a silica gel column eluting with DCM (A) and a 10% MeOH in a DCM solution (B), gradient from 100% (A) to 80%(A):20%(B) over 50 min, held at 80:20 ratio for 5 min then gradient to 70%(A):30%(B) over 5 min to give a white solid material as the desired product (67 mg, 90% yield). MS (*m/z*): 501.8 (M+H).

To a round bottom flask is added *N*-(4-(6-amino-1-methyl-1*H*-indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (47.5 mg, 94.7 μ mol) in DCM (2 mL, 31.2 mmol) and MeOH (2 mL, 49.4 mmol). MeSO₃H (6.2 μ L, 94.7 μ mol) in MeOH is added. The solution is concentrated to give a light yellow solid (54 mg, 96% yield). MS (*m/z*): 501.8 (M+H).

The following compounds are prepared essentially by the method of Example 48:

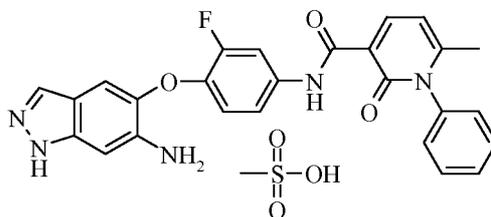
Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(M+H)
49	<i>N</i> -(4-(6-Amino-1-methyl-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		487.8

20

Example 50

N-(4-(6-Amino-1*H*-indazol-5-yloxy)-3-fluorophenyl)-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate

-60-



To a solution of *tert-butyl* 5-(4-amino-2-fluorophenoxy)-1 *H*-indazol-6-ylcarbamate (170 mg, 474 μ mol) and 6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxylic acid (120 mg, 0.52 mmol) in DMF (5 mL) is added HOBt (60 mg, 0.44
5 mmol), EDCI (90 mg, 0.47 mmol) and *N*-methylmorpholine (0.5 mL). After the reaction mixture is stirred at 60 $^{\circ}$ C overnight, it is partitioned between EtOAc (50 mL) and saturated aqueous NH_4Cl (30 mL). The organic phase is separated, dried and concentrated, and the residue is purified by silica gel column chromatography eluting with PE:EtOAc (1:1) to give the product (65 mg, 24.1% yield) MS (m/z): 570.2 [M+H].

10 To a solution of *tert-butyl* 5-(2-fluoro-4-(6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamido)phenoxy)-1 *H*-indazol-6-ylcarbamate (65 mg, 0.114 mmol) in DCM (10 mL) is added TFA (1 mL, 13.5 mmol). After the reaction is stirred at RT overnight, it is concentrated. The residue is partitioned with saturated aqueous NaHCO_3 (30 mL) and DCM (50 mL), and the organic phase is separated, dried and
15 concentrated. The residue is purified by silica gel column chromatography eluting with DCM:MeOH (20:1) to give the product (35 mg, 65.3% yield). MS (m/z): 470.1 (M+H).

To a solution of *N*-(4-(6-amino-1 *H*-indazol-5-yloxy)-3-fluorophenyl)-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (35 mg, 74.6 μ mol) in acetone (10 mL) is added MeSCl_3H (7.16 mg, 74.6 μ mol). After the reaction mixture is stirred at RT for
20 0.5 hour, it is concentrated. The residue is washed with ether and dried to give *N*-(4-(6-amino-1 *H*-indazol-5-yloxy)-3-fluorophenyl)-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide methanesulfonate (39 mg, 92.5 % yield). MS (m/z): 470.1 (M+H).

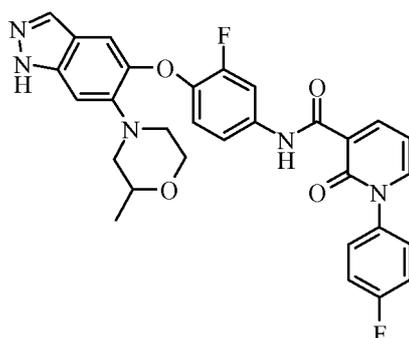
25 The following compounds are prepared essentially by the method of Example 50:

Ex. No.	Chemical name	Structure	Physical data MS(m/z)(M+H)
---------	---------------	-----------	--------------------------------

Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(<i>M</i> + <i>H</i>)
51	<i>N</i> -(4-(6-Amino-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide		474.1
52	<i>N</i> -(4-(6-Amino-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		502.2
53	<i>N</i> -(4-(6-Amino-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide		488.1
54	<i>N</i> -(4-(6-(6-Aminopyridin-3-yl)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide		552.1

Example 55

N-(3-Fluoro-4-(6-(2-methylmorpholino)-1*H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



5

To a 10 mL screw-cap vial is added 3-fluoro-4-(6-(2-methylmorpholino)-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-indazol-5-yloxy)aniline (44 mg, 103.17 μ mol), 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (42 mg, 0.18 mmol), EDCI (45.177 mg, 232.13 μ mol), HOBT (23.699 mg, 154.75 μ mol) followed by DMF (5 mL,

-62-

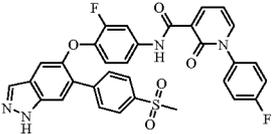
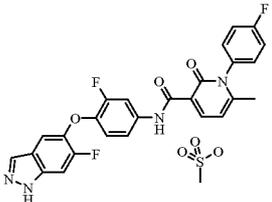
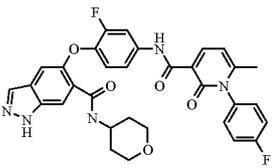
64.66 mmol) and DIPEA (44.980 μL , 257.92 μmol). The reaction mixture is stirred at RT overnight. The reaction is diluted into EtOAc (50 mL) and washed with saturated aqueous sodium chloride (5 x 25 mL). Organic layers are dried over Na_2SO_4 , filtered, and concentrated to dryness. The residue is purified on a silica gel column eluting with hexanes (A) and EtOAc (B), gradient from 80%(A):20%(B) to 30%(A):70%(B) over 40 min, hold at 30:70 ratio for 15 min to give a yellow solid as desired product *N*-(3-fluoro-4-(6-(2-methylmorpholino)-2-(tetrahydro-2 *H*-pyran-2-yl)-2*H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (70 mg, 99% yield). MS (m/z): 641.8 (M+H).

To a round bottom flask is added *N*-(3-fluoro-4-(6-(2-methylmorpholino)-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (66 mg, 102.86 μmol) and MeOH (5 mL, 123.54 mmol). To the resulting mixture is added MeSO_3H (20.229 μL , 308.57 μmol) and the reaction mixture is heated to 40 $^\circ\text{C}$ for 6 hours. The reaction mixture is concentrated and dissolved in DCM (100 mL). The solution is washed with a mixture of saturated aqueous sodium chloride (20 mL) and saturated aqueous sodium bicarbonate solution (1 x 20 mL). The organic solution is extracted with DCM (1 x 25 mL) and dried over Na_2SO_4 , filtered and concentrated. The residue is purified on a silica gel column eluting with DCM (A) and a 10% MeOH in DCM solution (B), gradient from 100% (A) to 70%(A):30%(B) over 60 min to give a light yellow solid as the desired product (40 mg, 62% yield). MS (m/z): 557.8 (M+H).

The following compounds are prepared essentially by the method of Example 55:

Ex. No.	Chemical name	Structure	Physical data MS(m/z)(M+H)
56	(<i>R</i>)- <i>N</i> -(3-Fluoro-4-(6-(2-methylmorpholino)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide		558.2

Ex. No.	Chemical name	Structure	Physical data MS(<i>m/z</i>)(M+H)
57	(<i>R</i>)- <i>N</i> -(3-Fluoro-4-(6-(2-methylmorpholino)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide		572.2
58	<i>N</i> -(4-(6-Cyclopropyl-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide		499
59	<i>N</i> -(4-(6-Cyclopropyl-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide		512.8
60	<i>N</i> -(4-(6-((2 <i>S</i> ,6 <i>R</i>)-2,6-Dimethylmorpholino)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide		572.2
61	<i>N</i> -(4-(6-(2,2-Dimethylmorpholino)-1 <i>H</i> -indazol-5-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide		572.2
62	<i>N</i> -(3-Fluoro-4-(6-morpholino-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxamide		571.8

63	<i>N</i> -(3-Fluoro-4-(6-(4-(methylsulfonyl)phenyl)-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide		613.1
64 *	<i>N</i> -(3-Fluoro-4-(6-fluoro-1 <i>H</i> -indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide methanesulfonate		491.2
65	5-(2-Fluoro-4-(1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-4-yl)-1 <i>H</i> -indazole-6-carboxamide		600.2

*: Methanesulfonate salt **is prepared** essentially by **the same method of salt formation step** in Example 3.

The following assays demonstrate that certain compounds of the present invention
5 potently inhibit c-Met phosphorylation in cells, potently inhibit c-Met *in vivo*, and demonstrate dose dependent anti-tumor activity in certain xenograft models.

c-Met protein expression and purification

The kinase domain (KD) of human c-Met (from Gly 966 to Ser 1390, NCBI
10 NM_000245) is cloned into a pFastBac® HT vector (Invitrogen, Carlsbad, CA). The His-c-Met KD construct is transposed into Baculovirus DNA using a Bac-to-Bac® system (Invitrogen). SF9 cells are infected with the recombinant baculovirus. The infected cells are harvested by centrifugation and the cell pellet is collected and stored at -80 °C. Cells are lysed in buffer A (40 mM tris(hydroxymethyl)aminomethane (Tris), pH 7.5, 500 mM
15 NaCl, 20% glycerol, and 10 mM imidazole). Cell lysates are homogenized and centrifuged. Supernatants are incubated with nickel-nitrilotriacetic (Ni-NTA) resin and

-65-

loaded onto a column. Proteins are eluted with buffer B (buffer A plus 0.3 M imidazole) and c-Met containing fractions are pooled together, loaded onto a Superdex®200 column (Amershan Bioscience, Piscataway, NJ), eluted with buffer C (40 mM Tris, pH 7.5, 250 mM NaCl, and 10% glycerol).

5

HGF Stimulated Met (pY1349) NCI-H460 Cell-based ELISA

NCI-H460 cells (purchased from ATCC) are cultured in RPMI 1640 media (Invitrogen) supplemented with 10% Fetal Bovine Serum (FBS) and plated (prior to becoming 70% confluent) in 96-well flat-bottom plates at a density of 20,000 cells per well in 80 µL volume. The cells are then incubated overnight in a cell culture incubator (5% CO₂, 95% Relative Humidity (RH) and 37 °C) and allowed to attach to the plate. The following morning the cells are washed with 2 volumes of a Reduced Serum Media (RSM) (RPMI 1640 media supplemented with 0.5% FBS). After removal of the last wash, 80 µL of RSM is added to each well of the cell plates. The cell plates are incubated for 2.5 hours in a cell culture incubator, and then dosed with compounds. Compound inhibitors are first solubilized at 10 mM in 100% DMSO and then diluted to 100 µM with 2% DMSO RSM. Subsequently compound serial dilutions (1:3) are prepared over a 100 µM to 0.005 µM range. Cells are dosed with the addition of 20 µL of compound stock to produce a final DMSO concentration of 0.4% and a final compound concentration dose range between 20 and 0.001 µM. After dosing with compounds the cells plates are gently agitated to mix and then allowed to incubate for 30 min in a cell culture incubator. After dose completion, the cells are stimulated with the addition of 20 µL per well of Hepatocyte Growth Factor (HGF) at a final concentration of 100 ng/mL in RSM (all wells except MIN wells are stimulated, MIN wells are dosed with 20 µL RSM). After 10 min incubation in a cell culture incubator, the liquid is removed from the cell plate wells, and the cells are lysed by the addition of 50 µL of ice-cold Meso Scale Discovery® (MSD, Gaithersburg, Maryland) IX Lysis Buffer (150 mM NaCl, 20 mM Tris, pH 7.5, 1 mM EDTA, 1 mM ethylene glycol tetraacetic acid, and 1% TRITON® X-100) supplemented with Phosphatase I and II and Protease inhibitors (Sigma, St. Louis, MO). After lysis at RT for 30 min the lysates are transferred to and captured on a MSD® Multi-Spot 96-well

-66-

4-spot PhosphoMet plate that is BSA-blocked (at 30 mg/mL Block A in IX Tris Wash Buffer) and then washed one time with Tris Wash Buffer. After 2 hours capture (at RT) the lysates are removed from the MSD® plate and the plate is washed with IX Tris Wash Buffer. After blotting, 25 µL of 5 nM Sulfo-Tag Anti-Total Met antibody (detection antibody, MSD® prepared in IX Tris Wash Buffer supplemented with 10 mg/mL BSA and 0.1% Blocker D-R (MSD®)) is added to the wells of the MSD® plate. After 1 hour capture (at RT) the MSD® plate wells are washed with IX Tris Wash Buffer, and then 150 µL of IX Read Buffer T (with surfactant, MSD®) is added. Immediately after the addition of the Read Buffer, the plates are analyzed with a SECTOR 6000 MSD® Imager plate reader. Relative IC₅₀ values are determined using MSD activity units by calculating percent inhibition with respect to on-plate "MIN" and "MAX" controls and then fitting the percent inhibition values and ten-point dose response data to a four-parameter logistic equation. This assay has a Minimum Significant Ratio (MSR) of 2.06. For all exemplified compounds the IC₅₀ values are less than 0.2 µM. For example, the average (n=6) IC₅₀ value (50% inhibitory concentration) of Example 1 in this assay is 0.0352 µM, indicating it potently inhibits c-Met phosphorylation in cells.

c-Met in vivo target inhibition assay

S114 cells (licensed from PHS, over-express both human HGF and human c-Met) are cultured in a growth media (Dulbecco's Modified Eagle Medium) supplemented with 10% fetal calf serum and expanded. Cells are harvested and washed twice with phosphate buffered saline and 2X10⁶ cells are mixed with equal volume of BD Matrigel™ matrix (BD Bioscience, Franklin, NJ), and injected subcutaneous ly into the flank of nude mice (athymic nude, from Harlan, Indianapolis, IN). At day 8 after implant, compounds (formulated in 10% acacia or 1% carboxymethylcellulose/0.5% sodium lauryl sulfate/0.05% antifoam as suspension) are administered to animals by oral gavage at 50 mg/kg. Animals are sacrificed at 2 hours post dose, and tumors are harvested and stored frozen until needed.

Frozen tumors are pulverized using mortar-pastel. The pulverized tissues are transferred to a tube containing Lysing Matrix D beads (MP Biomedicals, Solon, OH) and 600 µL lysis buffer (RIPA buffer, containing 50 mM Tris-HCl, pH 7.4, 150 mM NaCl,

-67-

1% NP-40, 0.5% sodium deoxycholate, 0.1% SDS, from Boston Bioproducts). A FastPrep® Cell Disrupter (MP Biomedicals) is used to disrupt the tissue and lyse the cells. Lysates are passed through a 20 gauge needle and transferred to a clean tube. Protein concentration is determined by Bradford method.

5 Tumor lysates are loaded onto MSD® phosphor-Met ELISA plates and phosphor-c-Met level is determined using the same protocol as H460 cell-based ELISA. For all exemplified compounds the S1 14 *in vivo* inhibition values are equal or greater than 50% at the dose of 50 mg/kg. For example, Example 1 is a potent inhibitor of c-Met phosphorylation with an ED₅₀ value (dose that produces 50% inhibition in tumor of 2.9
10 mg/kg, indicating it is a potent c-Met inhibitor *in vivo*.

Xenograft tumor models

Human glioblastoma cells U87MG, human gastric cancer cells MKN45, human non small cell lung cancer cells H44 1, and human renal carcinoma cells Caki- 1 are
15 expanded in culture, harvested, and injected subcutaneously onto the rear flank of athymic nude mice. Testing compound is prepared in an appropriate vehicle and is administered by oral gavage when tumors are established (7-21 days after implant). Tumor response is determined by tumor volume measurement performed twice a week during the course of treatment. Tumor volume inhibition (% growth inhibition) is
20 calculated by comparing treated groups to a vehicle control group. Body weight is taken as a general measurement of toxicity. The Compound of Example 1 demonstrates excellent dose dependent anti-tumor activity in these models. For example, when dosed at 1.3 mg/kg (oral (PO), bi-daily (BID) x 35), Example 1 is able to cause 59% growth inhibition of U87MG tumors. At 4 mg/kg dose (PO, BIDx35), 82% growth inhibition is
25 achieved. At 12 mg/kg dose (PO, BID x3 5), 92% growth inhibition reaches.

c-Met relevant tumors and xenograft models

c-Met overexpression is a common feature for many human tumors, including
30 lung, breast, colorectal, gastric, renal, pancreatic, head and neck (1,2). c-Met activating mutations in the kinase domain are implicated as the cause for several tumors, such as hereditary papillary renal cell carcinoma, childhood hepatocellular carcinoma, and gastric

cancer (3-7). c-Met inhibitors from Pfizer demonstrated antitumor efficacy in many human xenograft tumors, including U87MG, GTL16, H441, Caki-1, and PC3 (8).

1. Christinsen, JG., Burrows, J., and Salgia, R. *Cancer Letters* 225: 1-26, 2005.
- 5 2. Birchmeier, C, Birchmeier, W., Gherardi, E., and Vande Woude, GF. *Nat Rev MoI Cell Biol* 4: 915-925, 2003.
3. Di Renzo, MF., Olivero, M., Martone, T. Et al. *Oncogene* 19: 1547-1555, 2000.
4. Lee, JH., Han, SU, Cho, H. et al. *Oncogene* 19: 4947-4953, 2000.
5. Ma, PC, Kijima, T., Maulik, G. et al. *Cancer Res* 63 : 6272-6281, 2003.
- 10 6. Park, WS., Dong, SM., Kim, SY. et al. *Cancer Res* 59 : 307-310, 1999.
7. Schmidt, L., Duh, FM., Chen, F., et al. *Nat Genet* 16: 68-73, 1997.
8. Zou, HY., Li, Qihua., Lee, JH., et al. *Cancer Res* 67: 4408-4417, 2007.

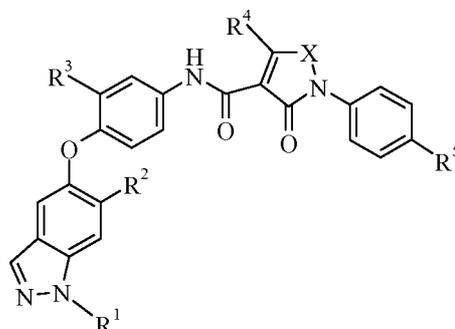
The compounds of the present invention are preferably formulated as
15 pharmaceutical compositions administered by a variety of routes. Most preferably, such compositions are for oral administration. Such pharmaceutical compositions and processes for preparing the same are well known in the art. *See, e.g.,* REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro, *et al*, eds., 19th ed., Mack Publishing Co., 1995).

20 The compounds of Formula I are generally effective over a wide dosage range. For example, dosages per day normally fall within the range of about 1 mg to about 200 mg total daily dose, preferably 1 mg to 150 mg total daily dose, more preferably 1 mg to 50 mg total daily dose. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be
25 employed. The above dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the
30 severity of the patient's symptoms.

-69-

We Claim:

1. A compound of the formula:

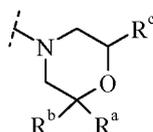


wherein:

5 R¹ is H or methyl;

R² is amino, dimethylamino, fluoro, cyclopropyl, pyridyl optionally substituted with an amino substituent or 1-2 methyl substituents, pyrazolyl optionally substituted with two methyl substituents, 2-methoxy-pyrimidin-5-yl, 4-methylsulfonylphenyl, tetrahydro-2H-pyran-4-ylamino, (tetrahydro-2H-pyran-4-yl)amino carbonyl, or a

10 morpholin-4-yl substituent:

where R^a, R^b and R^c are independently selected from H or methyl;R³ is H or F;15 R⁴ is H, methyl, piperidin-1-ylmethyl, morpholin-4-ylmethyl, or pyrazol-1-ylmethyl;R⁵ is H or F; and

X is CH=N, CH=CH, CH=C(CH₃), C(CH₃)=CH, C(CH₃)=N, N(CH₃), or C(morpholin-4-ylmethyl)=CH;

or a pharmaceutically acceptable salt thereof.

20

2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein R² is amino, dimethylamino, cyclopropyl, pyridyl optionally substituted with an amino substituent or 1-2 methyl substituents, pyrazol-4-yl, or a morpholin-4-yl.

-70-

3. The compound according to Claims 1, or a pharmaceutically acceptable salt thereof, wherein R² is amino, dimethylamino, pyrazol-4-yl, or a morpholin-4-yl.

5 4. The compound according to Claims 1, or a pharmaceutically acceptable salt thereof, wherein R² is pyrazol-4-yl.

5. The compound according to Claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R⁴ is H, methyl, or morpholin-4-ylmethyl.

10

6. The compound according to Claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R⁴ is H.

7. The compound according to Claims 1-6, or a pharmaceutically acceptable salt thereof, wherein X is CH=CH or CH=C(CH₃).

15

8. The compound according to Claim 1 which is *N*-(3-fluoro-4-(1-methyl-6-(1-*H*-pyrazol-4-yl)-1*H*-indazol-5-yloxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide or a pharmaceutically acceptable salt thereof.

20

9. The compound according to Claim 1 which is *N*-(3-fluoro-4-(1-methyl-6-(1-*H*-pyrazol-4-yl)-1*H*-indazol-5-yloxy)phenyl)-6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide or a pharmaceutically acceptable salt thereof.

25 10. The compound according to Claims 1-9 wherein the pharmaceutically acceptable salt is a methanesulfonate salt.

11. The compound according to Claims 1-10 wherein the particle size is less than 10 microns.

30

-71-

12. A pharmaceutical composition comprising a compound of Claims 1-11 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

5 13. A method of treating cancer selected from the group consisting of lung cancer, breast cancer, colorectal cancer, renal cancer, pancreatic cancer, head cancer, neck cancer, hereditary papillary renal cell carcinoma, childhood hepatocellular carcinoma, and gastric cancer in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of any of Claims 1-11 or a
10 pharmaceutically acceptable salt thereof.

14. A compound of any of Claims 1-11 or a pharmaceutically acceptable salt thereof for use as a medicament.

15 15. A compound or a pharmaceutically acceptable salt thereof according to any one of Claims 1-11 for use in the treatment of cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/050640

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 C07D401/14 C07D403/12 C07D403/14 C07D405/14
A61K31/4412 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal , WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/103308 A (ARRAY BIOPHARMA INC [US]; GENENTECH INC [US]; BLAKE JAMES F [US]; BOYD) 13 September 2007 (2007-09-13) cited in the application claims 1,68,72	1-15
A	US 2006/004006 A1 (BORZILLERI ROBERT M [US] ET AL) 5 January 2006 (2006-01-05) cited in the application paragraph [0002]; claims 1,20	1-15

D Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

3 September 2009

Date of mailing of the international search report

12/10/2009

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Johnson, Claire

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/050640

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
wo 2007103308 A	13-09-2007	AR 059887 A1	07-05-2008
		AU 2007224020 A1	13-09-2007
		CA 2645137 A1	13-09-2007
		EC SP088791 A	27-11-2008
		EP 2001880 A2	17-12-2008
		KR 20080110783 A	19-12-2008
		US 2006004006 A1	05-01-2006