

**(12) STANDARD PATENT**  
**(19) AUSTRALIAN PATENT OFFICE**

(11) Application No. **AU 2013323508 B2**

(54) Title  
**Novel compounds that are ERK inhibitors**

(51) International Patent Classification(s)  
**A61K 31/4745** (2006.01)      **A61K 9/66** (2006.01)

(21) Application No: **2013323508**      (22) Date of Filing: **2013.09.26**

(87) WIPO No: **WO14/052563**

(30) Priority Data

(31) Number	(32) Date	(33) Country
<b>61/707,081</b>	<b>2012.09.28</b>	<b>US</b>

(43) Publication Date: **2014.04.03**

(44) Accepted Journal Date: **2017.11.02**

(71) Applicant(s)  
**Merck Sharp & Dohme Corp.**

(72) Inventor(s)  
**Wilson, Kevin J.;Witter, David J.;Siliphaivanh, Phieng;Lipford, Kathryn;Sloman, David;Falcone, Danielle;O'Boyle, Brendan;Mansoor, Umar Faruk;Lim, Jongwon;Methot, Joey L.;Boyce, Christopher;Chen, Lei;Daniels, Matthew H.;Fevrier, Salem;Huang, Xianhai;Kurukulasuriya, Ravi;Tong, Ling;Zhou, Wei;Kozlowski, Joseph;Maletic, Milana M.;Shinkre, Bidhan A.;Thatai, Jayanth Thiruvellore;Bakshi, Raman Kumar;Karunakaran, Ganesh Babu**

(74) Agent / Attorney  
**Spruson & Ferguson, L 35 St Martins Tower 31 Market St, Sydney, NSW, 2000, AU**

(56) Related Art  
**WO 2007070398 A1**  
**WO 2008009335 A2**  
**US 9023865 B2**



- (51) International Patent Classification:  
*A61K 31/4745* (2006.01)
- (21) International Application Number:  
PCT/US2013/061878
- (22) International Filing Date:  
26 September 2013 (26.09.2013)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
61/707,081 28 September 2012 (28.09.2012) US
- (71) Applicant: **MERCK SHARP & DOHME CORP.**  
[US/US]; 126 East Lincoln Avenue, Rahway, New Jersey  
07065-0907 (US).
- (72) Inventors; and
- (71) Applicants (*for US only*): **WILSON, Kevin, J.** [GB/US];  
33 Avenue Louis Pasteur, Boston, Massachusetts 02115-  
5727 (US). **WITTER, David, J.** [US/US]; 33 Avenue  
Louis Pasteur, Boston, Massachusetts 02115-5727 (US).  
**SILIPHAIVANH, Phieng** [US/US]; 33 Avenue Louis  
Pasteur, Boston, Massachusetts 02115-5727 (US). **LIP-  
FORD, Kathryn** [US/US]; 33 Avenue Louis Pasteur, Bos-  
ton, Massachusetts 02115-5727 (US). **SLOMAN, David**  
[US/US]; 33 Avenue Louis Pasteur, Boston, Massachusetts  
02115-5727 (US). **FALCONE, Danielle** [US/US]; 33 Aven-  
ue Louis Pasteur, Boston, Massachusetts 02115-5727  
(US). **O'BOYLE, Brendan** [US/US]; 33 Avenue Louis  
Pasteur, Boston, Massachusetts 02115-5727 (US).  
**MANSOOR, Umar Faruk** [US/US]; 33 Avenue Louis  
Pasteur, Boston, Massachusetts 02115-5727 (US). **LIM,  
Jongwon** [KR/US]; 33 Avenue Louis Pasteur, Boston,  
Massachusetts 02115-5727 (US). **METHOT, Joey, L.**  
[US/US]; 33 Avenue Louis Pasteur, Boston, Massachusetts  
02115-5727 (US). **BOYCE, Christopher** [US/US]; 126  
East Lincoln Avenue, Rahway, New Jersey 07065-0907  
(US). **CHEN, Lei** [CN/US]; 126 East Lincoln Avenue,  
Rahway, New Jersey 07065-0907 (US). **DANIELS, Mat-  
thew, H.** [US/US]; 33 Avenue Louis Pasteur, Boston,  
Massachusetts 02115-5727 (US). **FEVRIER, Salem**  
[US/US]; 126 East Lincoln Avenue, Rahway, New Jersey  
07065-0907 (US). **HUANG, Xianhai** [CN/US]; 126 East  
Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

**KURUKULASURIYA, Ravi** [US/US]; 33 Avenue Louis  
Pasteur, Boston, Massachusetts 02115-5727 (US). **TONG,  
Ling** [CN/US]; 126 East Lincoln Avenue, Rahway, New  
Jersey 07065-0907 (US). **ZHOU, Wei** [US/US]; 126 East  
Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).  
**KOZLOWSKI, Joseph** [US/US]; 126 East Lincoln Aven-  
ue, Rahway, New Jersey 07065-0907 (US). **MALETIC,  
Milana, M.** [US/US]; 126 East Lincoln Avenue, Rahway,  
New Jersey 07065-0907 (US). **SHINKRE, Bidhan, A.**  
[IN/IN]; Biocon Special Economic Zone, Biocon Park, 5 2  
Block Bommasandra, IV Phase Jigani Link Road, Bang-  
alore 560099 (IN). **THATAI, Jayanth Thiruvellore**  
[IN/IN]; Biocon Special Economic Zone, Biocon Park, 5 2  
Block Bommasandra, IV Phase Jigani Link Road, Bang-  
alore 560099 (IN). **BAKSHI, Raman Kumar** [US/IN];  
Biocon Special Economic Zone, Biocon Park, 5 2 Block  
Bommasandra, IV Phase Jigani Link Road, Bangalore  
560099 (IN). **KARUNAKARAN, Ganesh Babu** [IN/IN];  
Biocon Special Economic Zone, Biocon Park, 5 2 Block  
Bommasandra, IV Phase Jigani Link Road, Bangalore  
560099 (IN).

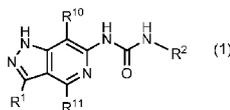
(74) Common Representative: **MERCK SHARP & DOHME  
CORP.**; 126 East Lincoln Avenue, Rahway, New Jersey  
07065-0907 (US).

(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, BN, 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, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,  
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,  
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,  
TM), European (AL, 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, RS, SE, SI, SK, SM,

[Continued on next page]

(54) Title: NOVEL COMPOUNDS THAT ARE ERK INHIBITORS



(57) Abstract: Disclosed are the ERK inhibitors of formula (1): and the pharmaceutically acceptable salts thereof. Also disclosed are methods of treating cancer using the compounds of formula (1).



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

**Declarations under Rule 4.17:**

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

**Published:**

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

## NOVEL COMPOUNDS THAT ARE ERK INHIBITORS

### 5 BACKGROUND

The processes involved in tumor growth, progression, and metastasis are mediated by signaling pathways that are activated in cancer cells. The ERK pathway plays a central role in regulating mammalian cell growth by relaying extracellular signals from ligand-bound cell surface tyrosine kinase receptors such as erbB family, PDGF, FGF, and VEGF receptor tyrosine kinase. Activation of the ERK pathway is via a cascade of phosphorylation events that begins with activation of Ras. Activation of Ras leads to the recruitment and activation of Raf, a serine-threonine kinase. Activated Raf then phosphorylates and activates MEK1/2, which then phosphorylates and activates ERK1/2. When activated, ERK1/2 phosphorylates several downstream targets involved in a multitude of cellular events including cytoskeletal changes and transcriptional activation. The ERK/MAPK pathway is one of the most important for cell proliferation, and it is believed that the ERK/MAPK pathway is frequently activated in many tumors. Ras genes, which are upstream of ERK1/2, are mutated in several cancers including colorectal, melanoma, breast and pancreatic tumors. The high Ras activity is accompanied by elevated ERK activity in many human tumors. In addition, mutations of BRAF, a serine-threonine kinase of the Raf family, are associated with increased kinase activity. Mutations in BRAF have been identified in melanomas (60%), thyroid cancers (greater than 40%) and colorectal cancers. These observations indicate that the ERK1/2 signalling pathway is an attractive pathway for anticancer therapies in a broad spectrum of human tumours.

25 Therefore, a welcome contribution to the art would be small-molecules (i.e., compounds) that inhibit ERK activity (ERK2 activity), which small-molecules would be useful for treating a broad spectrum of cancers, such as, for example, melanoma, pancreatic cancer, thyroid cancer, colorectal cancer, lung cancer, breast cancer, and ovarian cancer. Such a contribution is provided by this invention.

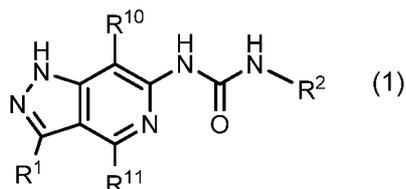
30

### SUMMARY OF THE INVENTION

This invention provides compounds that inhibit the activity of ERK2.

Thus, this invention provides compounds that are ERK inhibitors (i.e., ERK2 inhibitors), said compounds being of the formula (1):

- 2 -



or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>10</sup> and R<sup>11</sup> are defined below.

This invention provides: (1) compounds of formula (1); (2) compounds of formula (1)  
5 in pure or isolated form; (3) pharmaceutically acceptable salts of the compounds of formula (1); (4) solvates of the compounds of formula (1); (5) compounds of formula (1) wherein from one to all of the hydrogens are deuterium; (6) compounds of formula (1) wherein at least one H is deuterium; (7) compounds of formula (1) wherein 1 to 5 H are deuterium; (8) compounds of formula (1) wherein 1 to 2 H are deuterium; and (9) compounds of formula (1) wherein one  
10 H is deuterium.

This invention provides the final compounds of Examples 1-458.

This invention also provides the final compounds of Examples 1 to 60.

This invention also provides the final compounds of Examples 61 to 458.

This invention also provides a pharmaceutical composition comprising an effective  
15 amount of at least one (e.g., 1) compound of formula (1) and a pharmaceutically acceptable carrier. This invention also provides a pharmaceutical composition comprising an effective amount of at least one (e.g., 1) compound of formula (1) and an effective amount of at least one (e.g., 1) other pharmaceutically active ingredient (such as, for example, a chemotherapeutic agent), and a pharmaceutically acceptable carrier.

20 This invention also provides a method of inhibiting ERK (i.e., inhibiting the activity of ERK2) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1) compound of formula (1).

This invention also provides a method for treating cancer in a patient in need of such  
25 treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1) compound of formula (1). This invention also provides a method for treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one (e.g., 1) compound of formula (1), in combination with an effective amount of at least one chemotherapeutic agent. The methods of this invention include the administration of a pharmaceutical composition comprising at least one  
30 (e.g., 1) compound of this invention and a pharmaceutically acceptable carrier. This invention also provides any of the above methods of treating cancer wherein the cancer is colorectal.

- 3 -

This invention also provides any of the above methods of treating cancer wherein the cancer is melanoma.

The methods of treating cancers described herein can optionally include the administration of an effective amount of radiation (i.e., the methods of treating cancers described herein optionally include the administration of radiation therapy).

## DETAILED DESCRIPTION OF THE INVENTION

All patents, publications and pending patent applications identified herein are hereby incorporated by reference.

As described herein, unless otherwise indicated, the use of a drug or compound in a specified period is per treatment cycle. For example, once a day means once per day of each day of the treatment cycle, and once a week means one time per week during the treatment cycle.

The following abbreviations have the following meanings unless defined otherwise:  
DCM is dichloromethane; DIBAL-H is diisobutylaluminum hydride; DIEA is diisopropylethylamine; DMA is dimethylacetamide; DMF is dimethylformamide; DMSO is dimethyl sulfoxide; EtOAc is ethyl acetate; NBS is N-bromosuccinimide; RT is room temperature; Selectfluor® is 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); SFC is Supercritical fluid chromatography; TEA is triethylamine; TFA is trifluoroacetic acid; THF is tetrahydrofuran; TRCl is triphenyl methane chloride; TRT is trityl or triphenylmethane; MeOH is methanol; Cy is cyclohexyl;

As used herein, unless otherwise specified, the terms below have the meaning indicated.

The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "anti-cancer agent" means a drug (medicament or pharmaceutically active ingredient) for treating cancer.

The term "antineoplastic agent" means a drug (medicament or pharmaceutically active ingredient) for treating cancer (i.e., a chemotherapeutic agent).

The term "at least one" means one or more than one. In one example "at least one" means 1-4, and in another example 1-3, and in another example 1-2, and in another example 1.

- 4 -

The meaning of “at least one” with reference to the number of compounds of this invention is independent of the meaning with reference to the number of chemotherapeutic agents.

The term “chemotherapeutic agent” means a drug (medicament or pharmaceutically active ingredient) for treating cancer (i.e., antineoplastic agent);

5           The term “compound” with reference to the antineoplastic agents, includes the agents that are antibodies.

The term “consecutively” means one following the other.

10           The term “effective amount” means a “therapeutically effective amount”. The term “therapeutically effective amount” means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. Thus, for example, in the methods of treating cancer described herein “effective amount” (or “therapeutically effective amount”) means, the amount of the compound (or drug), or radiation, that results in: (a) the reduction, alleviation or disappearance of one or more symptoms caused by the cancer, (b) the reduction of tumor size, (c) the elimination of the tumor, and/or (d) long-term disease stabilization (growth arrest) of the tumor. Also, for example, an effective amount, or a therapeutically effective amount of the ERK inhibitor (i.e., a compound of this invention) is that amount which results in the reduction in ERK (ERK2) activity and phosphorylation. The reduction in ERK activity may be determined by the analysis of pharmacodynamic markers such as phosphorylated RSK1,2 using techniques well known in the art.

25           The term “treating cancer” or “treatment of cancer” refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, and also refers to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The term “one or more” has the same meaning as “at least one”.

The term “patient” means an animal, such as a mammal (e.g., a human being, and preferably a human being).

30           The term sequentially represents (1) administration of one component of the method ((a) compound of the invention, or (b) chemotherapeutic agent, signal transduction inhibitor and/or radiation therapy) followed by administration of the other component or components. After administration of one component, the next component can be administered substantially immediately after the first component, or the next component can be administered after an

- 5 -

effective time period after the first component. The effective time period is the amount of time given for realization of maximum benefit from the administration of the first component.

The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanlates, methanlates, and the like; "hydrate" is a solvate wherein the solvent molecule is H<sub>2</sub>O.

The term "fused" with reference to, for example, two fused rings, means that the two rings have two atoms in common.

The term "monocyclic", as used to describe a ring, means the ring is a single ring (i.e., the ring is not a fused ring). Thus, for example, a "monocyclic heteroaryl ring" means a single heteroaryl ring. A bridged monocyclic ring means a monocyclic ring wherein two atoms in the ring are connected by a bridge. Thus, for example, a "bridged monocyclic heterocycloalkyl ring" means a monocyclic heterocycloalkyl ring wherein two atoms in the ring are connected by a bridge.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, unless otherwise specified, the terms below have the meanings indicated, and unless otherwise specified, the definitions of each term (i.e., moiety or substituent) apply when that term is used individually or as a component of another term (e.g., the definition of heteroaryl is the same for heteroaryl and for the heteroaryl portion of -alkylheteroaryl, and the like).

The term "alkoxy" means an alkyl-O- group (i.e., the bond to the parent moiety is through the ether oxygen) in which the alkyl group is as defined below. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and heptoxy.

- 6 -

The term "alkyl" (including the alkyl portions of other moieties, such as alkoxy) means an aliphatic hydrocarbon group (chain) that can be straight or branched wherein said group comprises about 1 to about 20 carbon atoms in the chain. In one example said alkyl group comprises about 1 to about 12 carbon atoms in the chain, in another example about 1 to about 6 carbon atoms in the chain; in another example 1 to about 4 carbon atoms in the chain; and in another example 1 to about 2 carbon atoms in the chain. Branched alkyl means that one or more lower alkyl groups, such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group comprising about 1 to about 6 carbon atoms in the chain, and said chain can be straight or branched.

10 The term -alkylcycloalkyl (or cycloalkylalkyl-) means a cycloalkyl, as defined below, bound to an alkyl, as defined above, wherein the cycloalkyl moiety is bound to the rest of the molecule through the alkyl group.

The term "alkylene" (including the alkylene portions of other moieties) means a chain comprising at least one -(CH<sub>2</sub>)- group. Examples of alkylene chains include, but are not limited to: -(CH<sub>2</sub>)<sub>1-6</sub>-, -(CH<sub>2</sub>)<sub>1-4</sub>-, -(CH<sub>2</sub>)<sub>1-2</sub>- and -(CH<sub>2</sub>)-

The term "amino" means an -NH<sub>2</sub> group.

20 The term "aryl" (including the aryl portions of other moieties, and sometimes abbreviated "ar") means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

The term "cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 7, or 3 to about 6, carbon atoms, preferably about 3 to about 6 carbon atoms. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like.

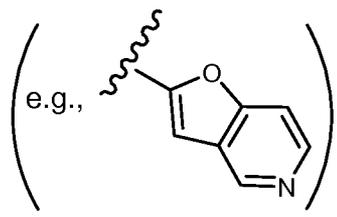
The term "halo" means fluoro, chloro, bromo, or iodo groups. Preferred halos are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

The term "halogen" means fluorine, chlorine, bromine, or iodine. Preferred halogens are fluorine, chlorine and bromine.

30 The term "heteroaryl" means an aromatic monocyclic or multicyclic ring system (e.g., a fused ring system) comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls comprise

- 7 -

about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom, respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. The heteroaryl multicyclic ring system includes two rings fused together (i.e., there are two atoms  
 5 common to both rings). Examples of the heteroaryl multicyclic ring system include fused heteroarylaryl rings (i.e., a heteroaryl ring fused to an aryl ring), and fused heteroarylheteroaryl rings (i.e., a heteroaryl ring fused to a heteroaryl ring). Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl,  
 10 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothieryl, benzopyrazolyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl, furopyridine



and the like.

The term “heteroarylalkyl-” (or heteroaralkyl-, or -alkylheteroaryl) means a heteroaryl-group (as defined above), bound to an alkyl- group (as defined above), wherein the heteroaryl group is bound to the rest of the molecule through the alkyl group; preferred heteroarylalkyls  
 20 comprise an alkyl group that is a lower alkyl group; non-limiting examples of suitable heteroaralkyl groups include pyridyl-CH<sub>2</sub>-, pyrimidinyl-CH<sub>2</sub>-, imidazolyl-CH<sub>2</sub>-, pyrazinyl-CH<sub>2</sub>-, and thiazolyl-CH<sub>2</sub>-.

The term “heterocycloalkyl” (or “heterocyclyl”) means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably  
 25 about 5 to about 10 ring atoms, and in one example 4 to 6 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or  
 30 sulfur atom respectively is present as a ring atom. The nitrogen or sulfur atom of the

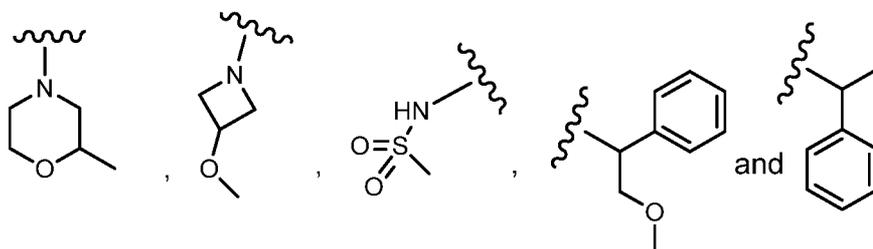
- 8 -

heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranlyl, tetrahydrothiophenyl, tetrahydrothiopyranlyl, and the like. The heterocycloalkyl rings of this invention can be “bridged heterocycloalkyl rings. The term “bridged heterocycloalkyl”” (or “bridged heterocyclyl”) means a heterocycloalkyl group as defined above having an alkylene chain (generally a 1 or 2 carbon alkylene chain, not counting the atoms in the ring to which the alkylene chain is bound to) bridging two carbon atoms in the ring.

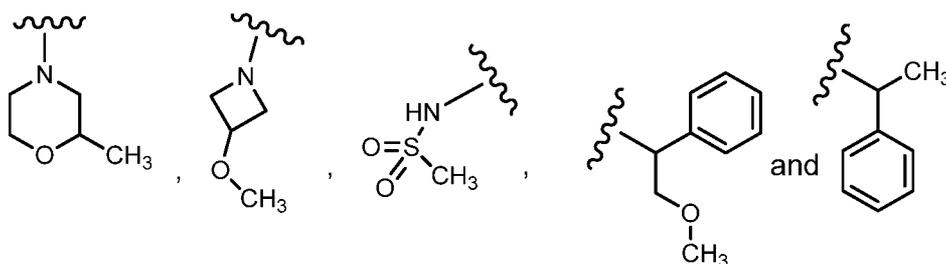
10 The term –heterocycloalkylaryl (or arylheterocycloalkyl-) means a heterocycloalkyl, as defined above, bound to an aryl, as defined above, wherein the aryl moiety is bound to the rest of the molecule through the heterocycloalkyl group.

Any carbon or heteroatom with unsatisfied valences in the text, schemes, examples, structural formulae, and any tables herein is assumed to have the hydrogen atom or atoms to satisfy the valences. And any one or more of these hydrogen atoms can be deuterium.

Those skilled the art will appreciate that formulas showing a bond that does not have a substituent at the end of the bond represents a methyl group. Thus, for example,



are the same moieties as:



20 , respectively.

One or more compounds of the invention may also exist as, or be optionally converted to, a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates,

- 9 -

hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The term “pharmaceutical composition” is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said “more than one pharmaceutically active agents”. The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, capsules, pills and the like. Similarly, the herein-described methods of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

Tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

- 10 -

Thus, all stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of formula (1) may be atropisomers and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

When any variable occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents indicate that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is bicyclic, it is intended that the bond be attached to any of the suitable atoms on either ring of the bicyclic moiety.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple

- 11 -

groups may be on the same carbon or on different carbons, so long as a stable structure results. Also, "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

5 It is understood that one or more silicon (Si) atoms can be incorporated into the compounds of the instant invention in place of one or more carbon atoms by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art from readily available starting materials. Carbon and silicon differ in their covalent radius leading to differences in bond distance and the steric arrangement when comparing analogous C-element and Si-element bonds. These differences  
10 lead to subtle changes in the size and shape of silicon-containing compounds when compared to carbon. One of ordinary skill in the art would understand that size and shape differences can lead to subtle or dramatic changes in potency, solubility, lack of off target activity, packaging properties, and so on. (Diass, J. O. *et al.* *Organometallics* (2006) 5:1188-1198; Showell, G.A. *et al.* *Bioorganic & Medicinal Chemistry Letters* (2006) 16:2555-2558).

15 Prodrugs of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of formula (1) or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987)  
20 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

This invention also includes the compounds of this invention in isolated and purified form.

25 Polymorphic forms of the compounds of formula (1), and of the salts, solvates and prodrugs of the compounds of formula (1), are intended to be included in the present invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional  
30 chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various

- 12 -

combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic  
5 instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic,  
10 maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic (TFA) and the like.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include  
15 aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic  
20 ion exchange resins, such as arginine, betaine caffeine, choline, N,N<sup>1</sup>-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine  
25 tripropylamine, tromethamine and the like.

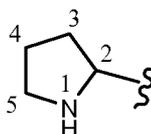
The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

It will also be noted that the compounds of the present invention are potentially  
30 internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

- 13 -

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

In hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, and there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

The term “purified”, “in purified form” or “in isolated and purified form” for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. Thus, the term “purified”, “in purified form” or “in isolated and purified form” for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

When a functional group in a compound is termed “protected”, this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

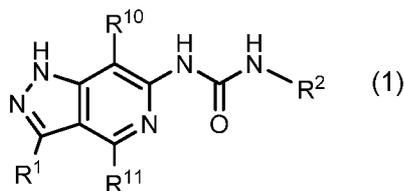
The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, chlorine, and iodine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ ,  $^{36}\text{Cl}$ , and  $^{123}\text{I}$ , respectively.

Certain isotopically-labelled compounds of formula (1) (e.g., those labeled with  $^3\text{H}$  and  $^{14}\text{C}$ ) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e.,  $^3\text{H}$ ) and carbon-14 (i.e.,  $^{14}\text{C}$ ) isotopes are particularly preferred for their ease of preparation and detectability. Certain isotopically-labelled compounds of Formula (1) can be useful for

- 14 -

medical imaging purposes. E.g., those labeled with positron-emitting isotopes like  $^{11}\text{C}$  or  $^{18}\text{F}$  can be useful for application in Positron Emission Tomography (PET) and those labeled with gamma ray emitting isotopes like  $^{123}\text{I}$  can be useful for application in Single photon emission computed tomography (SPECT). Further, substitution with heavier isotopes such as deuterium (i.e.,  $^2\text{H}$ ) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of formula (1), in particular those containing isotopes with longer half lives ( $T_{1/2} > 1$  day), can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an appropriate isotopically labeled reagent for a non-isotopically labeled reagent.

This invention provides compounds that are ERK inhibitors (i.e., ERK2 inhibitors), said compounds being of the formula (1):



or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof, wherein:

$R^1$  is  $-\text{NR}^4\text{R}^5$ ;

$R^2$  is selected from the group consisting of: H,  $(\text{C}_6\text{-C}_{10})\text{aryl}$ - $(\text{C}_1\text{-C}_3\text{alkyl})$ -heterocycloalkyl-,  $(\text{C}_1\text{-C}_6\text{alkyl})$ -,  $(\text{C}_1\text{-C}_6\text{alkyl})\text{-O-}(\text{C}_1\text{-C}_6\text{alkyl})$ -,  $(\text{C}_1\text{-C}_6\text{alkyl})$ -heterocycloalkyl- $(\text{C}_6\text{-C}_{10}\text{aryl})$ -,  $(\text{C}_1\text{-C}_4\text{alkyl})(\text{C}_6\text{-C}_{10}\text{aryl})$ -,  $(\text{C}_1\text{-C}_4\text{alkyl})\text{heteroaryl}$ -,  $(\text{C}_3\text{-C}_6\text{cycloalkyl})$ - $(\text{C}_6\text{-C}_{10}\text{aryl})$ -, heterocycloalkyl- $(\text{C}_6\text{-C}_{10}\text{aryl})$ -,  $(\text{C}_1\text{-C}_6\text{alkyl})$ - $(\text{C}_3\text{-C}_6\text{cycloalkyl})$ -,  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})(\text{C}_3\text{-C}_6\text{cycloalkyl})$ -,  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})((\text{C}_1\text{-C}_6\text{alkyl})\text{N}(\text{R}^{20})_2)$ -,  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})(\text{heterocycloalkyl})$ -,  $(\text{C}_3\text{-C}_6\text{cycloalkyl})\text{-O-}(\text{C}_1\text{-C}_6\text{alkyl})$ -,  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})\text{C}(\text{O})\text{N}(\text{R}^{21})_2$  wherein each  $\text{R}^{21}$  is independently selected, and -fused (heterocycloalkyl) $(\text{C}_6\text{-C}_{10}\text{aryl})$  wherein said heterocycloalkyl is a 5 to 8 membered ring (including the two atoms common with said aryl) comprising 1-3 heteroatoms selected from the group consisting of: O, S and N, and wherein the remaining atoms are carbon;

and wherein said aryl, heterocycloalkyl, heteroaryl, and cycloalkyl moieties of said  $\text{R}^2$  groups are optionally substituted with 1-3 substituents independently selected from the group consisting of: CN, halo (e.g., F, Br, and Cl),  $-\text{O-}(\text{C}_1\text{-C}_6\text{alkyl})$ -,  $-\text{OH}$ -,  $-\text{CF}_3$ -,  $(\text{C}_1\text{-C}_6\text{alkyl})$ -,  $-\text{O}(\text{halo substituted}(\text{C}_1\text{-C}_6\text{alkyl}))$ -,  $-\text{N}(\text{R}^{20})_2$ -, aryl and heteroaryl;

- 15 -

and wherein said alkyl moieties of said R<sup>2</sup> groups are optionally substituted with 1-3 substituents independently selected from the group consisting of: CN, halo (e.g., F, Br, and Cl),

-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -OH and -CF<sub>3</sub>, -O(halo substituted(C<sub>1</sub>-C<sub>6</sub>alkyl)) and -S(C<sub>1</sub>-C<sub>6</sub>alkyl);

- 5 R<sup>4</sup> and R<sup>5</sup> are each independently selected from the group consisting of: H, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>9</sup>, -(C<sub>1</sub>-C<sub>6</sub>alkyl) substituted with 1-3 substituents independently selected from the group consisting of: halo, -OH and -S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) substituted with 1-3 substituents independently selected from the group consisting of: halo, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, -(C<sub>3</sub>-C<sub>6</sub> cycloalkenyl), -(C<sub>3</sub>-C<sub>6</sub> oxocycloalkenyl), -(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>6</sub>-C<sub>10</sub>aryl) substituted with 1-3 substituents independently selected from the group consisting of: -CN, -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and halo, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)C(O)N(R<sup>20</sup>)<sub>2</sub> wherein each R<sup>20</sup> is independently selected, heteroaryl, heteroaryl substituted with 1-3 substituents independently selected from the group consisting of: -CN, halo and -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)(heteroaryl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)(heteroaryl) substituted with 1-3 substituents independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) substituted with 1-3 substituents independently selected from the group consisting of: -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(hydroxyC<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>2</sub>-C<sub>6</sub>alkenyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)heterocycloalkyl, -C(O)(substituted C<sub>1</sub>-C<sub>6</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>6</sub>alkyl) wherein said substituted alkyl is substituted with a heterocycloalkyl, -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>6</sub>alkyl), heterocycloalkyl, heterocycloalkyl substituted with 1-3 substituents independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl) and halo, -(C<sub>1</sub>-C<sub>6</sub>alkyl)heterocycloalkenyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)heterocycloalkenyl substituted with 1-3 substituents independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl); or

- 20 R<sup>4</sup> and R<sup>5</sup> taken together with the nitrogen to which they are bonded to form a 4-6 membered heterocycloalkyl ring, said ring optionally comprising 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S and N, and said heterocycloalkyl ring optionally comprising a 1-2 carbon bridge, and said ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>6</sub>alkyl), -OH, -SCH<sub>3</sub>, halo, -CF<sub>3</sub>, CN, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-OH and -C(O)OH; or

- 16 -

5 R<sup>4</sup> and R<sup>5</sup> taken together with the nitrogen to which they are bonded to form a spiro ring comprising two independently selected 4-6 membered heterocycloalkyl rings, wherein one of said rings comprises the nitrogen of the -NR<sup>4</sup>R<sup>5</sup> group, and wherein the other ring of the spiro ring comprises one heteroatom selected from the group consisting of: O, N and S, and wherein each heterocycloalkyl ring optionally comprises 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S and N, and wherein said spiro ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: -OH, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>6</sub> alkyl); or

10 R<sup>4</sup> and R<sup>5</sup> taken together with the nitrogen to which they are bonded to form a fused bicyclic heterocycloalkyl ring, said ring optionally comprising 1 to 3 additional heteroatoms independently selected from the group consisting of: O, S and N, and said ring optionally comprising a -O- bridge between two ring carbons (i.e., an epoxy bridge), and said ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: halogen, -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>6</sub> alkyl); or

15 R<sup>4</sup> and R<sup>5</sup> taken together with the nitrogen to which they are bonded to form a fused bicyclic ring wherein one ring is a heterocycloalkyl ring, and one ring is a heteroaryl ring, said heterocycloalkyl ring optionally comprising 1 to 3 additional heteroatoms independently selected from the group consisting of: O, S and N, and said bicyclic ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: halogen, -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>6</sub> alkyl); or

20 R<sup>4</sup> and R<sup>11</sup> taken together form a 5-8 membered heterocycloalkyl ring, said ring optionally comprising 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S, N, and -(C=O)-, and said ring is optionally substituted with 1-3 substituents independently selected from R<sup>14</sup> group.

25 R<sup>8</sup> and R<sup>9</sup> are each independently selected from the group consisting of: -OR<sup>12</sup>, -NHR<sup>12</sup>, -NR<sup>12</sup>R<sup>13</sup>, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl), and -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>10</sub>cycloalkyl), fused bicyclic heterocycloalkyl ring, and wherein said heterocycloalkyl is a 4-6 membered ring comprising 1-3 heteroatoms selected from the group consisting of: O, S and N and the remaining ring atoms are carbon, and wherein said aryl is a C<sub>6</sub> to C<sub>10</sub> aromatic ring, and wherein said heteroaryl is a 5 to 10 membered ring comprising 1-3 heteroatoms selected from the group consisting of: O, S and N and the remaining ring atoms

- 17 -

are carbon, and wherein said R<sup>8</sup> heterocycloalkyl is optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, -OH, and -(C<sub>1</sub>-C<sub>6</sub>alkyl), and wherein said R<sup>8</sup> -(C<sub>1</sub>-C<sub>6</sub>alkyl) is optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, -NH(C<sub>1</sub>-C<sub>6</sub>alkyl) and -N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, and wherein said R<sup>8</sup> heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl), and wherein said R<sup>8</sup> aryl is optionally substituted with 1-3 substituents independently selected from the group consisting of: halo; and

R<sup>10</sup> is independently selected from the group consisting of: H, halo, CN, OH, NH<sub>2</sub>, -CF<sub>3</sub>, -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub> to C<sub>6</sub>alkyl), -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), hydroxy substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, and -(C<sub>1</sub>-C<sub>6</sub>alkyl)-heterocycloalkyl.

R<sup>11</sup> is independently selected from the group consisting of: H, halo, CN, OH, NH<sub>2</sub>, aryl, heteroaryl, heterocycloalkyl, -NHR<sup>12</sup>, -NR<sup>12</sup>R<sup>13</sup>, -NHC(O)R<sup>8</sup>, -CF<sub>3</sub>, -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub> to C<sub>6</sub>alkyl), -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), hydroxy substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-heterocycloalkyl

each R<sup>12</sup> is independently selected from the group consisting of: (C<sub>1</sub>-C<sub>6</sub>alkyl), (C<sub>3</sub>-C<sub>6</sub>cycloalkyl), ((C<sub>3</sub>-C<sub>6</sub>cycloalkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-), (C<sub>3</sub>-C<sub>6</sub>cycloalkenyl), heterocycloalkyl, (heterocycloalkyl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, (C<sub>6</sub>-C<sub>10</sub>)aryl, (aryl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, heteroaryl, (heteroaryl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl R<sup>12</sup> groups is optionally substituted with 1 to 3 independently selected R<sup>14</sup> groups.

each R<sup>13</sup> is independently selected from the group consisting of: (C<sub>1</sub>-C<sub>6</sub>alkyl), (C<sub>3</sub>-C<sub>6</sub>cycloalkyl), ((C<sub>3</sub>-C<sub>6</sub>cycloalkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-), (C<sub>3</sub>-C<sub>6</sub>cycloalkenyl), heterocycloalkyl, (heterocycloalkyl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, (C<sub>6</sub>-C<sub>10</sub>)aryl, (aryl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, heteroaryl, (heteroaryl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl R<sup>13</sup> groups is optionally substituted with 1 to 3 independently selected R<sup>14</sup> groups, or

R<sup>12</sup> and R<sup>13</sup> taken together with the nitrogen to which they are bonded to form a 4-8 membered heterocycloalkyl ring, said ring optionally comprising 1 or 2 additional heteroatoms

- 18 -

independently selected from the group consisting of: O, S and N, and said ring is optionally substituted with 1-3 substituents independently selected from R<sup>14</sup> group.

each R<sup>14</sup> group is independently selected from the group consisting of halo, -CF<sub>3</sub>, -CN, OH, -OR<sup>15</sup>, (C<sub>1</sub>-C<sub>6</sub>alkyl), (C<sub>3</sub>-C<sub>6</sub>cycloalkyl), (C<sub>3</sub>-C<sub>6</sub>cycloalkenyl), heterocycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, heteroaryl and -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl);

each R<sup>15</sup> is independently selected from the group consisting of: (C<sub>1</sub>-C<sub>6</sub>alkyl), (C<sub>3</sub>-C<sub>6</sub>cycloalkyl), ((C<sub>3</sub>-C<sub>6</sub>cycloalkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-), (C<sub>3</sub>-C<sub>6</sub>cycloalkenyl), heterocycloalkyl, (heterocycloalkyl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, (C<sub>6</sub>-C<sub>10</sub>)aryl, (aryl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, heteroaryl, (heteroaryl(C<sub>1</sub>-C<sub>6</sub>alkyl))- and -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl);

R<sup>20</sup> is independently selected from the group consisting of H and (C<sub>1</sub>-C<sub>6</sub>alkyl); and R<sup>21</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl).

In one example, this invention provides compounds of formula (1) or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof, wherein:

R<sup>1</sup> is -NR<sup>4</sup>R<sup>5</sup>;

R<sup>2</sup> is selected from the group consisting of: H, (C<sub>6</sub>-C<sub>10</sub>)aryl-(C<sub>1</sub>-C<sub>3</sub>alkyl)-heterocycloalkyl-, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-heterocycloalkyl-(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>1</sub>-C<sub>4</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>)aryl, -(C<sub>1</sub>-C<sub>3</sub>alkyl)heteroaryl, -(C<sub>3</sub>-C<sub>6</sub>cycloalkyl)-(C<sub>6</sub>-C<sub>10</sub>aryl), -heterocycloalkyl-(C<sub>6</sub>-C<sub>10</sub>aryl); and wherein said aryl, heterocycloalkyl, heteroaryl, and cycloalkyl moieties of said R<sup>2</sup> groups are optionally substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Br, and Cl), -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -OH, -CF<sub>3</sub>, and -(C<sub>1</sub>-C<sub>6</sub>alkyl); and wherein said alkyl moieties of said R<sup>2</sup> groups are optionally substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Br, and Cl), -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -OH and -CF<sub>3</sub>;

R<sup>4</sup> and R<sup>5</sup> are each independently selected from the group consisting of: H, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>9</sup>; or

R<sup>4</sup> and R<sup>5</sup> taken together with the nitrogen to which they are bonded to form a 4-6 membered heterocycloalkyl ring, said ring optionally comprising 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S and N, and said ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>6</sub>alkyl);

R<sup>8</sup> and R<sup>9</sup> are each independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl,

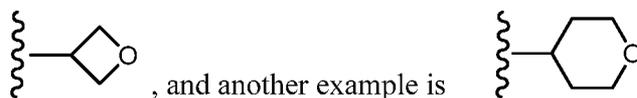
- 19 -

heterocycloalkyl, aryl, and heteroaryl, and wherein said heterocycloalkyl is a 4-6 membered ring comprising 1-3 heteroatoms selected from the group consisting of: O, S and N and the remaining ring atoms are carbon, and wherein said aryl is a C<sub>6</sub> to C<sub>10</sub> aromatic ring, and wherein said heteroaryl is a 5 to 10 membered ring comprising 1-3 heteroatoms selected from the group consisting of: O, S and N and the remaining ring atoms are carbon; and

R<sup>10</sup> and R<sup>11</sup> are each independently selected from the group consisting of: H, halo, -(C<sub>1</sub> to C<sub>6</sub>alkyl), -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), hydroxy substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, and -(C<sub>1</sub>-C<sub>6</sub>alkyl)-heterocycloalkyl.

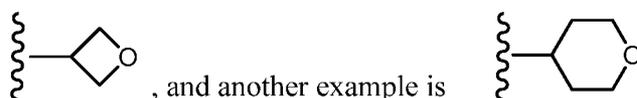
The following groups are as defined below, unless defined otherwise.

For the R<sup>2</sup>, R<sup>10</sup> and R<sup>11</sup> groups comprising a heterocycloalkyl, each heterocycloalkyl is independently selected and each heterocycloalkyl is a 4 to 8 membered ring, and in one example a 4 to 6 membered ring, comprising 1 to 3 heteroatoms independently selected from the group consisting of: O, N and S, and the remaining ring atoms are carbon. In one example, the heterocycloalkyl is a 4 to 6 membered ring comprising 1-2 heteroatoms independently selected from the group consisting of: O, N and S, and the remaining ring atoms are carbon. In another example, the heterocycloalkyl is a 4 to 6 membered ring comprising 1-2 heteroatoms independently selected from the group consisting of: O and N, and the remaining ring atoms are carbon. In another example, the heterocycloalkyl is a 4 to 6 membered ring comprising 1 heteroatom selected from the group consisting of: O, N and S, and the remaining ring atoms are carbon. In another example, the heterocycloalkyl is a 4 to 6 membered ring comprising 1 heteroatom selected from the group consisting of: O and N, and the remaining ring atoms are carbon. In another example the heterocycloalkyl is a 4 to 6 membered ring comprising 1-2 N atoms, and the remaining ring atoms are carbon. In another example the heterocycloalkyl is a 4 to 6 membered ring comprising 1 heteroatom and said heteroatom is O. In another example the R<sup>2</sup> heterocycloalkyl is a 4 membered ring, in another example a 5 membered ring, and in another example a 6 membered ring. Examples of the heterocycloalkyl include, but are not limited to: oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thietanyl, tetrahydrothiophenyl (tetrahydrothienyl), and tetrahydrothiopyranyl. In one example the heterocycloalkyl is



- 20 -

In another example, the heterocycloalkyl is selected from the group consisting of: piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, and morpholinyl. In another example the heterocycloalkyl is piperidinyl. Examples the R<sup>2</sup> heterocycloalkyl include, but are not limited to, piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, and morpholinyl. In another example the heterocycloalkyl is piperidinyl. Examples of the R<sup>2</sup> heterocycloalkyl include, but are not limited to: oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thietanyl, tetrahydrothiophenyl (tetrahydrothienyl), and tetrahydrothiopyranyl. In one example the R<sup>2</sup> heterocycloalkyl is



Examples the R<sup>10</sup> heterocycloalkyl include, but are not limited to, piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, and morpholinyl. In another example the heterocycloalkyl is piperidinyl. Examples the R<sup>11</sup> heterocycloalkyl include, but are not limited to, piperidinyl, pyrrolidinyl, azetidiny, piperazinyl, and morpholinyl. In another example the heterocycloalkyl is piperidinyl.

For the R<sup>2</sup> groups comprising a heteroaryl, said heteroaryl is a 5 to 6 membered ring comprising 1 to 3 heteroatoms independently selected from the group consisting of: O, N and S, and the remaining ring atoms are carbon. In one example the heteroaryl is a 6 membered ring comprising 1 or 2 heteroatoms independently selected from the group consisting of: O, N and S. In another example the heteroaryl is a 6 membered ring comprising 1 or 2 N atoms. In another example the heteroaryl is a 6 membered ring comprising 1 N.

For the R<sup>2</sup> groups comprising a C<sub>6</sub>-C<sub>10</sub> aryl, said C<sub>6</sub>-C<sub>10</sub> aryl is a single ring or two fused rings, and the total number of carbons is 6 to 10. In one example of the C<sub>6</sub>-C<sub>10</sub> aryl is phenyl. Another example of the C<sub>6</sub>-C<sub>10</sub> aryl is naphthyl.

For the R<sup>2</sup> optional substituent -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), one example of the alkyl moiety is -(C<sub>1</sub>-C<sub>4</sub>alkyl), and another is -(C<sub>1</sub>-C<sub>2</sub>alkyl), and another is methyl.

For the R<sup>2</sup> optional substituent -(C<sub>1</sub>-C<sub>6</sub>alkyl), one example of the alkyl moiety is -(C<sub>1</sub>-C<sub>4</sub>alkyl), and another is -(C<sub>1</sub>-C<sub>2</sub>alkyl), and another is methyl.

The R<sup>2</sup> heterocycloalkyl optional substituent, in one example, is a 4 to 6 membered ring (and in one example a 5-6 membered ring) comprising 1-3 heteroatoms selected from the group consisting of: O, N and S. In another example said heterocycloalkyl is a 5 to 6 membered ring comprising 1-3 heteroatoms selected from the group consisting of: O, N and S. In another example said heterocycloalkyl is a 5 to 6 membered ring comprising one

- 21 -

heteroatom. In another example said heterocycloalkyl is a 5-6 membered ring comprising one oxygen atom. In another example said heterocycloalkyl ring is tetrahydropyran.

5 Examples of the  $R^4$  and/or  $R^5$   $-(C_1-C_6\text{alkyl})$  group include:  $-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})$ . In one example the  $-(C_1-C_6\text{alkyl})$  group is methyl, in another example ethyl, in another example propyl, and in another example isopropyl, and in another example t-butyl.

10 In one Example of the  $R^4$  and/or  $R^5$  is  $-(C_1-C_6\text{alkyl})$  substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., Cl, Br and F, and in one example Cl, and in another F),  $-OH$  and  $-S(O)_2(C_1-C_6\text{alkyl})$  (such as, for example,  $S(O)_2(C_1-C_2\text{alkyl})$ ). In another example  $R^4$  and/or  $R^5$  is  $-\text{CH}(\text{CH}_3)\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$ , and in another example  $-\text{CH}(\text{CH}_3)\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$ , and in another example  $-\text{CH}(\text{CH}_3)\text{CH}_2\text{Cl}$ , and in another example  $-\text{CH}(\text{CH}_3)\text{CHF}_2$ . In another example  $R^5$  is any one of the substituted  $-(C_1-C_6\text{alkyl})$  groups described in this paragraph. In another example  $R^4$  is H and  $R^5$  is any one of the substituted  $-(C_1-C_6\text{alkyl})$  groups described in this paragraph.

15 Examples of the  $R^4$  and/or  $R^5$   $-(C_1-C_6\text{alkyl})-O-(C_1-C_6\text{alkyl})$  group include  $-(C_1-C_4\text{alkyl})-O-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})-O-(C_1-C_3\text{alkyl})$ ,  $-(C_1-C_2\text{alkyl})-O-(C_1-C_2\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})-O-\text{CH}_3$ . In one example the  $-(C_1-C_2\text{alkyl})-O-(C_1-C_2\text{alkyl})$  group is  $-(\text{CH}_2)_2-O-\text{CH}_3$ , and in another example  $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OCH}_3$ .

20 Examples of the  $R^4$  and/or  $R^5$   $-C(O)R^8$  group include groups wherein the  $R^8$   $-(C_1-C_6\text{alkyl})$  group is selected from the group consisting of:  $-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})$ . In one example  $R^8$  is methyl. In another example  $R^4$  and/or  $R^5$  is a  $-C(O)(C_1-C_4\text{alkyl})$ , and in another example  $-\text{C}(O)\text{CH}(\text{CH}_3)_2$ , and in another  $-\text{C}(O)\text{CH}_2\text{CH}(\text{CH}_3)_2$ , and in another  $-\text{C}(O)\text{C}(\text{CH}_3)_3$ . In other examples  $R^4$  is H, and  $R^5$  is  $-C(O)R^8$  wherein  $R^8$  is as defined in this paragraph. Thus, in one example  $R^4$  is H and  $R^5$  is  $-C(O)\text{CH}_3$ .

25 In one example  $R^4$  is  $-(C_1-C_6\text{alkyl})$  and  $R^5$  is a  $-C(O)R^8$  wherein  $R^8$  is a  $-(C_1-C_6\text{alkyl})$  moiety (i.e.,  $R^5$  is a  $-C(O)(C_1-C_6\text{alkyl})$  group). In another example  $R^4$  is  $-(C_1-C_4\text{alkyl})$ , and  $R^5$  is any one of the  $-C(O)R^8$  groups described in this paragraph. In another example  $R^4$  is  $-(C_1-C_2\text{alkyl})$ , and  $R^5$  is any one of the  $-C(O)R^8$  groups described in this paragraph. In one example  $R^5$  is  $-C(O)(C_1-C_4\text{alkyl})$ , and in another example  $-\text{C}(O)\text{CH}(\text{CH}_3)_2$ , and in another example  
30  $-\text{C}(O)\text{CH}_2\text{CH}(\text{CH}_3)_2$ , and in another example  $-\text{C}(O)(\text{CH}_3)$ . In another example  $R^4$  is methyl and  $R^5$  is  $-C(O)\text{CH}_3$ , and in another example  $R^4$  is ethyl and  $R^5$  is  $-C(O)\text{CH}_3$ .

- 22 -

In one example  $R^4$  and/or  $R^5$  is a  $-C(O)R^8$  wherein  $R^8$  is a substituted  $-(C_1-C_6\text{alkyl})$  (i.e.,  $R^4$  and/or  $R^5$  is a substituted  $-C(O)(C_1-C_6\text{alkyl})$ , and in another example a substituted  $-C(O)(C_1-C_4\text{alkyl})$ ). In one example the  $R^4$  and/or  $R^5$  substituted  $-C(O)(C_1-C_6\text{alkyl})$  is substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Br, and Cl and in one example F),  $-NH(C_1-C_6\text{alkyl})$ , and  $-N(C_1-C_6\text{alkyl})_2$  wherein each alkyl is independently selected. Examples of the  $C_1-C_6\text{alkyl}$  moiety in the  $-NH(C_1-C_6\text{alkyl})$ , and  $-N(C_1-C_6\text{alkyl})_2$  substituents include  $C_1-C_4\text{alkyl}$  and  $C_1-C_2\text{alkyl}$ , and in one example methyl. In one example said substituted  $-C(O)(C_1-C_6\text{alkyl})$  is  $-C(O)CH_2CF_3$ , and in another  $-C(O)CH_2N(CH_3)_2$ . In another example  $R^5$  is any one of the substituted  $-C(O)(C_1-C_6\text{alkyl})$  groups described in this paragraph. In another example  $R^4$  is H and  $R^5$  is any one of the substituted  $-C(O)(C_1-C_6\text{alkyl})$  groups described in this paragraph.

In one example the  $R^4$  and/or  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is a  $-(C_1-C_6\text{alkyl})$ . In one example  $R^9$  is selected from the group consisting of:  $-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})$ . In another example,  $R^9$  is methyl, and in another example  $R^9$  is ethyl. In other examples  $R^4$  is H, and  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is as defined in any one of the examples in this paragraph.

In one example the  $R^4$  and/or  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is a  $-(C_1-C_6\text{alkyl})-O-(C_1-C_6\text{alkyl})$ . In one example  $R^9$  is selected from the group consisting of:  $-(C_1-C_4\text{alkyl})-O-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_4\text{alkyl})-O-(C_1-C_2\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})-O-(C_1-C_2\text{alkyl})$ . In another example  $R^9$  is  $-CH_2CH_2OCH_3$ . In other examples  $R^4$  is H, and  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is as defined in any one of the examples in this paragraph.

In one example the  $R^4$  and/or  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is a  $-(C_3-C_6)\text{cycloalkyl}$ . In one example  $R^9$  is a  $-(C_3-C_5)\text{cycloalkyl}$ . In another example  $R^9$  is cyclopropyl. In another example  $R^9$  is cyclobutyl. In other examples  $R^4$  is H, and  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is as defined in any one of the examples in this paragraph.

In one example the  $R^4$  and/or  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is a  $-(C_1-C_6\text{alkyl})-(C_3-C_6)\text{-cycloalkyl}$ . In one example  $R^9$  is selected from the group consisting of:  $-(C_1-C_4\text{alkyl})-(C_3-C_6)\text{cycloalkyl}$ ,  $-(C_1-C_4\text{alkyl})-(C_3-C_4)\text{cycloalkyl}$  and  $-(C_1-C_2\text{alkyl})-(C_3-C_4)\text{cycloalkyl}$ . In another example  $R^9$  is  $-CH_2\text{-cyclopropyl}$ . In other examples  $R^4$  is H, and  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is as defined in any one of the examples in this paragraph.

In one example the  $R^4$  and/or  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is a heterocycloalkyl ring. In one example  $R^9$  is a 4-6 membered heterocycloalkyl comprising 1 to 3 heteroatoms selected

- 23 -

from the group consisting of O, N and S wherein the remaining ring atoms are carbon. In another example  $R^9$  is a 4-6 membered heterocycloalkyl ring comprising 1 to 3 heteroatoms selected from the group consisting of O and N wherein the remaining ring atoms are carbon. In another example  $R^9$  is a 4-6 membered heterocycloalkyl ring comprising 1 to 2

5 heteroatoms selected from the group consisting of O, N and S wherein the remaining ring atoms are carbon. In another example  $R^9$  is a 4-6 membered heterocycloalkyl ring comprising 1 to 2 heteroatoms selected from the group consisting of O and N wherein the remaining ring atoms are carbon. In another example  $R^9$  is a 4-5 membered heterocycloalkyl ring comprising 1 or 2 nitrogen atoms wherein the remaining atoms are carbon. In another

10 example  $R^9$  is a 4-5 membered ring comprising 1 nitrogen atom wherein the remaining atoms are carbon. In another example  $R^9$  is azetidiny. In another example  $R^9$  is pyrrolidiny. In another example  $R^9$  is a 6 membered heterocycloalkyl ring comprising 1 to 3 hetero atoms independently selected from the group consisting of: O, N and S wherein the remaining ring atoms are carbon. In another example  $R^9$  is a 6 membered heterocycloalkyl ring comprising 1

15 to 2 hetero atoms independently selected from the group consisting of O and N wherein the remaining atoms are carbon. In another example  $R^9$  is a 6 membered heterocycloalkyl ring comprising 1 or 2 nitrogen atoms wherein the remaining atoms are carbon. In another example  $R^9$  is piperidiny. In another example  $R^9$  is piperaziny. In another example  $R^9$  is morpholiny. In other examples  $R^4$  is H, and  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is as defined in any

20 one of the examples in this paragraph.

In one example the  $R^4$  and/or  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is an aryl. In one example  $R^9$  is phenyl. In another example  $R^9$  is naphthyl. In other examples  $R^4$  is H, and  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is as defined in any one of the examples in this paragraph.

In one example the  $R^4$  and/or  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is heteroaryl. In another

25 example  $R^9$  is a 5 or 6 membered heteroaryl ring. In another example  $R^9$  is a 5 or 6 membered heteroaryl ring comprising 1-3 nitrogen atoms wherein the remaining atoms are carbon. In another example  $R^9$  is a 5 or 6 membered heteroaryl ring comprising 1-2 nitrogen atoms wherein the remaining atoms are carbon. In another example  $R^9$  is a 5 or 6 membered heteroaryl ring comprising one nitrogen atom wherein the remaining atoms are carbon. In

30 another example  $R^9$  is pyridyl, and in another pyrimidinyl, and in another pyrazinyl, and in another triazolyl, and in another pyrazolyl, and in another imidazolyl, in another pyrrolyl, in another thiazolyl, in another thienyl, and in another oxazolyl. In other examples  $R^4$  is H, and  $R^5$  is  $-S(O)_2R^9$  wherein  $R^9$  is as defined in any one of the examples in this paragraph.

- 24 -

In one example the R<sup>4</sup> and/or R<sup>5</sup> is -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl). In another example R<sup>4</sup> and/or R<sup>5</sup> is -(C<sub>4</sub>-C<sub>6</sub> cycloalkyl). In another example, R<sup>4</sup> and/or R<sup>5</sup> is cyclopropyl, and in another example cyclobutyl, and in another example cyclopentyl, and in another example cyclohexyl. In another example, R<sup>5</sup> is any one of the -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) groups described in this paragraph. In another example, R<sup>4</sup> is H and R<sup>5</sup> is any one of the -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) groups described in this paragraph.

In one example the R<sup>4</sup> and/or R<sup>5</sup> is -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Cl and Br, and in one example F), -(C<sub>1</sub>-C<sub>6</sub>alkyl) (e.g., -(C<sub>1</sub>-C<sub>4</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl), and in another example methyl), -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub>alkyl), and -N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected. In one example, said -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) moiety is -(C<sub>4</sub>-C<sub>6</sub> cycloalkyl). In another example, said -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) is cyclobutyl, and in another example cyclohexyl. In another example the -NH(C<sub>1</sub>-C<sub>6</sub>alkyl) substituent is -NH(C<sub>1</sub>-C<sub>3</sub>alkyl). In another example said -N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> substituent is -N(C<sub>1</sub>-C<sub>3</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected. In another example said -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) moiety is substituted with -N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, and in another example substituted with -N(CH<sub>3</sub>)<sub>2</sub>. In another example the substituted -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) group is dimethylaminocyclobutyl, and in another example dimethylaminocyclohexyl, and in another example difluorocyclohexyl, and in another example methylcyclobutyl, and in another example aminocyclobutyl. In another example, R<sup>5</sup> is any one of the substituted -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) groups defined in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the substituted -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) groups defined in this paragraph.

In one example the R<sup>4</sup> and/or R<sup>5</sup> is -(C<sub>3</sub>-C<sub>6</sub> cycloalkenyl). In another example R<sup>4</sup> and/or R<sup>5</sup> is -(C<sub>3</sub>-C<sub>5</sub> cycloalkenyl). In another example, R<sup>4</sup> and/or R<sup>5</sup> is cyclopentenyl. In another example, R<sup>5</sup> is cyclopentenyl. In another example, R<sup>4</sup> is H and R<sup>5</sup> is cyclopentenyl.

In one example the R<sup>4</sup> and/or R<sup>5</sup> is -(C<sub>3</sub>-C<sub>6</sub> oxocycloalkenyl) (i.e., a C<sub>3</sub>-C<sub>6</sub> cycloalkenyl substituted with a =O). In another example R<sup>4</sup> and/or R<sup>5</sup> is -(C<sub>3</sub>-C<sub>5</sub>oxocycloalkenyl). In another example, R<sup>4</sup> and/or R<sup>5</sup> is oxocyclopentenyl-. In another example, R<sup>5</sup> is oxocyclopentenyl-. In another example, R<sup>4</sup> is H and R<sup>5</sup> is oxocyclopentenyl-.

In one example the R<sup>4</sup> and/or R<sup>5</sup> is -(C<sub>6</sub>-C<sub>10</sub> aryl). In another example R<sup>4</sup> and/or R<sup>5</sup> is phenyl. In another example, R<sup>4</sup> is H and R<sup>5</sup> is phenyl.

In one example the R<sup>4</sup> and/or R<sup>5</sup> is -(C<sub>6</sub>-C<sub>10</sub>aryl) (e.g., phenyl) substituted with 1-3 substituents independently selected from the group consisting of: -CN, -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and

- 25 -

halo (e.g., Br, Cl and F). Examples of the  $-(C_1-C_6\text{alkyl})$  substituent include, for example,  $-(C_1-C_3\text{alkyl})$ , and in another example  $-\text{OCH}_3$ . In one example phenyl is substituted with  $-\text{CN}$ . In one example the halo substituent is F. In one example, the  $R^4$  and/or  $R^5$  group is phenyl substituted with 1-3 substituents, as the substituents are as defined in this paragraph. In  
5 another example the  $R^4$  and/or  $R^5$  is methoxyphenyl. In one example,  $R^5$  is any one of the substituted  $-(C_6-C_{10}\text{aryl})$  (e.g., phenyl) groups defined in this paragraph. In another example,  $R^4$  is H and  $R^5$  is any one of the substituted  $-(C_6-C_{10}\text{aryl})$  (e.g., phenyl) groups defined in this paragraph.

In one example  $R^4$  and or  $R^5$  is  $-(C_1-C_6\text{alkyl})(C_6-C_{10}\text{aryl})$ , and in another example  $-(C_1-C_2\text{alkyl})(C_6-C_{10}\text{aryl})$ , and in another example  $-(C_1-C_2\text{alkyl})(\text{phenyl})$ , and in another example  $-\text{CH}_2\text{phenyl}$ . In another example  $R^5$  is any one of the  $-(C_1-C_6\text{alkyl})(C_6-C_{10}\text{aryl})$  groups described in this paragraph, and in another example  $R^5$  is  $-\text{CH}_2\text{phenyl}$ . In another example  $R^4$  is H, and  $R^5$  is any one of the  $-(C_1-C_6\text{alkyl})(C_6-C_{10}\text{aryl})$  groups described in this paragraph. In  
10 another example  $R^4$  is H and  $R^5$  is  $-\text{CH}_2\text{phenyl}$ .

In one example  $R^4$  and/or  $R^5$  is  $-(C_1-C_6\text{alkyl})C(O)N(R^{20})_2$  wherein each  $R^{20}$  is independently selected, and in another example  $-(C_1-C_3\text{alkyl})C(O)N(R^{20})_2$  wherein each  $R^{20}$  is independently selected, and in another example  $-(C_1-C_3\text{alkyl})C(O)N(R^{20})_2$  wherein each  $R^{20}$  is independently selected from the group consisting of:  $-(C_1-C_3\text{alkyl})$ , and in another example each  $R^{20}$  is methyl. In another example said  $-(C_1-C_6\text{alkyl})C(O)N(R^{20})_2$  is  $-\text{CH}_2C(O)N(\text{CH}_3)_2$ ,  
20 and in another example  $-(\text{CH}_2)_2C(O)N(\text{CH}_3)_2$ . In another example  $R^5$  is any one of the  $-(C_1-C_6\text{alkyl})C(O)N(R^{20})_2$  groups described in this paragraph. In another example  $R^4$  is H and  $R^5$  is any one of the  $-(C_1-C_6\text{alkyl})C(O)N(R^{20})_2$  groups described in this paragraph.

In one example the  $R^4$  and/or  $R^5$  is heteroaryl. In another example  $R^4$  and/or  $R^5$  is a 5 to 6 membered ring comprising 1-2 heteroatoms independently selected from the group consisting of: N, O and S. In another example  $R^4$  and/or  $R^5$  is a 5 to 6 membered ring comprising 1-2 nitrogen atoms. In another example  $R^4$  and/or  $R^5$  is pyridyl. In another example  $R^5$  is any one of the heteroaryl groups, as described in this paragraph. In another example,  $R^4$  is H and  $R^5$  is any one of the heteroaryl groups as defined in this paragraph. In  
25 another example  $R^4$  is H, and  $R^5$  is pyridyl.

In one example the  $R^4$  and/or  $R^5$  is heteroaryl substituted with 1-3 substituents independently selected from the group consisting of:  $-\text{CN}$ , halo (e.g., F, Cl and Br, and in one example F) and  $-(C_1-C_6\text{alkyl})$ . In another example the  $-(C_1-C_6\text{alkyl})$  substituent is  $-(C_1-C_3\text{alkyl})$ , and in another example methyl. In another example the  $R^4$  and/or  $R^5$  heteroaryl  
30

- 26 -

moiety is a 5 to 6 membered ring comprising 1-2 heteroatoms independently selected from the group consisting of: N, O and S. In another example the R<sup>4</sup> and/or R<sup>5</sup> heteroaryl moiety is a 5 to 6 membered ring comprising 1-2 nitrogen atoms. In another example the R<sup>4</sup> and/or R<sup>5</sup> heteroaryl moiety is pyridyl. In another example the substituted heteroaryl is methylpyridyl, and in another example methylpyrazolyl, and in another example cyanopyridyl, and in another example fluoropyridyl. In another example R<sup>5</sup> is any one of the substituted heteroaryl groups described in this paragraph. In another example, R<sup>4</sup> is H and R<sup>5</sup> is any one of the substituted heteroaryl groups described in this paragraph.

In one example R<sup>4</sup> and/or R<sup>5</sup> is -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>6</sub>alkyl), and in another example -C(O)(C<sub>1</sub>-C<sub>4</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>4</sub>alkyl), and in another example -C(O)CH(CH(CH<sub>3</sub>)<sub>2</sub>)NHC(O)OCH<sub>3</sub>. In another example, R<sup>5</sup> is any one of the -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>6</sub>alkyl) groups described in this paragraph. In another example, R<sup>4</sup> is H and R<sup>5</sup> is any one of the -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>6</sub>alkyl) groups described in this paragraph.

In one example R<sup>4</sup> and/or R<sup>5</sup> is -C(O)(substituted C<sub>1</sub>-C<sub>6</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>6</sub>alkyl), wherein said substituted alkyl is substituted with a heterocycloalkyl, and in another example, -C(O)(substituted C<sub>1</sub>-C<sub>4</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>4</sub>alkyl), wherein said substituted alkyl is substituted with a heterocycloalkyl. In another example said heterocycloalkyl substituent on said substituted alkyl is a 5 to 6 membered ring comprising 1-2 heteroatoms selected from the group consisting of: O, S and N. In another example said heterocycloalkyl substituent on said substituted alkyl is a 6 membered ring comprising 1-2 heteroatoms selected from the group consisting of: O, S, and N. In another example, said heterocycloalkyl substituent is tetrahydropyran. In another example, R<sup>5</sup> is any one of the -C(O)(substituted C<sub>1</sub>-C<sub>6</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>6</sub>alkyl) groups described in this paragraph. In another example, R<sup>4</sup> is H and R<sup>5</sup> is any one of the -C(O)(substituted C<sub>1</sub>-C<sub>6</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>6</sub>alkyl) groups described in this paragraph.

In one example R<sup>4</sup> and/or R<sup>5</sup> is heterocycloalkyl. In one example, said heterocycloalkyl is a 4 to 6 membered ring comprising 1-2 heteroatoms selected from the group consisting of: O, N and SO (i.e., S=O). In another example said heterocycloalkyl is a 4 membered ring. In another example, said heterocycloalkyl is a 5 membered ring, and in another example a six membered ring. In another example said heterocycloalkyl ring is a 4 membered ring comprising one oxygen atom. In another example, said heterocycloalkyl ring is a 5 membered ring comprising one oxygen atom. In another example said heterocycloalkyl

- 27 -

is a 5 membered ring, and in another example a 6 membered ring, comprising one nitrogen. In another example said heterocycloalkyl is tetrahydrofuranyl, and in another example piperidinyl, and in another example azetidiny, and in another example tetrahydropyran, and in another example pyrrolidinyl, and in another example oxetanyl, and in another example tetrahydrothiophenyl, and in another example oxidotetrahydrothiophenyl. In another example  $R^5$  is any one of the heterocycloalkyls described in this paragraph. In another example  $R^4$  is H, and  $R^5$  is any one of the heterocycloalkyls described in this paragraph.

In one example  $R^4$  and/or  $R^5$  is a heterocycloalkyl substituted with 1-3 substituents independently selected from the group consisting of  $-(C_1-C_6 \text{ alkyl})$  and halo (e.g., F, Br and Cl, and in one example F). In one example, the substituted heterocycloalkyl is a 5 to 6 membered ring comprising 1-2 heteroatoms selected from the group consisting of: O, N, and S. In another example, the substituted heterocycloalkyl is a 5 membered ring, and in another example a six membered ring. In another example the substituted heterocycloalkyl comprises one oxygen atom. In another example, the substituted heterocycloalkyl is a 5 membered ring comprising one oxygen atom. In another example, the substituted heterocycloalkyl is a 5-6 membered ring (and in one example a 5 membered ring) comprising one oxygen and 1-2  $-(C_1-C_6 \text{ alkyl})$  substituents (and in one example said substituents are methyl). In another example, the substituted heterocycloalkyl is a 5-6 membered ring (and in one example a 5 membered ring) comprising one oxygen and 1-2 and a halo atom substituent (e.g., F). In another example said substituted heterocycloalkyl is dimethyltetrahydrofuranyl, and in another example fluorotetrahydrofuran. In another example  $R^5$  is any one of the substituted heterocycloalkyls described in this paragraph. In another example  $R^4$  is H, and  $R^5$  is any one of the substituted heterocycloalkyls described in this paragraph.

In one example  $R^4$  and/or  $R^5$  is  $-(C_1-C_6 \text{ alkyl})\text{heteroaryl}$ , and in one example  $-(C_1-C_2 \text{ alkyl})\text{heteroaryl}$ . In one example the heteroaryl moiety is a 5-6 membered ring (e.g. 6) comprising 1-3 heteroatoms selected from the group consisting of: O, N and S. In one example the heteroaryl moiety is a 5 to 6 membered ring comprising 1-2 nitrogen atoms, and in one example the heteroaryl moiety is pyridyl. In another example the  $R^4$  and/or  $R^5$  is a  $-(C_1-C_2 \text{ alkyl})\text{pyridyl}$ , and in another example  $-\text{CH}_2\text{pyridyl}$ . In another example  $R^5$  is any one of the alkylheteroaryls described in this paragraph. In another example  $R^4$  is H and  $R^5$  is any one of the alkylheteroaryls described in this paragraph.

In one example  $R^4$  and/or  $R^5$  is substituted  $-(C_1-C_6 \text{ alkyl})\text{heterocycloalkenyl}$ , and in another example substituted  $-(C_1-C_2 \text{ alkyl})\text{heterocycloalkenyl}$ , substituted with 1-3 substituents

- 28 -

independently selected from the group consisting of:  $-(C_1-C_6\text{alkyl})$  (such as, for example,  $-(C_1-C_3\text{alkyl})$ ), and in one example methyl), and wherein said heterocycloalkenyl comprises 1-2 double bonds (and in one example one double bond). In one example the heterocycloalkenyl moiety is a substituted 5-6 membered ring (and in one example 5) comprising 1-3 heteroatoms (and in one example 1-2) selected from the group consisting of: O, N and S. In another example the  $R^4$  and/or  $R^5$  is a substituted  $-(C_1-C_2\text{alkyl})$  heterocycloalkenyl, and in another example  $-\text{CH}_2$  (methyldihydroisoxazolyl). In another example  $R^5$  is any one of the substituted  $-(C_1-C_6\text{alkyl})$  heterocycloalkenyls described in this paragraph. In another example  $R^4$  is H and  $R^5$  is any one of the substituted  $-(C_1-C_6\text{alkyl})$  heterocycloalkenyls described in this paragraph.

In one example  $R^4$  and/or  $R^5$  is  $-\text{C}(\text{O})R^8$  wherein  $R^8$  is heterocycloalkyl (i.e.,  $R^4$  and/or  $R^5$  is  $-\text{C}(\text{O})$  heterocycloalkyl). In another example said heterocycloalkyl moiety is a 4 to 6 membered (and in one example 4, and in another example 5 and in another example 6) ring comprising 1-2 heteroatoms selected from the group consisting of: O, N and S. In another example said heterocycloalkyl is a 4 to 6 membered ring comprising 1-2 heteroatoms independently selected from O and N. In another example said heterocycloalkyl moiety is a 4 to 6 membered ring comprising 1-2 nitrogen atoms. In another example said heterocycloalkyl moiety is a 4 to 5 membered ring comprising one nitrogen. In another example said heterocycloalkyl moiety is azetidiny, and in another example pyrrolidinyl, and in another example morpholinyl, and in another example tetrahydropyran. In another example said  $R^5$  is any one of the  $-\text{C}(\text{O})$  heterocycloalkyl groups described in this paragraph. In another example  $R^4$  is H and  $R^5$  is any one of the  $-\text{C}(\text{O})$  heterocycloalkyl groups described in this paragraph.

In one example  $R^4$  and/or  $R^5$  is  $-\text{C}(\text{O})R^8$  wherein  $R^8$  is a substituted  $-\text{heterocycloalkyl}$  (i.e.,  $R^4$  and/or  $R^5$  is a substituted  $-\text{C}(\text{O})$  heterocycloalkyl group). In one example said substituted heterocycloalkyl moiety is substituted with 1-3 substituents independently selected from the group consistin of: halo (e.g., F, Cl and Br, and in another example F, and in another example two F atoms),  $-\text{OH}$ ,  $-(C_1-C_6\text{alkyl})$  (such as, for example, methyl). In another example said substituted heterocycloalkyl moiety is a 4 to 6 membered (and in one example 4, and in another example 5 and in another example 6) ring comprising 1-2 heteroatoms selected from the group consisting of: O, N and S. In another example said substituted heterocycloalkyl moiety is a 4 to 6 membered ring comprising one nitrogen and one oxygen atom. In another example said substituted heterocycloalkyl moiety is a 4 to 6 membered ring comprising 1-2 nitrogen atoms. In another example said substituted heterocycloalkyl moiety is a 4 membered ring, and in another example a 5 membered ring, and in another example a 6 membered ring.

- 29 -

In another example said substituted heterocycloalkyl moiety is a 4 to 6 membered ring comprising 1 nitrogen. In another example said substituted heterocycloalkyl moiety is difluoroazetidiny, and in another example difluoropyrrolidiny, and in another example difluoropiperidiny, and in another example hydroxymethylazetidiny. In another example  
5 said R<sup>5</sup> is any one of the substituted -C(O)heterocycloalkyl groups described in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the substituted -C(O)heterocycloalkyl groups described in this paragraph.

In one example R<sup>4</sup> and/or R<sup>5</sup> is a -C(O)R<sup>8</sup> wherein R<sup>8</sup> is a heteroaryl (i.e., R<sup>4</sup> and/or R<sup>5</sup> is -C(O)heteroaryl). In one example said heteroaryl moiety is a 5 membered ring comprising  
10 1-3 heteroatoms, and in another example said heteroaryl moiety is a 5 membered ring comprising 3 heteroatoms. In another example said heteroaryl ring is thiadiazoly, and in another example furany, and in another pyridy. In another example, R<sup>5</sup> is any one of the -C(O)heteroaryls described in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the -C(O)heteroaryls described in this paragraph.

In one example R<sup>4</sup> and/or R<sup>5</sup> is a -C(O)R<sup>8</sup> wherein R<sup>8</sup> is a substituted heteroaryl (i.e., R<sup>4</sup> and/or R<sup>5</sup> is a substituted -C(O)heteroaryl) wherein said substituted heteroaryl is substituted with 1-3 substituents independently selected from the group consisting of -(C<sub>1</sub>-C<sub>6</sub>alkyl) (e.g.,  
-C<sub>1</sub>-C<sub>4</sub>alkyl) and in another example methyl). In one example said substituted heteroaryl  
20 moiety is a 5 membered ring comprising 1-3 heteroatoms, and in another example said substituted heteroaryl moiety is a 5 membered ring comprising 3 heteroatoms. In another example, said 5 membered ring is substituted with a -(C<sub>1</sub>-C<sub>4</sub>alkyl) (e.g., methyl). In another example said substituted heteroaryl ring is thiadiazoly, and in another example said substituted heteroaryl is methylthiadiazoly. In another example, R<sup>5</sup> is any one of the  
25 -C(O)heteroaryls described in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the -C(O)heteroaryls described in this paragraph.

In one example R<sup>4</sup> and/or R<sup>5</sup> is a -C(O)R<sup>8</sup> wherein R<sup>8</sup> is a -(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl (i.e., R<sup>4</sup> and or R<sup>5</sup> is -C(O)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl). In another example R<sup>8</sup> is cyclopropyl, and in another cyclobutyl, and in another cyclopentyl, and in another cyclohexyl. In another example R<sup>5</sup> is  
30 any one of the -C(O)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) sdescribed in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the -C(O)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl)s described in this paragraph.

In one example R<sup>4</sup> and/or R<sup>5</sup> is a -C(O)R<sup>8</sup> wherein R<sup>8</sup> is a -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) (i.e., R<sup>4</sup> and/or R<sup>5</sup> is a -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) group). In another example said R<sup>8</sup> is

- 30 -

-(C<sub>1</sub>-C<sub>2</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl), and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl)(phenyl), and in another example -CH<sub>2</sub>phenyl. In another example, R<sup>5</sup> is any one of the -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) groups described in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the

5 -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) groups described in this paragraph.

In one example R<sup>4</sup> and/or R<sup>5</sup> is a -C(O)R<sup>8</sup> wherein R<sup>8</sup> is a substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) (i.e., R<sup>4</sup> and/or R<sup>5</sup> is a substituted -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) group) wherein said substituted -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) group is substituted with 1-3 substituents independently selected from the group consisting of halo (e.g., Br, Cl and F, and in one  
10 example F). In another example said R<sup>8</sup> is a substituted -(C<sub>1</sub>-C<sub>2</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl), and in another example substituted -(C<sub>1</sub>-C<sub>2</sub>alkyl)(phenyl). In other examples the C<sub>6</sub>-C<sub>10</sub>aryl moiety is substituted and the C<sub>1</sub>-C<sub>6</sub>alkyl moiety is unsubstituted. In another example said R<sup>8</sup> is a substituted -CH<sub>2</sub>phenyl, and in another example -CH<sub>2</sub>(fluorophenyl). In another example, R<sup>5</sup> is any one of the -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) groups described in this paragraph. In  
15 another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) groups described in this paragraph.

In one example R<sup>4</sup> and/or R<sup>5</sup> is a -C(O)R<sup>8</sup> wherein R<sup>8</sup> is a -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) (i.e., R<sup>4</sup> and/or R<sup>5</sup> is a -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) group). In another example said R<sup>8</sup> is -(C<sub>1</sub>-C<sub>2</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), and in another example -(C<sub>1</sub>-  
20 C<sub>2</sub>alkyl)(cyclohexyl), and in another example -CH<sub>2</sub>cyclohexyl, and in another -CH<sub>2</sub>cyclopentyl. In another example, R<sup>5</sup> is any one of the -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) groups described in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) groups described in this paragraph.

In one example R<sup>4</sup> and/or R<sup>5</sup> is a -C(O)R<sup>8</sup> wherein R<sup>8</sup> is -OR<sup>12</sup> wherein R<sup>12</sup> is a -(C<sub>1</sub>-C<sub>6</sub>alkyl), i.e., said -C(O)R<sup>8</sup> group is -C(O)OR<sup>12</sup>. In one example R<sup>12</sup> is -(C<sub>1</sub>-C<sub>4</sub>alkyl). In another example R<sup>12</sup> is -C(CH<sub>3</sub>)<sub>3</sub>, and in another -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, and in another -CH<sub>3</sub>, and in another example -CH(CH<sub>3</sub>)<sub>2</sub>, and in another example -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>. In another example R<sup>5</sup> is any one of the -C(O)OR<sup>12</sup> groups described in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the -C(O)OR<sup>12</sup> groups described in this paragraph. In one example R<sup>4</sup> is H  
30 and R<sup>5</sup> is -C(O)CH<sub>3</sub>.

In one example R<sup>4</sup> and/or R<sup>5</sup> is a -C(O)R<sup>8</sup> wherein R<sup>8</sup> is -OR<sup>12</sup> wherein R<sup>12</sup> is a -(C<sub>1</sub>-C<sub>6</sub>alkyl) that is substituted with R<sup>14</sup>. In one example said R<sup>14</sup> is -OR<sup>15</sup>. In another example said R<sup>15</sup> is a -(C<sub>1</sub>-C<sub>6</sub>alkyl). In other examples the -(C<sub>1</sub>-C<sub>6</sub>alkyl) moiety of said R<sup>12</sup> and said R<sup>15</sup>

- 31 -

are  $-(C_1-C_4\text{alkyl})$ , and each alkyl is independently selected. In one example said  $R^8$  moiety is  $-\text{CH}_2\text{CH}_2\text{OCH}_3$ . In other examples  $R^5$  is any one of the  $-\text{C}(\text{O})\text{R}^8$  groups described in this paragraph. In other examples  $R^4$  is H and  $R^5$  is any one of the  $-\text{C}(\text{O})\text{R}^8$  groups described in this paragraph.

5 In one example  $R^4$  and/or  $R^5$  is a  $-\text{C}(\text{O})\text{R}^8$  wherein  $R^8$  is  $-\text{OR}^{12}$  wherein  $R^{12}$  is a  $(C_6-C_{10}\text{aryl})$ , such as, for example phenyl. In other examples  $R^5$  is any one of the  $-\text{C}(\text{O})\text{R}^8$  groups described in this paragraph. In other examples  $R^4$  is H and  $R^5$  is any one of the  $-\text{C}(\text{O})\text{R}^8$  groups described in this paragraph.

10 In one example  $R^4$  and/or  $R^5$  is a  $-\text{C}(\text{O})\text{R}^8$  wherein  $R^8$  is  $-\text{OR}^{12}$  wherein  $R^{12}$  is a  $-(C_1-C_6\text{alkyl})(C_6-C_{10}\text{aryl})$ . In one example said  $R^{12}$  is  $-(C_1-C_2\text{alkyl})(C_6-C_{10}\text{aryl})$ , and in another example  $-(C_1-C_2\text{alkyl})(\text{phenyl})$ , and in another example  $-\text{CH}_2\text{phenyl}$ . In other examples  $R^5$  is any one of the  $-\text{C}(\text{O})\text{R}^8$  groups described in this paragraph. In other examples  $R^4$  is H and  $R^5$  is any one of the  $-\text{C}(\text{O})\text{R}^8$  groups described in this paragraph.

15 In one example  $R^4$  and/or  $R^5$  is a  $-\text{C}(\text{O})\text{R}^8$  wherein  $R^8$  is  $-\text{NHR}^{12}$  wherein  $R^{12}$  is a  $-(C_1-C_6\text{alkyl})$ , i.e., said  $-\text{C}(\text{O})\text{R}^8$  group is  $-\text{C}(\text{O})\text{NHR}^{12}$ . In one example  $R^{12}$  is  $-(C_1-C_4\text{alkyl})$ . In another example  $R^{12}$  is  $-\text{CH}(\text{CH}_3)_2$ , and in another example  $-\text{CH}_2\text{CH}_3$ . In another example  $R^5$  is any one of the  $-\text{C}(\text{O})\text{NHR}^{12}$  groups described in this paragraph. In another example  $R^4$  is H and  $R^5$  is any one of the  $-\text{C}(\text{O})\text{NH}^{12}$  groups described in this paragraph.

20 In one example  $R^4$  and/or  $R^5$  is a  $-\text{C}(\text{O})\text{R}^8$  wherein  $R^8$  is  $-\text{NHR}^{12}$  wherein  $R^{12}$  is a  $(C_1-C_6\text{alkyl})(C_6-C_{10}\text{aryl})$  optionally substituted with 1-3 independently selected  $R^{14}$  groups. In one example said  $R^{12}$   $(C_1-C_6\text{alkyl})(C_6-C_{10}\text{aryl})$  moiety is substituted with 1-3 substituents independently selected from the group consisting of  $R^{14}$ . In another example said  $R^{12}$   $(C_1-C_6\text{alkyl})(C_6-C_{10}\text{aryl})$  moiety is substituted with 1-3 substituents independently selected from the group consisting of:  $-\text{CF}_3$ , halo (e.g., F, Cl and Br, and in one example F, and in another Cl),  $-\text{O}(C_1-C_6\text{alkyl})$ , and  $-\text{OH}$ . In another example said  $R^{12}$  is a  $(C_1-C_2\text{alkyl})(\text{phenyl})$  optionally substituted with 1-3 independently selected  $R^{14}$  groups. In another example said  $R^{12}$  is a  $(C_1-C_2\text{alkyl})(\text{phenyl})$  substituted with 1-3 independently selected  $R^{14}$  groups. In another example said  $R^{12}$  is a  $(C_1-C_2\text{alkyl})(\text{phenyl})$  substituted with 1-3 substituents independently selected from the group consisting of:  $-\text{CF}_3$  halo (e.g., F, Cl and Br, and in one example F, and in another Cl),  $-\text{O}(C_1-C_6\text{alkyl})$ , and  $-\text{OH}$ . In one example said  $R^8$  group is  $-\text{NHCH}(\text{CH}_3)(\text{hydroxychlorophenyl})$ , and in another  $-\text{NHCH}(\text{CH}_3)(\text{trifluoromethylchlorophenyl})$ , and in another example  $-\text{NHCH}(\text{CH}_3)(\text{chloromethoxyphenyl})$ . In another example  $R^5$  is any one of the  $-\text{C}(\text{O})\text{R}^8$

25

30

- 32 -

groups described in this paragraph. In another example  $R^4$  is H and  $R^5$  is any one of the  $-C(O)R^8$  groups described in this paragraph.

In one example  $R^4$  and/or  $R^5$  is a  $-C(O)R^8$  wherein  $R^8$  is  $-NHR^{12}$  wherein  $R^{12}$  is a (C<sub>1</sub>-C<sub>6</sub>alkyl)(heteroaryl) optionally substituted with 1-3 independently selected  $R^{14}$  groups. In one example said  $R^{12}$  (C<sub>1</sub>-C<sub>6</sub>alkyl)(heteroaryl) moiety is substituted with 1-3 substituents independently selected from the group consisting of  $R^{14}$ . In another example said  $R^{12}$  (C<sub>1</sub>-C<sub>6</sub>alkyl)(heteroaryl) moiety is substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Cl and Br, and in another Cl). In another example said  $R^{12}$  is a (C<sub>1</sub>-C<sub>2</sub>alkyl)(pyridyl) optionally substituted with 1-3 independently selected  $R^{14}$  groups. In another example said  $R^{12}$  is a (C<sub>1</sub>-C<sub>2</sub>alkyl)(pyridyl) substituted with 1-3 independently selected  $R^{14}$  groups. In another example said  $R^{12}$  is a (C<sub>1</sub>-C<sub>2</sub>alkyl)(pyridyl) substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Cl and Br, and in another Cl). In one example said  $R^8$  group is  $-NHCH(CH_3)(\text{chloropyridyl})$ . In another example  $R^5$  is any one of the  $-C(O)R^8$  groups described in this paragraph. In another example  $R^4$  is H and  $R^5$  is any one of the  $-C(O)R^8$  groups described in this paragraph.

In one example  $R^4$  and/or  $R^5$  is a  $-C(O)R^8$  wherein  $R^8$  is  $-(C_1-C_6\text{alkyl})-O-(C_1-C_6\text{alkyl})$ . In another example  $R^8$  is  $-(C_1-C_2\text{alkyl})-O-(C_1-C_2\text{alkyl})$ . In another example  $R^8$  is  $-CH_2OCH_3$ . In another example  $R^5$  is any one of the  $-C(O)R^8$  groups described in this paragraph. In another example  $R^4$  is H and  $R^5$  is any one of the  $-C(O)R^8$  groups described in this paragraph.

In one example  $R^4$  and/or  $R^5$  is a  $-C(O)R^8$  wherein  $R^8$  is a fused bicyclic heterocycloalkyl ring. The  $R^8$  fused bicyclic heterocycloalkyl ring comprises two fused heterocycloalkyl rings, wherein each heterocycloalkyl ring is 5-6 members (the ring size includes the atoms common to both rings) and each heterocycloalkyl ring comprises 1-3 heteroatoms independently selected from the group consisting of: O, N and S. The ring sizes of the rings of the bicyclic ring are, in one example, 5-6, and in another example 5-5, and in another example 6-5, and in another example, 6-6, wherein the ring size numbers include the atoms common to both rings. In one example, each heterocycloalkyl ring is a 5 membered ring (including the atoms common to both rings). In one example, one ring comprises one nitrogen atom and the other ring comprises one oxygen atom. In one example said fused bicyclic heterocycloalkyl bicyclic ring is tetrahydrofuro-pyrrolidinyl (i.e., a tetrahydrofuran fused to pyrrolidine).

- 33 -

In one example R<sup>4</sup> and/or R<sup>5</sup> is a -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl). In another example R<sup>4</sup> and/or R<sup>5</sup> is a -(C<sub>1</sub>-C<sub>2</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), and in another example a -(C<sub>1</sub>-C<sub>2</sub>alkyl)(C<sub>3</sub>-C<sub>4</sub>cycloalkyl), and in another example a -CH<sub>2</sub>(C<sub>3</sub>-C<sub>4</sub>cycloalkyl), and in another example -CH<sub>2</sub>cyclobutyl. In another example R<sup>5</sup> is any one of the -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) groups described in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) groups in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is -CH<sub>2</sub>cyclobutyl. In another example, R<sup>4</sup> and R<sup>5</sup> are each the same or different -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl). In another example, R<sup>4</sup> and R<sup>5</sup> are each the same or different -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>4</sub>cycloalkyl). In another example R<sup>4</sup> and R<sup>5</sup> are each -CH<sub>2</sub>cyclobutyl.

10 In one example R<sup>4</sup> and/or R<sup>5</sup> is a substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) substituted with 1-3 substituents independently selected from the group consisting of: -O-(C<sub>1</sub>-C<sub>6</sub>alkyl) (such as, for example, -O-C<sub>4</sub>-C<sub>6</sub>alkyl, and in another example -OCH<sub>3</sub>), (- hydroxyC<sub>1</sub>-C<sub>6</sub>alkyl) (such as for example, (hydroxyC<sub>1</sub>-C<sub>3</sub>alkyl, such as, for example, -C(CH<sub>3</sub>)<sub>2</sub>OH), and -(C<sub>2</sub>-C<sub>6</sub>alkenyl) (such as, for example, -(C<sub>2</sub>-C<sub>6</sub>alkenyl) (such as, for example, -(C<sub>2</sub>-C<sub>4</sub>alkenyl), such as, for example, -CH(CH<sub>3</sub>)C=CH<sub>2</sub>). In another example R<sup>4</sup> and/or R<sup>5</sup> is a substituted -(C<sub>1</sub>-C<sub>2</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), and in another example a substituted -(C<sub>1</sub>-C<sub>2</sub>alkyl)(C<sub>3</sub>-C<sub>4</sub>cycloalkyl), and in another example a substituted -CH<sub>2</sub>(C<sub>3</sub>-C<sub>4</sub>cycloalkyl), and in another example substituted -CH<sub>2</sub>cyclobutyl, and in another example -CH<sub>2</sub>-cyclobutyl-OCH<sub>3</sub>, and in another example -CH<sub>2</sub>cyclobutyl-C(CH<sub>3</sub>)<sub>2</sub>OH, and in another example -CH<sub>2</sub>cyclobutyl-CH(CH<sub>3</sub>)C=CH<sub>2</sub>, and in another example -CH<sub>2</sub>cyclobutyl-C(CH<sub>3</sub>)<sub>2</sub>OH. In another example R<sup>5</sup> is any one of the substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) groups described in this paragraph. In another example R<sup>4</sup> is H and R<sup>5</sup> is any one of the substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) groups in this paragraph.

25 In one example R<sup>4</sup> and/or R<sup>5</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl)heterocycloalkyl, and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl)heterocycloalkyl, and in another example a -CH<sub>2</sub>heterocycloalkyl. In one example said heterocycloalkyl moiety is a 4 to 6 membered ring, and in another example a 5-6 membered ring, and in another example a 6 membered ring, comprising 1-3 heteroatoms independently selected from the group consisting of O, N and S. In another example said heterocycloalkyl moiety comprises one heteroatom, and in another example said heteroatom is N, and in another example O. In another example said -(C<sub>1</sub>-C<sub>6</sub>alkyl)heterocycloalkyl is -CH<sub>2</sub>piperidinyl, and in another example -CH<sub>2</sub>tetrahydropyran, and in another example -CH(CH<sub>3</sub>)-tetrahydropyran, and in another example -CH(CH<sub>3</sub>)CH<sub>2</sub>morpholinyl, and in another example -CH(CH<sub>3</sub>)CH<sub>2</sub>piperidinyl, and in another example -CH<sub>2</sub>tetrahydrofuran, and in

- 34 -

another example  $-(\text{CH}_2)_2\text{morpholinyl}$ . In another example  $\text{R}^5$  is any one of the  $-(\text{C}_1\text{-C}_6\text{alkyl})\text{heterocycloalkyl}$  groups described in this paragraph. In another example  $\text{R}^4$  is H and  $\text{R}^5$  is any one of the  $-(\text{C}_1\text{-C}_6\text{alkyl})\text{heterocycloalkyl}$  groups described in this paragraph.

In one example  $\text{R}^4$  and  $\text{R}^5$ , taken together with the nitrogen to which they are bonded to, form a 4 to 6 membered heterocycloalkyl ring. In one example said heterocycloalkyl ring is a 4 membered ring, and in another example a 5 membered ring (e.g., pyrrolidinyl), and in another example a 6 membered ring. In another example at least one (e.g., 1-10) H atoms are deuterium (D) atoms (e.g., 1-10 H atoms in a 6 membered ring are deuterium). In another example the heterocycloalkyl ring is substituted. In another example the heterocycloalkyl ring (e.g., a 4 membered ring, and in another example a 5 membered ring) is substituted with a hydroxy group, and in another example a  $-\text{C}(\text{O})\text{OH}$  group, and in another example a  $-(\text{C}_1\text{-C}_6\text{alkyl})\text{-O-}(\text{C}_1\text{-C}_6\text{alkyl})$  (e.g., a  $-(\text{C}_1\text{-C}_2\text{alkyl})\text{-O-}(\text{C}_1\text{-C}_2\text{alkyl})$ ) group, and in another example a  $-(\text{C}_1\text{-C}_6\text{alkyl})\text{-OH}$  (e.g.,  $-(\text{C}_1\text{-C}_2\text{alkyl})\text{-OH}$ ) group, and in another example 1-2 halo atoms (e.g., F and in one example difluoro), and in another example a  $-\text{CH}_2\text{OCH}_3$  group, and in another example a  $-\text{CH}_2\text{OH}$  group. In another example the heterocycloalkyl ring is substituted with  $-(\text{C}_1\text{-C}_6\text{alkyl})$  (e.g., a  $-(\text{C}_1\text{-C}_2\text{alkyl})$ , such as, for example, methyl). In another example said heterocycloalkyl is substituted with a  $-\text{OH}$  and a  $-(\text{C}_1\text{-C}_6\text{alkyl})$  (e.g., a  $-(\text{C}_1\text{-C}_2\text{alkyl})$ , such as, for example, methyl). In another example said heterocycloalkyl ring (e.g., a 6 membered heterocycloalkyl ring) has a one carbon bridge, and in another example said heterocycloalkyl ring is morpholinyl with a one carbon bridge. In another example said heterocycloalkyl ring (e.g., a 6 membered heterocycloalkyl ring) has a two carbon bridge (e.g., morpholinyl with a two carbon bridge). In another example, said heterocycloalkyl is a methoxypiperidinyl, and in another example cyanopiperidinyl, and in another example hydroxymethylpiperidinyl, and in another example methylsulfanylpiperidinyl, and in another example a dimethylmorpholinyl. In another example said heterocycloalkyl ring is hydroxyazetidiny, and in another example methoxymethylazetidiny, and in another example hydroxymethylazetidiny, and in another example methylazetidiny, and in another example hydroxymethylazetidiny, and in another example prolinyl, and in another example difluoropiperidinyl, and in another example difluoroazetidiny, and in another example morpholinyl wherein the 8 hydrogen atoms are deuterium atoms.

In one example  $\text{R}^4$  and  $\text{R}^5$  taken together with the nitrogen to which they are bonded to form a spiro ring comprising two independently selected 4-6 membered heterocycloalkyl rings

- 35 -

(i.e., there is one atom in common with both rings of the spiro ring), wherein one of said rings comprises the nitrogen of the  $-NR^4R^5$  group, and wherein the other ring of the spiro ring comprises one heteroatom selected from the group consisting of: O, N and S (and in one example O), and each heterocycloalkyl ring of the spiro ring optionally comprises 1 or 2  
5 additional heteroatoms independently selected from the group consisting of: O, S and N, and wherein said spiro ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: -OH,  $-(C_1-C_6\text{alkyl})-O-(C_1-C_6\text{alkyl})$ ,  $-(C_1-C_6\text{alkyl})-OH$ ,  $-O(C_1-C_6\text{alkyl})$  and  $-(C_1-C_6\text{alkyl})$ . In one example the heterocycloalkyl ring comprising the nitrogen of the  $-NR^4R^5$  is a 6 membered ring (including the atom in common with each  
10 heterocycloalkyl ring of the spiro ring) and the other heterocycloalkyl ring is a 4-6 membered ring (e.g., a 4 membered ring, including the atom in common with each heterocycloalkyl ring of the spiro ring) comprising an oxygen atom. In one example the ring comprising the nitrogen of the  $-NR^4R^5$  group is pyridyl, and the other ring of the spiro ring is oxetanyl.

In one example  $R^4$  and  $R^5$ , taken together with the nitrogen to which they are bonded  
15 to, form a fused bicyclic ring wherein one ring is a heterocycloalkyl ring, and one ring is a heteroaryl ring, said heterocycloalkyl ring optionally comprising 1 to 3 additional heteroatoms independently selected from the group consisting of: O, S and N, and said bicyclic ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: halogen,  $-O(C_1-C_6\text{alkyl})$  and  $-(C_1-C_6\text{alkyl})$ . The one or two of the optional heteroatoms in  
20 said heterocycloalkyl ring of said bicyclic ring can be common to the the heterocycloalkyl ring and the heteroaryl ring. The heterocycloalkyl ring can be a 5 or 6 membered ring (including the atoms common to both rings), and the heteroaryl ring can be a 5 or 6 membered ring (including the atoms common to both rings). For example, the heterocycloalkyl-heteroaryl ring size can be 5-6, 5-5, 6-5, or 6-6 (wherein the first number represents the heterocycloalkyl  
25 ring size and the second number represents the heteroaryl ring size, and the numbers include the atoms common to both rings). The heteroaryl ring comprises 1-3 heteroatoms selected from the group consisting of: O, N and S. In one example, the heteroatoms are selected from the group consisting of: N and S. In one example the bicyclic ring is tetrahydrothiazolopyridine.

30 In one example  $R^4$  and  $R^5$ , taken together with the nitrogen to which they are bonded to, form a fused bicyclic heterocycloalkyl ring, i.e., each ring of the fused bicyclic ring is a heterocycloalkyl ring. The ring sizes of the rings of the bicyclic ring are, in one example, 5-6, and in another example 5-5, and in another example 6-5, and in another example, 6-6, wherein

- 36 -

the ring size numbers include the atoms common to both rings. The heterocycloalkyl bicyclic ring optionally comprises 1 to 3 additional heteroatoms independently selected from the group consisting of: O, S and N, and said ring optionally comprises a -O- bridge between two ring carbons (i.e., an epoxy bridge), and said heterocycloalkyl bicyclic ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: halogen, -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>6</sub>alkyl)(e.g., methyl). One or both of the optional heteroatoms in said heterocycloalkyl bicyclic ring can be common to both rings of the heterocycloalkyl bicyclic ring. In one example the bicyclic ring is methyloctahydroepoxyisoindolyl, and in another example tetrahydrothiazolopyridinyl.

10 In another example, R<sup>4</sup> and R<sup>11</sup> taken together form a 5-8 membered heterocycloalkyl ring, said ring optionally comprising 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S, N, and -(C=O)-, and said ring is optionally substituted with 1-3 substituents independently selected from R<sup>14</sup> group. In one example said heterocycloalkyl ring is an unsubstituted piperidinyl ring (see, for example A21 below). In another example said heterocycloalkyl ring is substituted with a -(C<sub>1</sub>-C<sub>6</sub>alkyl, (e.g., methyl, ethyl or isopropyl) group, and in one example said alkyl group is bonded to a ring carbon, and in another example said alkyl group is bonded to a ring nitrogen. In another example said heterocycloalkyl ring is methyl substituted piperidinyl ring (see A22 and A23, for example), and in another example N-ethyl substituted piperidinyl (see A24, for example), and in another example N-isopropyl substituted piperidinyl (see A25, for example), and in another example N-C(O)CH<sub>3</sub> substituted piperidinyl (see A26, for example). In another example said heterocycloalkyl ring is oxepan-one (see A29, for example).

25 In one example of this invention, R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of: H, methyl, ethyl, propyl, isopropyl, -(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>, -C(O)CH<sub>3</sub>, -S(O)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -S(O)<sub>2</sub>-azetindinyl, -S(O)<sub>2</sub>-CH<sub>2</sub>-cyclopropyl, -S(O)<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>, -S(O)<sub>2</sub>-cyclobutyl, -S(O)<sub>2</sub>-cyclopropyl, and -S(O)<sub>2</sub>-CH<sub>3</sub>. In another example, R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of: H, methyl, ethyl, isopropyl, -(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>, -C(O)CH<sub>3</sub>, -S(O)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -S(O)<sub>2</sub>-azetindinyl, -S(O)<sub>2</sub>-CH<sub>2</sub>-cyclopropyl, -S(O)<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>, -S(O)<sub>2</sub>-cyclobutyl, -S(O)<sub>2</sub>-cyclopropyl, and -S(O)<sub>2</sub>-CH<sub>3</sub>. In another example, R<sup>4</sup> and R<sup>5</sup> are 30 independently selected from the group consisting of: H, methyl, ethyl, isopropyl, and -(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>. In other examples R<sup>4</sup> is H and R<sup>5</sup> is any one of the groups defined in this paragraph.

In one example, R<sup>4</sup> is H.

- 37 -

In one example  $R^4$  is H and  $R^5$  is H.

In one example,  $R^4$  is H, and  $R^5$  is  $-(C_1-C_6\text{alkyl})$ . Examples of the  $R^5$   $-(C_1-C_6\text{alkyl})$  group include:  $-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})$ . In another example  $R^5$  is  $-\text{CH}_3$ .

5 In one example,  $R^4$  is H, and  $R^5$  is  $-(C_1-C_6\text{alkyl})-O-(C_1-C_6\text{alkyl})$ . Examples of this  $R^5$  group include  $-(C_1-C_4\text{alkyl})-O-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})-O-(C_1-C_3\text{alkyl})$ ,  $-(C_1-C_2\text{alkyl})-O-(C_1-C_2\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})-O-\text{CH}_3$ .

10 In one example  $R^4$  is H, and  $R^5$  is selected from the group consisting of: H, methyl, ethyl, propyl, isopropyl, and  $-(\text{CH}_2)_2-O-\text{CH}_3$ . In another example,  $R^4$  is H, and  $R^5$  is selected from the group consisting of: H, methyl, ethyl, isopropyl, and  $-(\text{CH}_2)_2-O-\text{CH}_3$ .

In another example,  $R^4$  is H and  $R^5$  is methyl. In another example  $R^4$  is H and  $R^5$  is ethyl. In another example  $R^4$  is H and  $R^5$  is isopropyl. In another example  $R^4$  is H and  $R^5$  is  $-(\text{CH}_2)_2-O-\text{CH}_3$ .

15 In another example,  $R^4$  and  $R^5$  are independently selected from the group consisting of:  $-(C_1-C_6\text{alkyl})$  (e.g.,  $-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})$ ,  $-(C_1-C_2\text{alkyl})$  and  $-\text{CH}_3$ ). In another example  $R^4$  and  $R^5$  are independently selected from the group consisting of  $-(C_1-C_4\text{alkyl})$ . In another example  $R^4$  and  $R^5$  are the same  $-(C_1-C_6\text{alkyl})$ , and in another example the same  $-(C_1-C_4\text{alkyl})$ . In one example  $R^4$  and  $R^5$  are independently selected from the group consisting of: methyl, ethyl, and isopropyl. In one example  $R^4$  and  $R^5$  are each methyl. In another example 20  $R^4$  and  $R^5$  are independently selected from the group consisting of methyl and ethyl. In another example  $R^4$  and  $R^5$  are each ethyl. In another example  $R^4$  is methyl, and  $R^5$  is ethyl.

25 In another example of this invention,  $R^4$  is a  $-(C_1-C_6\text{alkyl})-O-(C_1-C_6\text{alkyl})$  group (e.g.  $-(C_1-C_4\text{alkyl})-O-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})-O-(C_1-C_3\text{alkyl})$ ,  $-(C_1-C_2\text{alkyl})-O-(C_1-C_2\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})-O-\text{CH}_3$ ) and  $R^5$  is a  $-(C_1-C_6\text{alkyl})$  (e.g.,  $-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})$ ,  $-(C_1-C_2\text{alkyl})$  and  $-\text{CH}_3$ ). In one example  $R^4$  is  $-(\text{CH}_2)_2-O-\text{CH}_3$ , and  $R^5$  is selected from the group consisting of: methyl, ethyl, and isopropyl. In one example  $R^4$  is  $-(\text{CH}_2)_2-O-\text{CH}_3$ , and  $R^5$  is methyl.

30 In another example,  $R^4$  and  $R^5$  are taken together with the nitrogen to which they are bound to form a 4-6 membered heterocycloalkyl ring, wherein said ring optionally comprises 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S and N, and wherein the remaining ring atoms are carbon, and said ring is optionally substituted with 1-3 substituents independently selected from the group consisting of:  $-(C_1-C_6\text{alkyl})$  (such as,

- 38 -

for example,  $-O(C_1-C_4\text{alkyl})$ ,  $-O(C_1-C_3\text{alkyl})$ , and  $-O(C_1-C_2\text{alkyl})$ , and  $-(C_1-C_6\text{ alkyl})$  (such as, for example,  $-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})$ ,  $-(C_1-C_2\text{alkyl})$  and  $-\text{CH}_3$ ).

In one example the  $R^{14}-C(O)(C_1-C_6\text{alkyl})$  optional substituent is  $-C(O)(C_1-C_4\text{alkyl})$ , and in another example  $-C(O)CH_3$ .

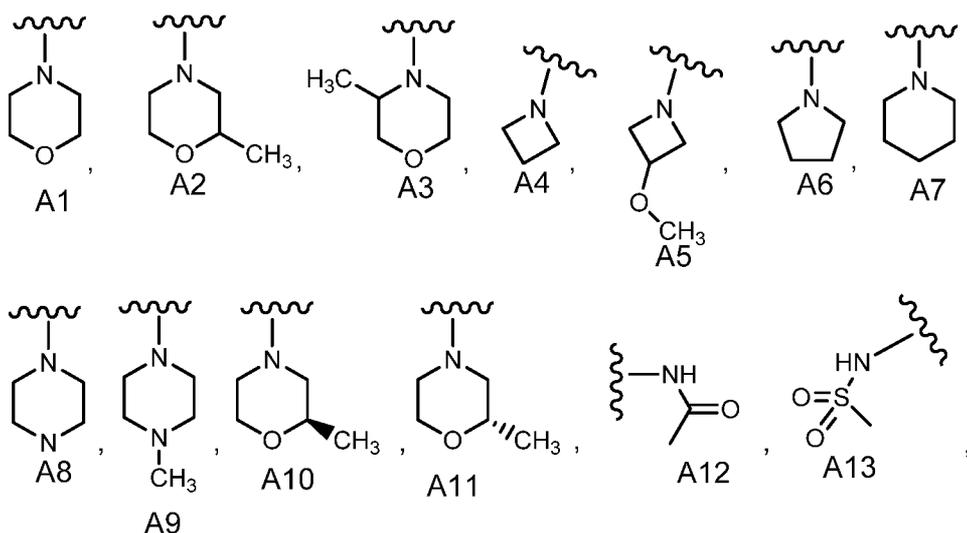
5 In one example,  $R^1$  is a four membered heterocycloalkyl ring. In another example  $R^1$  is a five membered heterocycloalkyl ring. In another example,  $R^1$  is a six membered heterocycloalkyl ring. In one example  $R^1$  is azetidiny, in another example  $R^1$  is pyrrolidiny, in another example  $R^1$  is piperazinyl, in another example  $R^1$  is piperidiny, and in another example  $R^1$  is morpholinyl.

10 In another example,  $R^1$  is a substituted four membered heterocycloalkyl ring. In another example  $R^1$  is a substituted five membered heterocycloalkyl ring. In another example,  $R^1$  is a substituted six membered heterocycloalkyl ring. In one example  $R^1$  is a substituted azetidiny ring, in another example a substituted pyrrolidiny ring, in another example a substituted piperazinyl ring, in another example a substituted piperidiny ring, and in another example a substituted morpholinyl ring. In another example the substituted rings are substituted with a  $-C_1-C_2\text{alkyl}$  or a  $-O(C_1-C_2\text{alkyl})$  group. In another example the substituted rings are substituted with one methyl. In another example the substituted rings are substituted with a  $-\text{OCH}_3$ . In one example  $R^1$  is a methyl substituted piperazinyl ring, in another example a methyl substituted morpholinyl ring, and in another example a methyl substituted azetidiny ring.

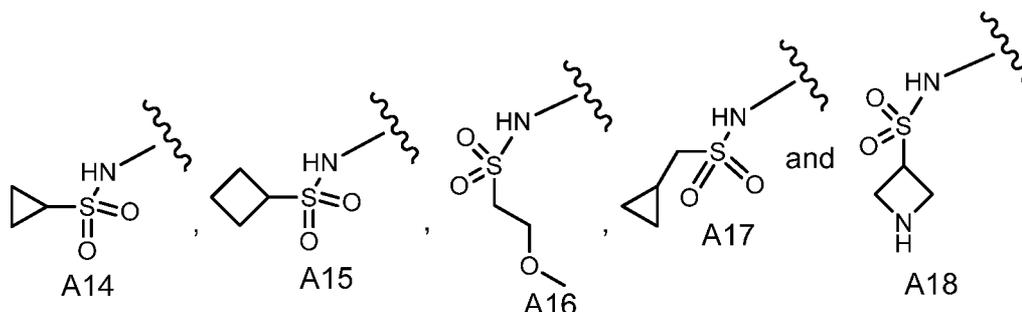
15

20

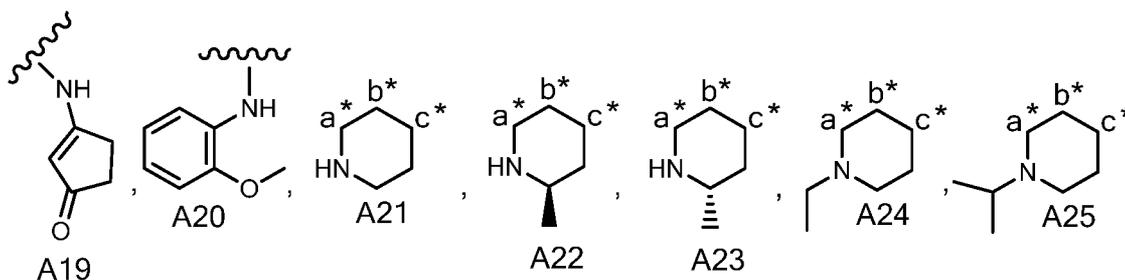
In another example  $R^1$  is selected from the group consisting of:

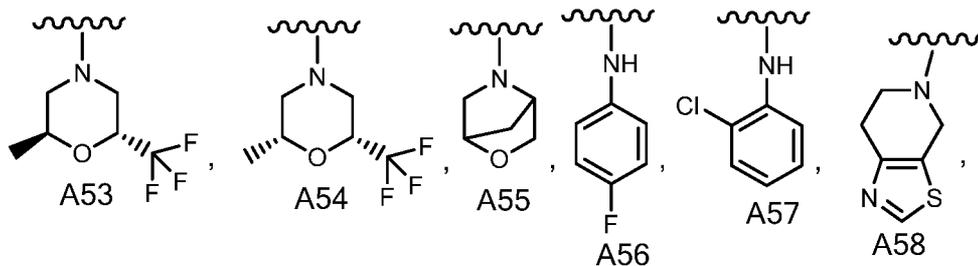
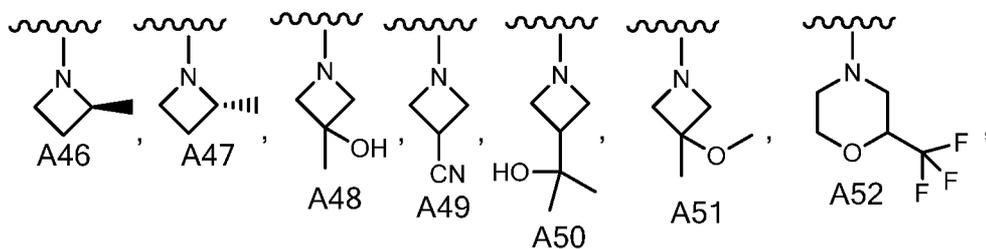
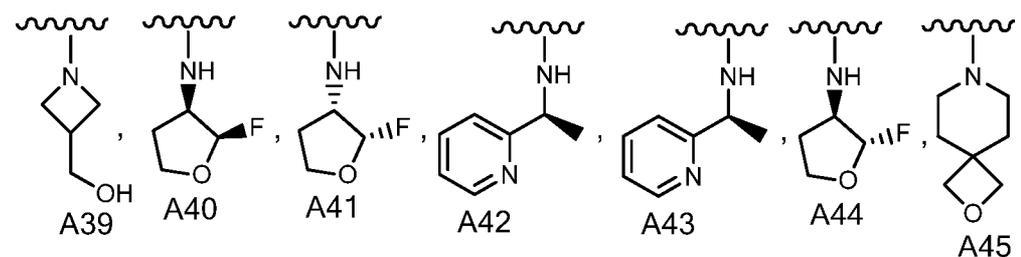
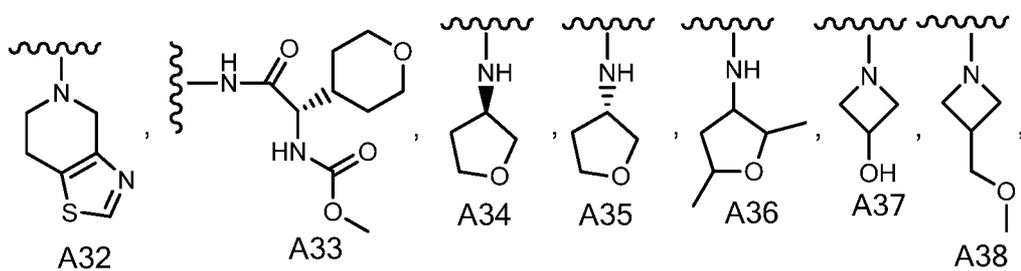
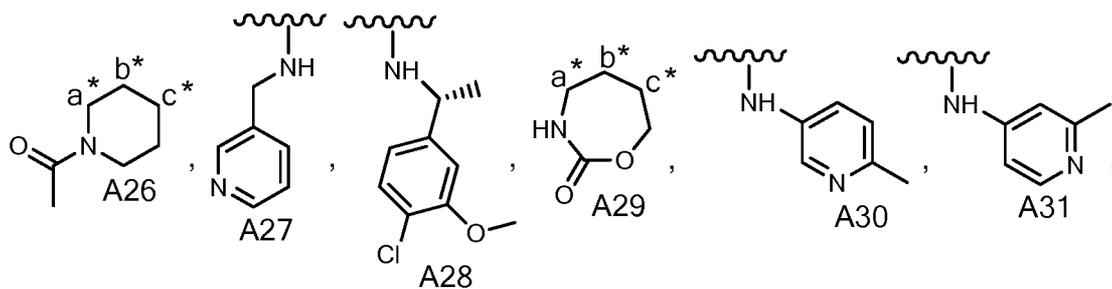


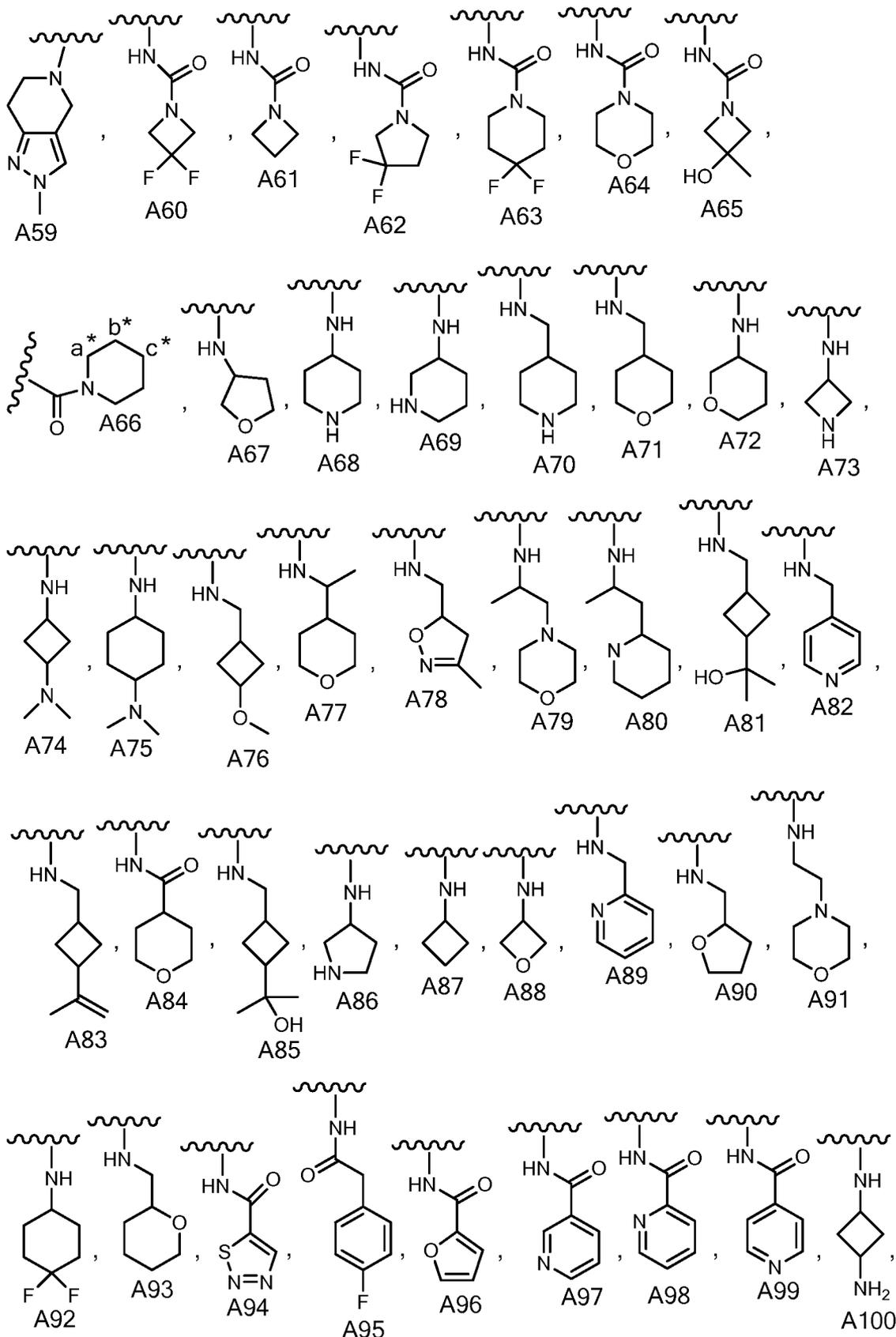
- 39 -

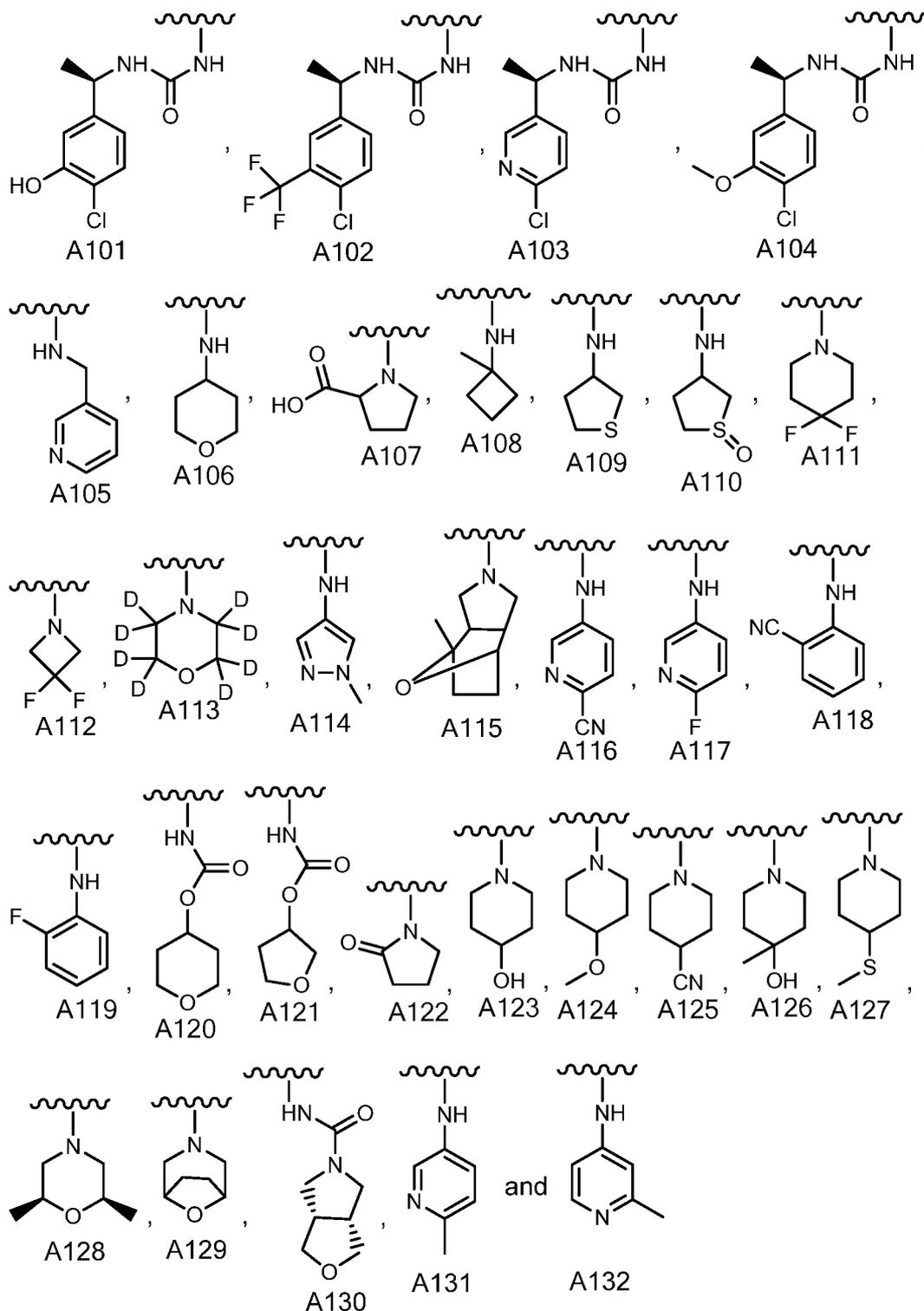


- In another example R<sup>1</sup> is selected from the group consisting of: -NH<sub>2</sub>, -NHCH<sub>3</sub>, -NHCH<sub>2</sub>CH<sub>3</sub>, -NHCH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>3</sub>, -NHC(O)NHCH<sub>2</sub>CH<sub>3</sub>, -NHC(O)cyclopropyl, -NHC(O)OCH<sub>3</sub>, -NHC(O)OCH<sub>2</sub>CHF, -NHC(O)CH(CH<sub>3</sub>)<sub>2</sub>NHC(O)OCH<sub>3</sub>,
- 5 -NH-tetrahydrofuran, -NHC(D<sub>2</sub>)CD<sub>3</sub> (wherein D represents deuterium), -NHC(O)CD<sub>3</sub>, -NHCH<sub>2</sub>cyclobutyl, -NH(CH<sub>2</sub>cyclobutyl)<sub>2</sub>, -NHCH<sub>2</sub>cyclopropyl, -NH(CH<sub>2</sub>cyclopropyl)<sub>2</sub>, -NHC(O)CH(CH<sub>3</sub>)<sub>2</sub>, -NHCH<sub>2</sub>phenyl, -NHCH(CH<sub>3</sub>)CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>OH, -NHCH(CH<sub>3</sub>)CH<sub>2</sub>S(O)<sub>2</sub>CH<sub>3</sub>, -NHCH(CH<sub>3</sub>)CH<sub>2</sub>Cl, -NHC(O)CHCF<sub>3</sub>, -NHC(O)cyclobutyl, -NHC(O)CH<sub>2</sub>phenyl, -NHC(O)CH<sub>2</sub>cyclohexyl, -NHC(O)cyclohexyl, -NHC(O)cyclopentyl,
- 10 -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>cyclopentyl, -NHC(O)C(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)OC(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)NHCH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)OCH<sub>3</sub>, -NHC(O)O(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, -NHC(O)Ophenyl, -NHC(O)OCH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)OCH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)OCH<sub>2</sub>phenyl, -NHC(O)OCH<sub>2</sub>CH<sub>3</sub>, -NHC(O)cyclopropyl, -NHC(O)CH<sub>2</sub>OCH<sub>3</sub>, -NHTetrahydropyran,
- 15 -NHcyclopropyl, -NHCH<sub>2</sub>CF<sub>3</sub>, -NHcyclobutyl, -NHCH<sub>2</sub>C(O)N(CH<sub>3</sub>)<sub>2</sub>, -NH(CH<sub>2</sub>)<sub>2</sub>C(O)N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>3</sub>)C(O)CH<sub>3</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)C(O)CH<sub>3</sub>, -NHC(CH<sub>3</sub>)<sub>3</sub>, -NHCH(CH<sub>3</sub>)CHF<sub>2</sub>, -NHC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NH(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, -NHphenyl, -NHcyanopyridyl, -NHfluoropyridyl, -NHcyanophenyl, -NHcyclopentyl, -NHcyclohexyl,









5

wherein A21-A25 and A29 represent heterocycloalkyl rings formed when  $R^4$  is taken together with  $R^{11}$ , and wherein in said heterocycloalkyl rings  $a^*$  represents the carbon atom in common with said heterocycloalkyl rings and the pyrazolyl ring in formula (1),  $b^*$  represents the carbon

- 43 -

atom in common with said heterocycloalkyl rings and with the pyrazolyl and pyridyl rings in formula (1), and c\* represents the carbon atom in common with said heterocycloalkyl rings and with the pyridyl ring in formula (1). In other examples R<sup>1</sup> is any one of the groups in this paragraph as if each was individually listed as a separate example. Thus, in one example R<sup>1</sup> is  
 5 -NH<sub>2</sub>, and in another -NHCH<sub>3</sub>, and in another -NHCH<sub>2</sub>CH<sub>3</sub>, and in another -NHCH(CH<sub>3</sub>)<sub>2</sub>, and in another -NHC(O)CH<sub>3</sub>, and in another -NHC(O)NH<sub>2</sub>CH<sub>3</sub>, and the like through to A132.

In another example R<sup>1</sup> is A1. In another example R<sup>1</sup> is A2. In another example R<sup>1</sup> is A3. In another example R<sup>1</sup> is A4. In another example R<sup>1</sup> is A5. In another example R<sup>1</sup> is A6. In another example R<sup>1</sup> is A7. In another example R<sup>1</sup> is A8. In another example R<sup>1</sup> is A9. In  
 10 another example R<sup>1</sup> is A10. In another example R<sup>1</sup> is A11. In another example R<sup>1</sup> is A12. In another example R<sup>1</sup> is A13. In another example R<sup>1</sup> is A14. In another example R<sup>1</sup> is A15. In another example R<sup>1</sup> is A16. In another example R<sup>1</sup> is A17. In another example R<sup>1</sup> is A18.

In one example R<sup>2</sup> is -(C<sub>1</sub>-C<sub>4</sub>alkyl)heteroaryl.

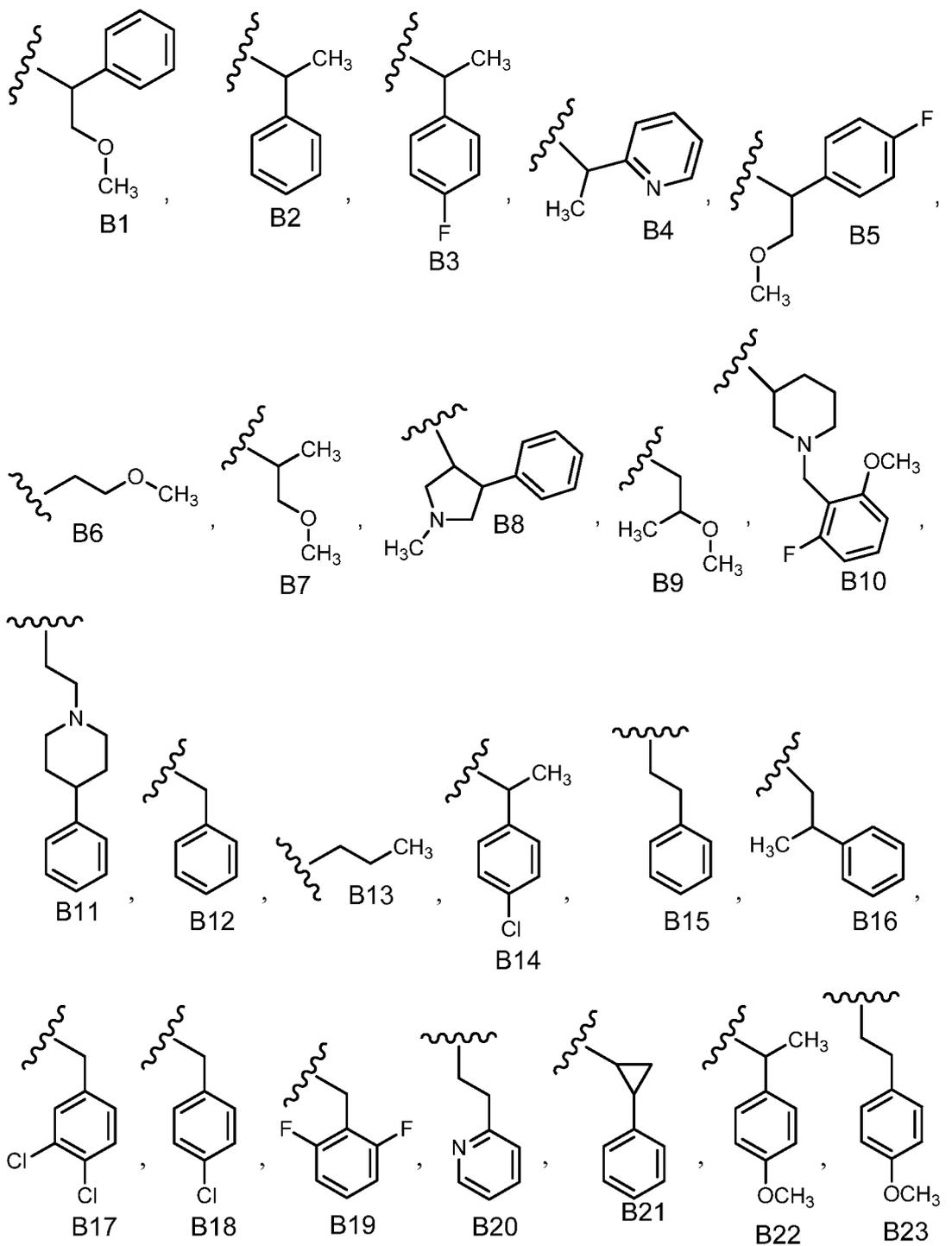
In one example, R<sup>2</sup> is selected from the group consisting of: H, -(C<sub>1</sub>-C<sub>3</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl), -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(C<sub>1</sub>-C<sub>3</sub>alkyl-O-(C<sub>1</sub>-C<sub>3</sub>alkyl)), -(C<sub>1</sub>-C<sub>3</sub>alkyl)heteroaryl, -heterocycloalkyl(C<sub>6</sub>-C<sub>10</sub>aryl), and -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl) and wherein said aryl (e.g. phenyl and naphthyl, and usually phenyl), heteroaryl and heterocycloalkyl groups are optionally substituted with 1-3 substituents independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl) (e.g., -(C<sub>1</sub>-C<sub>4</sub>alkyl), -(C<sub>1</sub>-C<sub>3</sub>alkyl), and -(C<sub>1</sub>-C<sub>2</sub>alkyl), and in one example methyl), halo (e.g., F, Br, and Cl, and in one example F); and wherein said heteroaryl group is a 5 to 6 membered aromatic ring comprising 1 to 3 heteroatoms independently selected from the group consisting of: N, O and S, and the remaining ring members are carbon; and wherein said heterocycloalkyl group is a 4-6 membered ring comprising 1-2 heteroatoms independently selected from the group consisting of: N, O and S, and wherein the remaining ring members  
 25 are carbon.

For R<sup>2</sup> examples of the -(C<sub>1</sub>-C<sub>4</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) group include -(C<sub>1</sub>-C<sub>2</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>1</sub>-C<sub>3</sub>alkyl)phenyl, -CH(CH<sub>3</sub>)phenyl, -CH<sub>2</sub>CH<sub>2</sub>phenyl, and -CH<sub>2</sub>phenyl. Examples of the -CH(C<sub>6</sub>-C<sub>10</sub>aryl)((C<sub>1</sub>-C<sub>3</sub>alkyl)-O-(C<sub>1</sub>-C<sub>3</sub>alkyl)) group include: -CH(phenyl)((C<sub>1</sub>-C<sub>2</sub>alkyl)-O-(C<sub>1</sub>-C<sub>2</sub>alkyl)), and -CH(phenyl)CH<sub>2</sub>OCH<sub>3</sub>. Examples of the -(C<sub>1</sub>-C<sub>3</sub>alkyl)-  
 30 heteroaryl group include -(C<sub>1</sub>-C<sub>2</sub>alkyl)heteroaryl, -(C<sub>1</sub>-C<sub>3</sub>alkyl)pyridyl, -(C<sub>1</sub>-C<sub>2</sub>alkyl)pyridyl, and -CH(CH<sub>3</sub>)pyridyl. Examples of the -heterocycloalkyl(C<sub>6</sub>-C<sub>10</sub>aryl) group include -heterocycloalkylphenyl, and -pyrrolidinylphenyl. Examples of the -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl) include -(C<sub>1</sub>-C<sub>3</sub>alkyl)-O-(C<sub>1</sub>-C<sub>2</sub>alkyl), -(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>, and -CH(CH<sub>3</sub>)CH<sub>2</sub>OCH<sub>3</sub>.

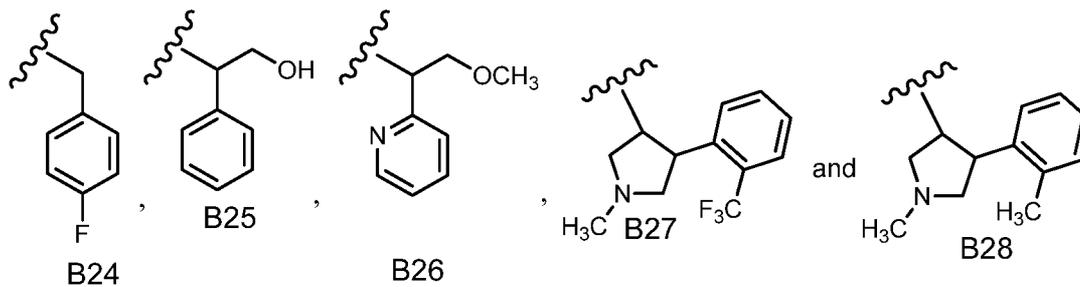
- 44 -

For  $R^2$  examples of the substituted groups include groups wherein the phenyl moiety is substituted with halo (e.g., F), and the heterocycloalkyl (e.g., pyrrolidinyl) moiety is substituted with a  $-C_1-C_2$ alkyl (e.g., methyl).

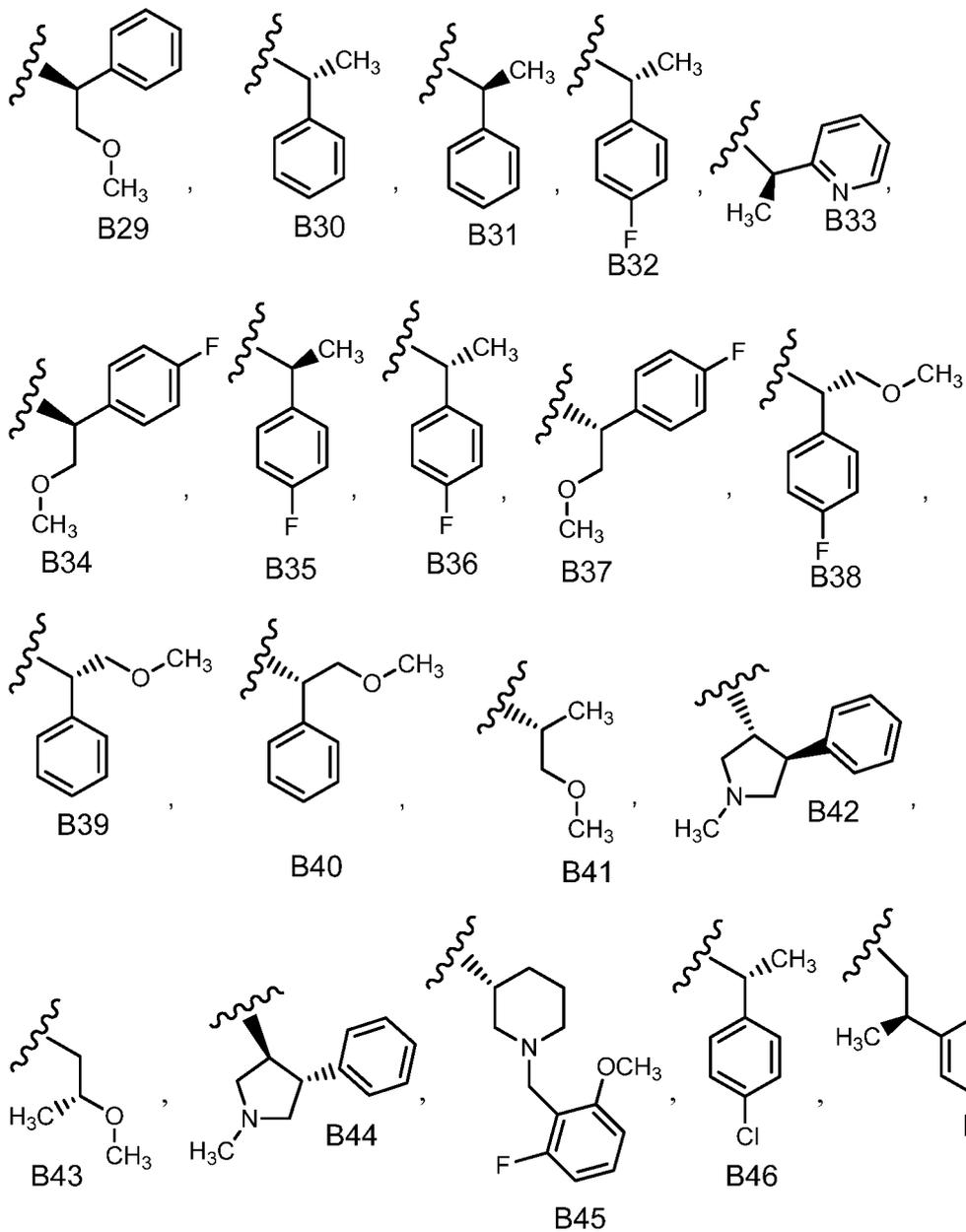
In one example  $R^2$  is selected from the group consisting of: H,



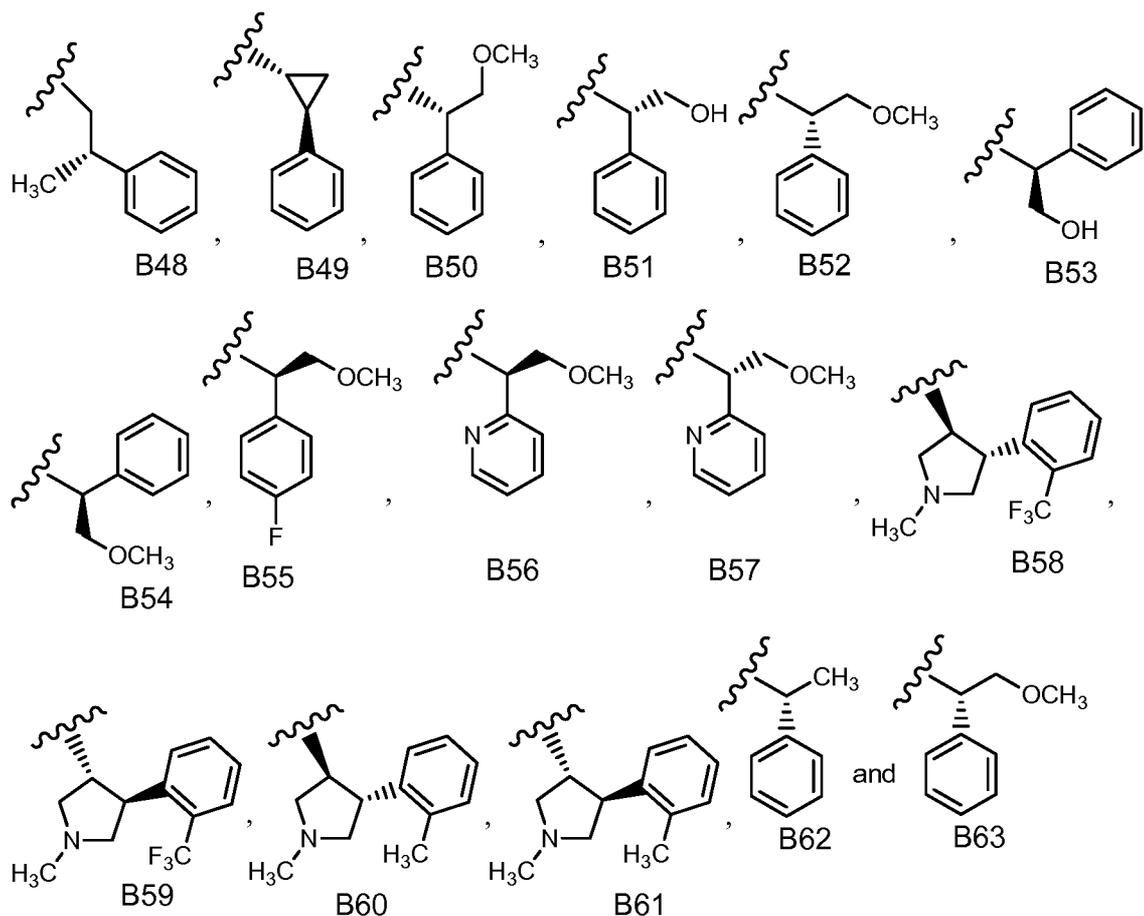
- 45 -



In another example R<sup>2</sup> is selected from the group consisting of: H,



- 46 -

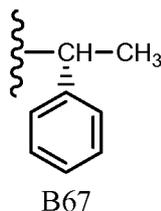


In one example  $R^2$  is selected from the group consisting of: H, B1, B2, B3, B4, B5, B6, B7, B8, B9, B29, B30, B31, B32, B33, B34, B35, B36, B37, B38, B39, B40, B41, B42, B43 and B44.

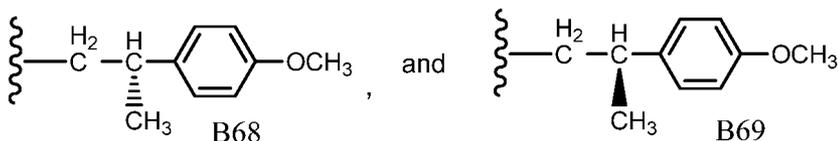
In one example  $R^2$  is (C<sub>6</sub>-C<sub>10</sub>aryl)-(C<sub>1</sub>-C<sub>3</sub>alkyl)-heterocycloalkyl-. One example of this  $R^2$  group is (C<sub>6</sub>-C<sub>10</sub>aryl)-(C<sub>1</sub>-C<sub>2</sub>alkyl)-heterocycloalkyl-, and another is phenyl-(C<sub>1</sub>-C<sub>2</sub>alkyl)-heterocycloalkyl-, and another is phenyl-CH<sub>2</sub>-heterocycloalkyl-. In another example  $R^2$  is a substituted (C<sub>6</sub>-C<sub>10</sub>aryl)-(C<sub>1</sub>-C<sub>3</sub>alkyl)-heterocycloalkyl- and in another example substituted (C<sub>6</sub>-C<sub>10</sub>aryl)-(C<sub>1</sub>-C<sub>2</sub>alkyl)-heterocycloalkyl-, and in another example substituted phenyl-(C<sub>1</sub>-C<sub>2</sub>alkyl)-heterocycloalkyl-, and in another example substituted phenyl-CH<sub>2</sub>-heterocycloalkyl-. In another example the phenyl moiety is substituted with 1-3 substituents, and in another example 1-2 substituents, independently selected from the group consisting of: halo (e.g., F, Br, and Cl), and -O-(C<sub>1</sub>-C<sub>6</sub>alkyl) (and in one example -O-(C<sub>1</sub>-C<sub>2</sub>)alkyl). In another example the phenyl moiety is substituted with 1-2 substituents independently selected from the group consisting of: F and -O-(C<sub>1</sub>-C<sub>6</sub>alkyl) (and in one example -O-(C<sub>1</sub>-C<sub>2</sub>)alkyl, and in another -OCH<sub>3</sub>). In one example the heterocycloalkyl moiety is piperidinyl. One example of the  $R^2$



- 48 -



In another example the  $R^2$   $-(C_1-C_4\text{alkyl})(C_6-C_{10}\text{aryl})$  group is substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Br, and Cl),  $-O-$   $(C_1-C_6\text{alkyl})$  (and in one example  $-O-(C_1-C_2)\text{alkyl}$ ), and  $-OH$ . In one example the  $R^2$  group is  $-\text{CH}(\text{CH}_3)\text{-methoxyphenyl}$ , and in another example  $-(\text{CH}_2)_2\text{-methoxyphenyl}$ . Examples of  $-O-(C_1-C_6\text{alkyl})$  substituted  $R^2$  groups include, but are not limited to:



For the  $R^2$   $-O(\text{halo substituted } (C_1-C_6\text{alkyl}))$  optional substituent, examples of said halo include Cl, F and Br, and in one example said halo is F. Examples of the  $(C_1-C_6\text{alkyl})$  moiety for said  $-O(\text{halo substituted } (C_1-C_6\text{alkyl}))$  substituent include  $(C_1-C_4\text{alkyl})$ , and  $(C_1-C_2\text{alkyl})$ . In one example the  $-O(\text{halo substituted } (C_1-C_6\text{alkyl}))$  substituent is  $-\text{OCHF}_2$ . In one example the  $-(C_1-C_4\text{alkyl})$  moiety of the  $R^2$   $-(C_1-C_4\text{alkyl})(C_6-C_{10}\text{aryl})$  group is substituted with  $-O(\text{halo substituted } (C_1-C_6\text{alkyl}))$ , and in one example  $-\text{OCHF}_2$ .

For the  $R^2$   $-S(C_1-C_6\text{alkyl})$  optional substituent, examples of the alkyl moiety include  $-(C_1-C_4\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})$ . In one example, said  $-S(C_1-C_6\text{alkyl})$  optional substituent is  $-\text{SCH}_3$ .

In one example, the  $R^2$  aryl optional substituent is phenyl.

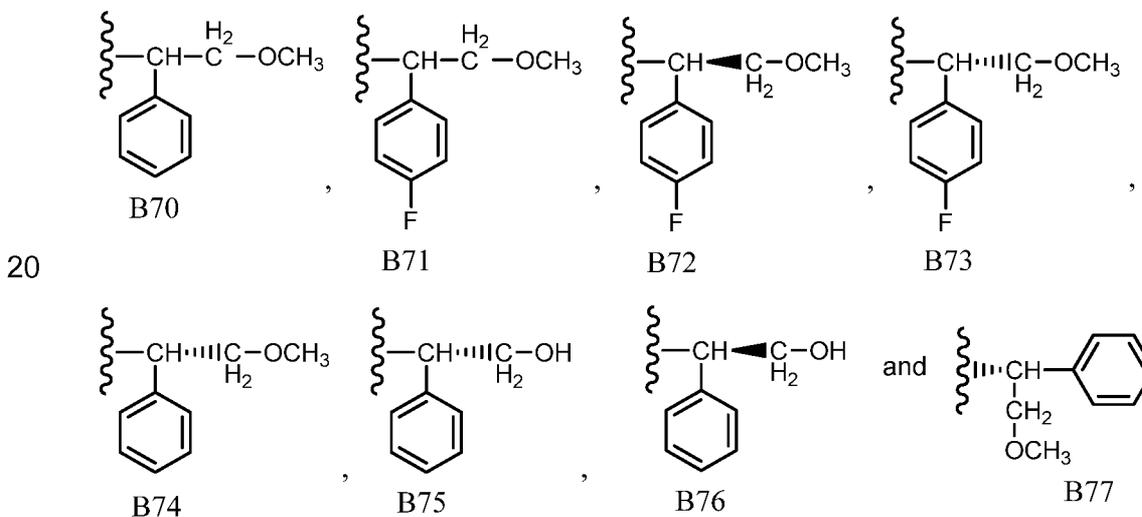
In one example the  $R^2$  heteroaryl optional substituent is a 5-6 membered ring comprising 1 to 3 heteroatoms (e.g., 1-2) independently selected from the group consisting of: O, N and S. In another example the  $R^2$  heteroaryl optional substituent is a 5 membered ring comprising 1-2 heteroatoms independently selected from the group consisting of: O, N and S, and in another example independently selected from the group consisting of O and N. In another example the  $R^2$  heteroaryl optional substituent is oxazolyl.

In one example the  $R^2$   $-(C_1-C_4\text{alkyl})(C_6-C_{10}\text{aryl})$  group is substituted with 1-3 substituents independently selected from the group consisting of:  $-OH$ , halo (e.g., F, Br, and Cl),  $-O-(C_1-C_6\text{alkyl})$  (and in one example  $-O-(C_1-C_2)\text{alkyl}$ ),  $-O(\text{halo substituted } (C_1-C_6\text{alkyl}))$ , and  $-S(C_1-C_6\text{alkyl})$ , wherein for example, the  $-O(\text{halo substituted } (C_1-C_6\text{alkyl}))$ , and  $-S(C_1-C_6\text{alkyl})$  substituents are as above defined. In one example the  $R^2$  group is  $-\text{CH}(\text{CH}_3)\text{chloro-}$

- 49 -

methoxyphenyl, and in another example  $-\text{CH}(\text{phenyl})\text{CH}_2\text{OCHF}_2$ , and in another example  $-\text{CH}(\text{phenyl})\text{CH}_2\text{SCH}_3$ , and in another example  $-\text{CH}(\text{phenyl})\text{CH}_2\text{OH}$ , and in another example  $-\text{CH}(\text{fluorophenyl})\text{C}(\text{CH}_3)_2\text{OCH}_3$ , and in another example  $-\text{CH}(\text{phenyl})\text{C}(\text{CH}_3)_2\text{OCH}_3$ .

In one example the  $\text{R}^2$   $-(\text{C}_1\text{-C}_4\text{alkyl})-(\text{C}_6\text{-C}_{10}\text{aryl})$  group is substituted on the  $(\text{C}_1\text{-C}_4\text{alkyl})$  moiety with a  $-\text{O}-(\text{C}_1\text{-C}_6\text{alkyl})$ . An example of this  $\text{R}^2$  group is  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})(\text{C}_1\text{-C}_3\text{alkyl})-\text{O}-(\text{C}_1\text{-C}_6\text{alkyl})$ . Another example is  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})(\text{C}_1\text{-C}_3\text{alkyl})-\text{O}-(\text{C}_1\text{-C}_3\text{alkyl})$ . Another example is  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})(\text{C}_1\text{-C}_3\text{alkyl})-\text{O}-(\text{C}_1\text{-C}_2\text{alkyl})$ . Another example is  $-\text{CH}(\text{phenyl})(\text{C}_1\text{-C}_3\text{alkyl})-\text{O}-(\text{C}_1\text{-C}_6\text{alkyl})$ , another example is  $-\text{CH}(\text{phenyl})(\text{C}_1\text{-C}_3\text{alkyl})-\text{O}-(\text{C}_1\text{-C}_4\text{alkyl})$ , and another example is  $-\text{CH}(\text{phenyl})(\text{C}_1\text{-C}_3\text{alkyl})-\text{O}-(\text{C}_1\text{-C}_2\text{alkyl})$ . In one example  $\text{R}^2$  is  $-\text{CH}(\text{CH}_2\text{OCH}_3)\text{-phenyl}$ , and in another example  $-\text{CH}(\text{CH}_2\text{OH})\text{-phenyl}$ . In another example the  $(\text{R}^2\text{-CH}(\text{C}_6\text{-C}_{10}\text{aryl})(\text{C}_1\text{-C}_3\text{alkyl})-\text{O}-(\text{C}_1\text{-C}_6\text{alkyl}))$  group is substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Br, and Cl),  $-\text{O}-(\text{C}_1\text{-C}_6\text{alkyl})$  (and in one example  $-\text{O}-(\text{C}_1\text{-C}_2\text{alkyl})$ ), and  $-\text{OH}$ . In another example the  $\text{R}^2$  group is substituted  $-\text{CH}(\text{phenyl})(\text{C}_1\text{-C}_3\text{alkyl})-\text{O}-(\text{C}_1\text{-C}_4\text{alkyl})$ , and in another example substituted  $-\text{CH}(\text{phenyl})(\text{C}_1\text{-C}_3\text{alkyl})-\text{O}-(\text{C}_1\text{-C}_2\text{alkyl})$ , wherein in each example the  $\text{R}^2$  group is substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Br, and Cl),  $-\text{O}-(\text{C}_1\text{-C}_6\text{alkyl})$  (and in one example  $-\text{O}-(\text{C}_1\text{-C}_2\text{alkyl})$ ), and  $-\text{OH}$ . In one example the  $\text{R}^2$  group is  $-\text{CH}(\text{fluorophenyl})\text{CH}_2\text{OCH}_3$ . Examples of the  $\text{R}^2$  groups include, but are not limited to:

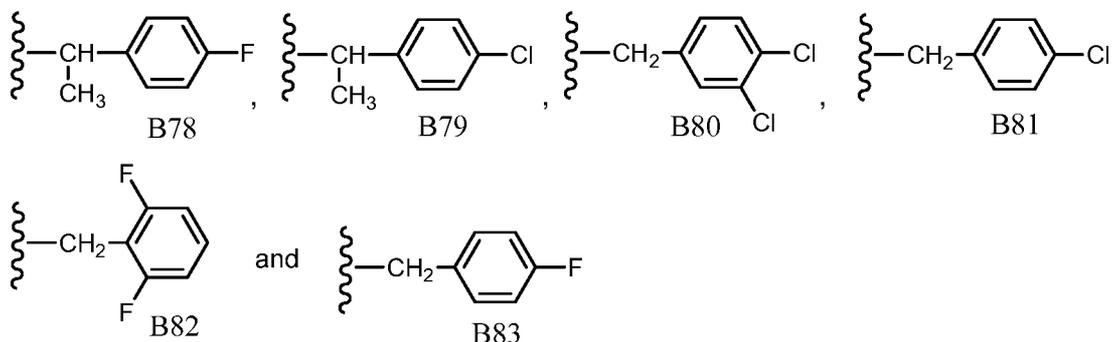


In one example, the  $\text{R}^2$   $-(\text{C}_1\text{-C}_4\text{alkyl})(\text{C}_6\text{-C}_{10}\text{aryl})$  (and in another  $-(\text{C}_1\text{-C}_2\text{alkyl})(\text{C}_6\text{-C}_{10}\text{aryl})$ ), and in another  $-(\text{C}_1\text{-C}_2\text{alkyl})\text{phenyl}$ , and in another  $-\text{CH}(\text{CH}_3)\text{phenyl}$ , and in another  $-\text{CH}\text{-phenyl}$ , and in another  $-\text{CH}_2\text{CH}_2\text{phenyl}$ , and in another  $-\text{CH}_2\text{CH}(\text{CH}_3)\text{phenyl}$  is substituted with 1-3 independently selected halo atoms, and in another example, 1-2

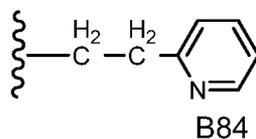
25

- 50 -

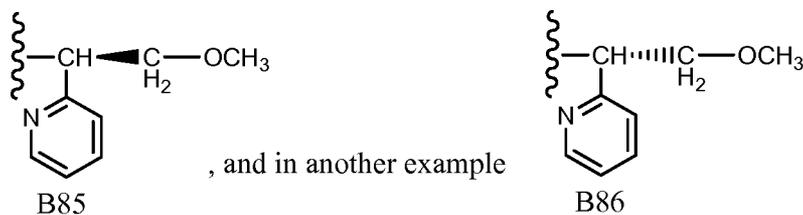
independently selected halo atoms, and in another example one halo atom. In one example the  $R^2$   $-(C_1-C_3\text{alkyl})(C_6-C_{10}\text{aryl})$  group is  $-\text{CH}(\text{CH}_3)\text{fluorophenyl}$ , and in another example  $-\text{CH}(\text{CH}_3)\text{-chlorophenyl}$ , and in another example  $-\text{CH}_2\text{-chlorophenyl}$ , and in another example  $-\text{CH}_2\text{-dichlorophenyl}$ , and in another example  $-\text{CH}_2\text{-difluorophenyl}$ , and in another example  $-\text{CH}_2\text{fluorophenyl}$ . Examples of the halo substituted  $R^2$   $-(C_1-C_4\text{alkyl})(C_6-C_{10}\text{aryl})$  groups include, but are not limited to:



In one example  $R^2$  is  $-(C_1-C_3\text{alkyl})\text{heteroaryl}$ . One example of the  $-(C_1-C_3\text{alkyl})\text{heteroaryl}$   $R^2$  group is  $-(C_1-C_2\text{alkyl})\text{heteroaryl}$ , and another is  $-(C_1-C_3\text{alkyl})\text{pyridyl}$ , and another is  $-(C_1-C_2\text{alkyl})\text{pyridyl}$ . In one example  $R^2$  is  $-\text{CH}_2\text{CH}_2\text{-pyridyl}$ , and in another example  $R^2$  is



In one example the  $R^2$   $-(C_1-C_3\text{alkyl})\text{heteroaryl}$  group is substituted on the  $(C_1-C_4\text{alkyl})$  moiety with a  $-\text{O}-(C_1-C_6\text{alkyl})$ . Thus, in one example  $R^2$  is  $-\text{CH}(\text{heteroaryl})-(C_1-C_6\text{alkyl})-\text{O}-(C_1-C_6\text{alkyl})$ . Examples of this  $R^2$  group include, but are not limited to:  $-\text{CH}(\text{heteroaryl})-(C_1-C_4\text{alkyl})-\text{O}-(C_1-C_4\text{alkyl})$ ,  $-\text{CH}(\text{heteroaryl})-(C_1-C_2\text{alkyl})-\text{O}-(C_1-C_2\text{alkyl})$ , and  $-\text{CH}(\text{pyridyl})-(C_1-C_2\text{alkyl})-\text{O}-(C_1-C_2\text{alkyl})$ . In one example the  $R^2$  group is  $-\text{CH}(\text{pyridyl})-\text{CH}_2-\text{OCH}_3$ . In another example the  $R^2$  group is



20

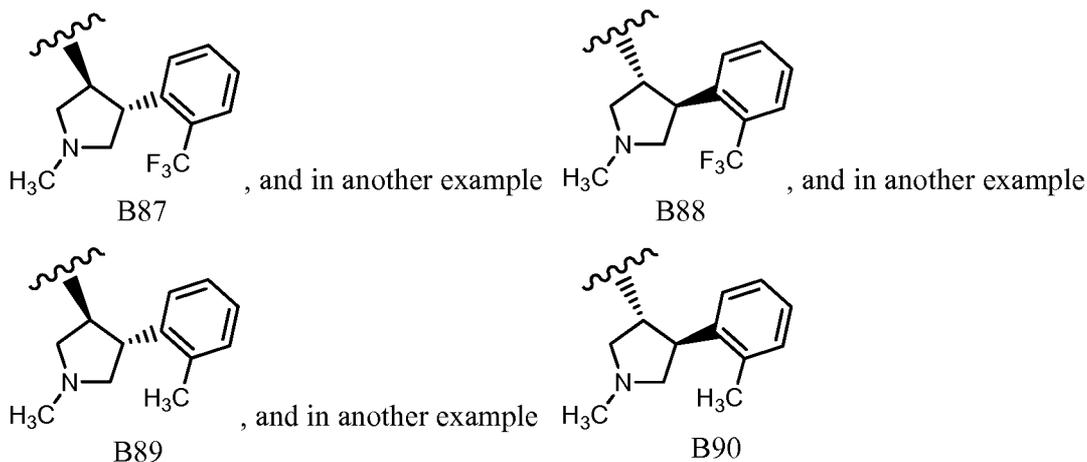
In one example the  $R^2$   $-(C_1-C_3\text{alkyl})\text{heteroaryl}$  is  $-\text{CH}_2\text{thiadiazolyl}$ , and in another example  $-\text{CH}_2\text{pyridyl}$ , and in another example  $-\text{CH}(\text{CH}_2\text{CH}_3)\text{pyridyl}$ .

- 51 -

In one example the  $R^2$   $-(C_1-C_3\text{alkyl})\text{heteroaryl}$  group is substituted, and in one example said substituted  $R^2$   $-(C_1-C_3\text{alkyl})\text{heteroaryl}$  group is  $-(C_1-C_3\text{alkyl})(\text{substituted heteroaryl})$ . In another example the substituent on said substituted heteroaryl moiety is  $-O(C_1-C_6\text{alkyl})$ , and in another example  $-O(C_1-C_4\text{alkyl})$ , and in another example  $-OCH_2CH_3$ . In another example said substituent is  $-N(R^{20})_2$ , and in another example  $-NHR^{20}$  and in another example  $-N(CH_3)_2$ . In another example said substituent is halo, and in another example Cl, and in another example F. In another example said substituent is  $-(C_1-C_6\text{alkyl})$ , and in another example  $-(C_1-C_3\text{alkyl})$ , and in another example methyl. In one example said substituted heteroaryl moiety is substituted pyridyl. In one example said  $R^2$  group is  $-CH_2\text{ethoxypyridyl}$ , and in another example  $-CH_2\text{dimethylaminopyridyl}$ , and in another example  $-CH_2\text{chloropyridyl}$ , and in another example  $-CH_2\text{fluoropyridyl}$ , and in another example  $-CH(CH_3)\text{methylpyridyl}$ , and in another example  $-CH(CH_3)\text{fluoropyridyl}$ .

In one example  $R^2$  is  $-(C_3-C_6\text{cycloalkyl})-(C_6-C_{10}\text{aryl})$ . One example of this  $R^2$  group is  $-(C_3-C_6\text{cycloalkyl})\text{-phenyl}$ , another is  $(C_3-C_4\text{cycloalkyl})\text{-phenyl}$ , and another is  $-\text{cyclopropyl-phenyl}$ . Another example is  $-\text{cyclopentylphenyl}$ .

In one example  $R^2$  is  $-\text{heterocycloalkyl-}(C_6-C_{10}\text{aryl})$ . One example of this  $R^2$  group is  $-\text{heterocycloalkyl-phenyl}$ , and another is a  $-\text{pyrrolidinyl-phenyl}$ . In another example  $R^2$  is  $-\text{heterocycloalkyl-}(C_6-C_{10}\text{aryl})$  substituted with 1-3 substituents independently selected from the group consisting of:  $-\text{CF}_3$ , and  $-(C_1-C_6\text{alkyl})$  (and in one example  $-(C_1-C_4\text{alkyl})$ , and in another example  $-(C_1-C_2\text{alkyl})$ , and in another example methyl). In one example  $R^2$  is:



In one example  $R^2$  is a  $-\text{fused (heterocycloalkyl)}(C_6-C_{10}\text{aryl})$  group. In another example said  $R^2$  group is a  $-\text{fused (heterocycloalkyl)}(C_6-C_{10}\text{aryl})$  wherein said heterocycloalkyl moiety is a seven membered ring (including the two atoms in common with said aryl). In another example said  $R^2$  group is a  $-\text{fused(heterocycloalkyl)}(C_6-C_{10}\text{aryl})$  wherein

- 52 -

said heterocycloalkyl moiety is a 6 membered ring (including the two atoms in common with said aryl). In another example said R<sup>2</sup> group is a -fused (heterocycloalkyl)(phenyl) group. In another example said R<sup>2</sup> group is a -fused (heterocycloalkyl)(phenyl) group wherein said heterocycloalkyl moiety is a seven membered ring (including the two atoms in common with said phenyl ring. In another example said R<sup>2</sup> group is a -fused (heterocycloalkyl)(phenyl) group wherein said heterocycloalkyl moiety is a six membered ring (including the two atoms in common with said phenyl ring. In another example said R<sup>2</sup> is a tetrahydrobenzoxepine, and in another example tetrahydroquinolinyl, and in another example dihydrochromenyl, and in another example tetrahydroquinolinyl, and in another example dihydrochromenyl, and in another example dihydrobenzofuranyl. In another example said -fused (heterocycloalkyl)(C<sub>6</sub>-C<sub>10</sub>)aryl group is substituted, and in one example substituted with -OH. In one example said -fused (heterocycloalkyl)(C<sub>6</sub>-C<sub>10</sub>)aryl group is hydroxytetrahydrobenzoxepine.

In one example R<sup>2</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl)-(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl)-(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl)-(cyclohexyl), and in another example -CH(CH<sub>3</sub>)cyclohexyl.

In one example R<sup>2</sup> is -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), and in another example -CH(phenyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), and in another example -CH(phenyl)(C<sub>5</sub>-C<sub>6</sub>cycloalkyl), and in another example -CH(phenyl)(cyclopentyl).

In another example said R<sup>2</sup> -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) is substituted. In one example said substituted -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) is -CH(phenyl)(hydroxy substituted C<sub>3</sub>-C<sub>6</sub>cycloalkyl), and in another example said substituted R<sup>2</sup> group is -CH(phenyl)(hydroxycyclopentyl).

In one example R<sup>2</sup> is -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) substituted with 1-3 substituents independently selected from the group consisting of: -OH and halo (e.g., F, Br and Cl, and in one example F). In one example said substituted -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) is a substituted -CH(phenyl)(C<sub>3</sub>-C<sub>5</sub>cycloalkyl), and in another example a substituted -CH(phenyl)(cyclobutyl), and in another example a -CH(phenyl)(cyclopentyl). In one example said substituted -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) is -CH(phenyl)(hydroxy substituted C<sub>3</sub>-C<sub>6</sub>cycloalkyl), and in another example said substituted R<sup>2</sup> group is -CH(phenyl)(hydroxycyclopentyl), and in another example -CH(phenyl)(hydroxycyclobutyl). In another example said substituted -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) is substituted with -OH and halo (e.g., F), and in one example said substituted -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) is -CH(hydroxycyclobutyl)(fluorophenyl).

- 53 -

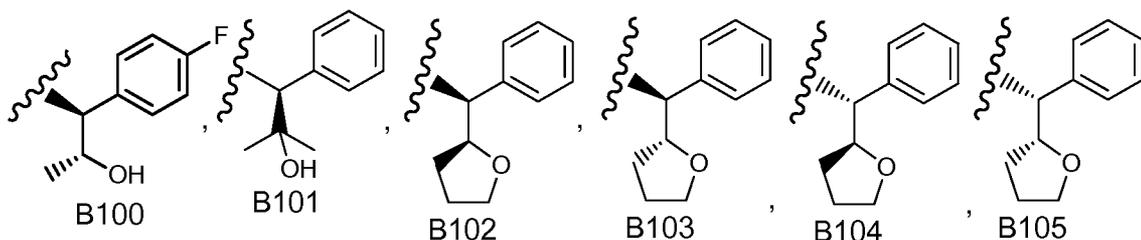
In one example  $R^2$  is  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})(\text{heterocycloalkyl})$ , and in another example  $-\text{CH}(\text{phenyl})(\text{heterocycloalkyl})$ , and in another example  $-\text{CH}(\text{phenyl})(\text{heterocycloalkyl})$  wherein said heterocycloalkyl is a 5-6 membered ring comprising 1-3 heteroatoms selected from the group consisting of: O, S, and N. In one example said heterocycloalkyl ring is a 5 membered ring. In another example said heterocycloalkyl ring is a 5 membered ring comprising one oxygen atom. In another example said  $R^2$  group is  $-\text{CH}(\text{phenyl})\text{tetrahydrofuranlyl}$ .

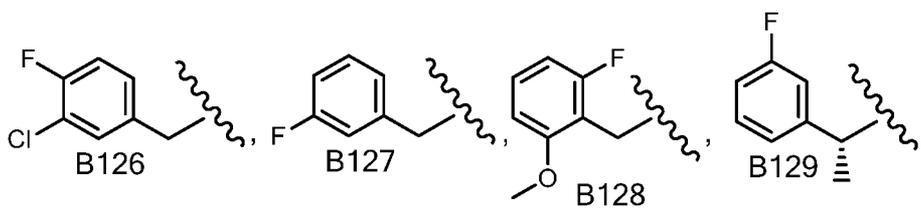
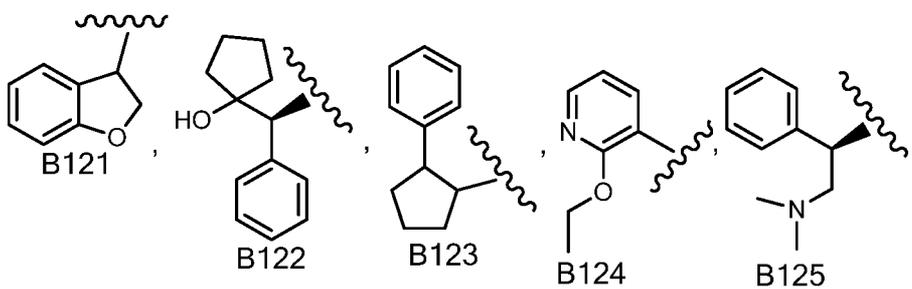
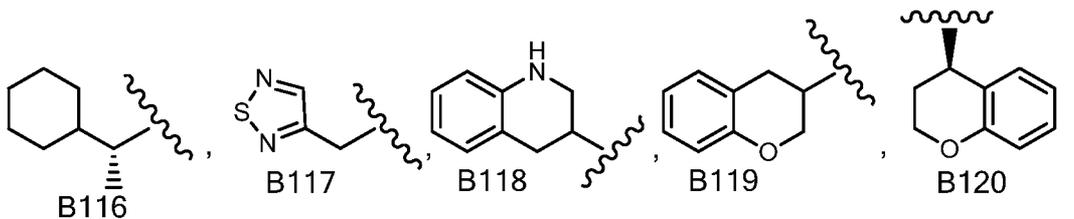
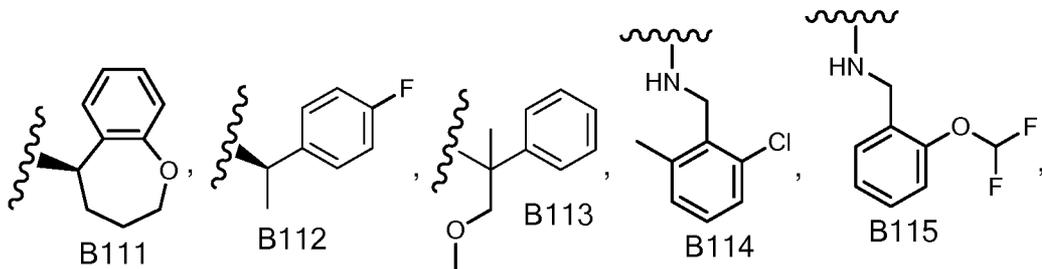
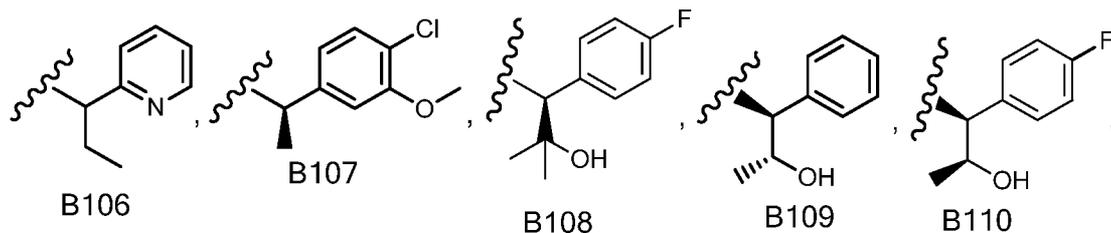
In one example  $R^2$  is  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})((\text{C}_1\text{-C}_6\text{alkyl})\text{N}(\text{R}^{20})_2)$  wherein each  $\text{R}^{20}$  is independently selected from the group consisting of H and  $(\text{C}_1\text{-C}_6\text{alkyl})$ . In another example said  $R^2$  group is  $-\text{CH}(\text{phenyl})((\text{C}_1\text{-C}_6\text{alkyl})\text{N}(\text{R}^{20})_2)$ , and in another example  $-\text{CH}(\text{phenyl})((\text{C}_1\text{-C}_2\text{alkyl})\text{N}(\text{R}^{20})_2)$ , and in another example  $-\text{CH}(\text{phenyl})\text{CHN}(\text{R}^{20})_2$ , wherein each  $\text{R}^{20}$  is independently selected. In one example each  $\text{R}^{20}$  is alkyl, and in another example each  $\text{R}^{20}$  is the same alkyl, and in another example each  $\text{R}^{20}$  is methyl.

In one example  $R^2$  is a  $-(\text{C}_3\text{-C}_6\text{cycloalkyl-O}-(\text{C}_1\text{-C}_6\text{alkyl}))$ . In another example  $R^2$  is a  $-(\text{C}_5\text{-C}_6\text{cycloalkyl-O}-(\text{C}_1\text{-C}_2\text{alkyl}))$ , and in another example methoxycyclopentyl.

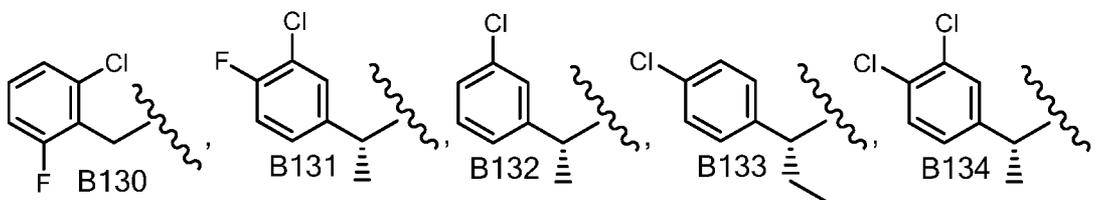
In one example  $R^2$  is a  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})\text{C}(\text{O})\text{N}(\text{R}^{21})_2$  wherein each  $\text{R}^{21}$  is independently selected. Each  $\text{R}^{21}$  is an independently selected  $-(\text{C}_1\text{-C}_6\text{alkyl})$ , and in one example each  $\text{R}^{21}$  is an independently selected  $-(\text{C}_1\text{-C}_2\text{alkyl})$ , and in another example each  $\text{R}^{21}$  is independently selected from the group consisting of: methyl and ethyl, and in another example both  $\text{R}^{21}$  groups are the same. In one example  $R^2$  is  $-\text{CH}(\text{phenyl})\text{C}(\text{O})\text{N}(\text{R}^{21})_2$  wherein  $\text{R}^{21}$  is as defined in this paragraph. In another example  $R^2$  is a  $-\text{CH}(\text{C}_6\text{-C}_{10}\text{aryl})\text{C}(\text{O})\text{N}(\text{R}^{21})_2$  substituted with a halo (e.g., F), wherein the  $\text{C}_6\text{-C}_{10}\text{aryl}$  moiety, and  $\text{R}^{21}$  is as defined in this paragraph. In one example  $R^2$  is  $-\text{CH}(\text{fluorophenyl})\text{C}(\text{O})\text{N}(\text{CH}_3)_2$ , and in another example  $-\text{CH}(\text{fluorophenyl})\text{C}(\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$ .

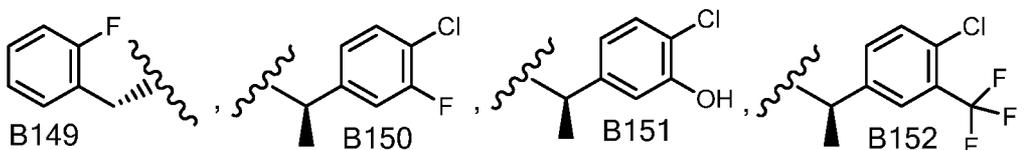
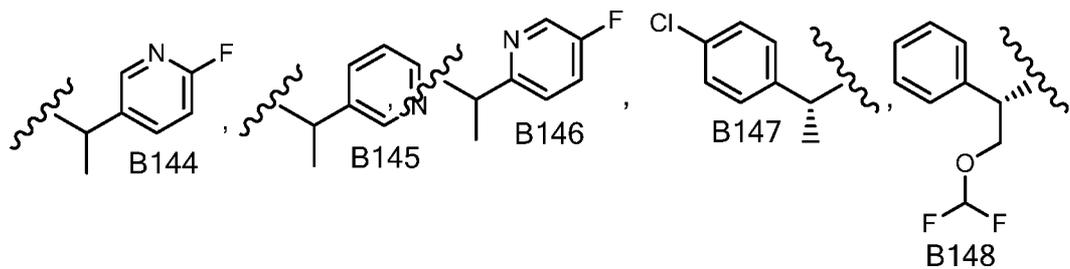
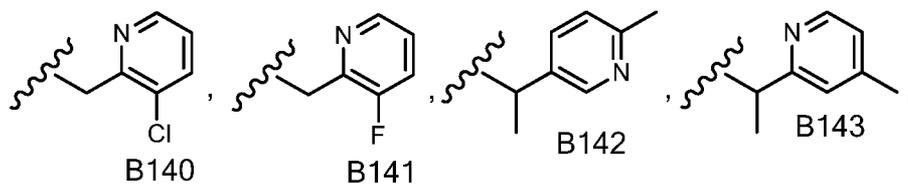
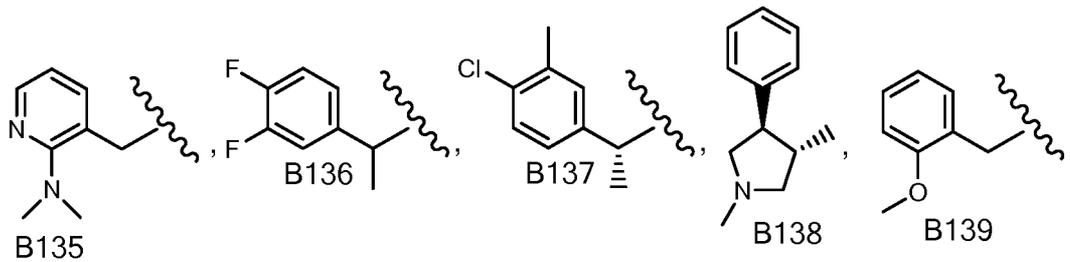
Examples  $R^2$  include, for example:



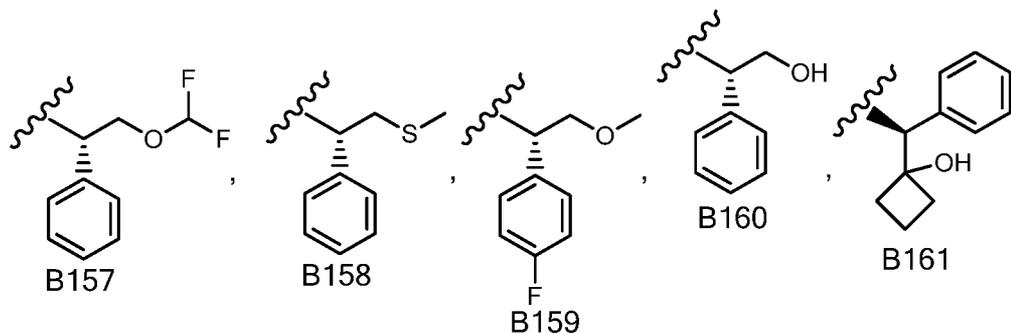
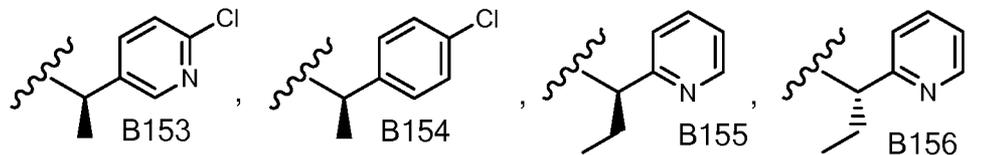


5

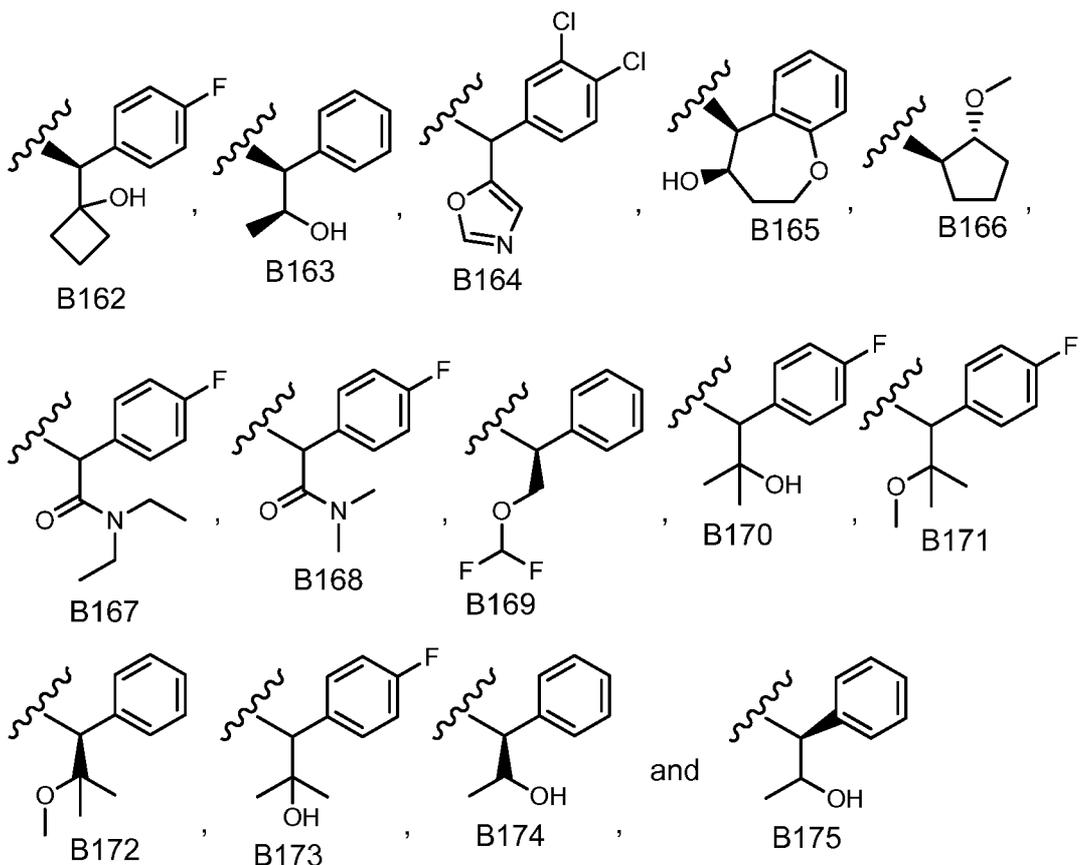




5



- 56 -



Examples of substituted  $R^2$  groups include groups comprising a phenyl substituted with  
 5 1 to 3 substituents independently selected from the group consisting of: halo (e.g., F and Cl),  
 $-CF_3$ , and  $-(C_1-C_3\text{alkyl})$  (and in one example methyl). Examples of substituted  $R^2$  groups  
 include groups comprising a heterocycloalkyl (e.g., pyrrolidinyl) substituted with a  $-(C_1-$   
 $C_2\text{alkyl})$  (and in one example methyl).

Examples of substituted  $R^2$  groups include groups comprising a phenyl substituted with  
 10 1-3 substituents selected from the group consisting of: Cl, F and  $-OCH_3$ . For example  
 wherein  $R^2$  is a  $-CH_2\text{phenyl}$ , or a  $-CH(CH_3)\text{phenyl}$ , or a  $-CH(CH_2CH_3)\text{phenyl}$ , wherein the  
 phenyl moiety is substituted with 1-3 substituents selected from the group consisting of: Cl, F  
 and  $-OCH_3$ .

In one example  $R^2$  is  $-(C_1-C_6\text{alkyl})-O-(C_1-C_6\text{alkyl})$ . One example of this  $R^2$  group is  
 15  $-(C_1-C_3\text{alkyl})-O-(C_1-C_3\text{alkyl})$ . In one example  $R^2$  is  $-(CH_2)_2-O-CH_3$ , and in another  
 $-CH(CH_3)CH_2-O-CH_3$ .

In one example  $R^2$  is selected from the group consisting of: (F,  $OCH_3$ -phenyl)- $CH_2-$   
 piperidinyl-,  $-CH_2CH_2$ -piperidyl-phenyl, methyl, ethyl, propyl,  $-CH(CH_3)\text{phenyl}$ ,  $-CH-$   
 phenyl,  $-CH_2CH_2\text{phenyl}$ ,  $-CH_2CH(CH_3)\text{phenyl}$ ,  $-CH(CH_3)$ -methoxyphenyl,  $-(CH_2)_2-$

- 57 -

methoxyphenyl,  $-\text{CH}(\text{CH}_2\text{OCH}_3)\text{-phenyl}$ ,  $-\text{CH}(\text{CH}_2\text{OH})\text{-phenyl}$ ,  $-\text{CH}(\text{fluorophenyl})\text{CH}_2\text{OCH}_3$ ,  
 $-\text{CH}(\text{CH}_3)\text{phenyl}$ ,  $-\text{CH}(\text{CH}_3)\text{fluorophenyl}$ ,  $-\text{CH}(\text{CH}_3)\text{-chlorophenyl}$ ,  $-\text{CH}_2\text{-chlorophenyl}$ ,  
 $-\text{CH}_2\text{-dichlorophenyl}$ ,  $-\text{CH}_2\text{-difluorophenyl}$ ,  $-\text{CH}_2\text{fluorophenyl}$ ,  $-\text{CH}_2\text{CH}_2\text{-pyridyl}$ ,  
5  $-\text{CH}(\text{pyridyl})\text{-CH}_2\text{-OCH}_3$ ,  $-\text{cyclopropyl-phenyl}$ ,  $-\text{pyrrolidinyl-phenyl}$ , B64-B89, and B90.

In one example  $R^2$  is B1. In another example  $R^2$  is B2. In another example  $R^2$  is B3.  
In another example  $R^2$  is B4. In another example  $R^2$  is B5. In another example  $R^2$  is B6. In  
another example  $R^2$  is B7. In another example  $R^2$  is B8. In another example  $R^2$  is B9. In  
another example  $R^2$  is B10. In another example  $R^2$  is B11. In another example  $R^2$  is B12. In  
10 another example  $R^2$  is B13. In another example  $R^2$  is B14. In another example  $R^2$  is B15. In  
another example  $R^2$  is B16. In another example  $R^2$  is B17. In another example  $R^2$  is B18. In  
another example  $R^2$  is B19. In another example  $R^2$  is B20. In another example  $R^2$  is B21. In  
another example  $R^2$  is B22. In another example  $R^2$  is B23. In another example  $R^2$  is B24. In  
another example  $R^2$  is B25. In another example  $R^2$  is B26. In another example  $R^2$  is B27. In  
15 another example  $R^2$  is B28. In another example  $R^2$  is B29. In another example  $R^2$  is B30. In  
another example  $R^2$  is B31. In another example  $R^2$  is B32. In another example  $R^2$  is B33. In  
another example  $R^2$  is B34. In another example  $R^2$  is B35. In another example  $R^2$  is B36. In  
another example  $R^2$  is B37. In another example  $R^2$  is B38. In another example  $R^2$  is B39. In  
another example  $R^2$  is B40. In another example  $R^2$  is B41. In another example  $R^2$  is B42. In  
20 another example  $R^2$  is B43. In another example  $R^2$  is B44. In another example  $R^2$  is B45. In  
another example  $R^2$  is B46. In another example  $R^2$  is B47. In another example  $R^2$  is B48. In  
another example  $R^2$  is B49. In another example  $R^2$  is B50. In another example  $R^2$  is B51. In  
another example  $R^2$  is B52. In another example  $R^2$  is B53. In another example  $R^2$  is B54. In  
another example  $R^2$  is B55. In another example  $R^2$  is B56. In another example  $R^2$  is B57. In  
25 another example  $R^2$  is B58. In another example  $R^2$  is B59. In another example  $R^2$  is B60. In  
another example  $R^2$  is B61. In another example  $R^2$  is B62. In another example  $R^2$  is B63. In  
another example  $R^2$  is B64. In another example  $R^2$  is B65. In another example  $R^2$  is B66. In  
another example  $R^2$  is B67. In another example  $R^2$  is B68. In another example  $R^2$  is B69. In  
another example  $R^2$  is B70. In another example  $R^2$  is B71. In another example  $R^2$  is B72. In  
30 another example  $R^2$  is B73. In another example  $R^2$  is B74. In another example  $R^2$  is B75. In  
another example  $R^2$  is B76. In another example  $R^2$  is B77. In another example  $R^2$  is B78. In  
another example  $R^2$  is B79. In another example  $R^2$  is B80. In another example  $R^2$  is B81. In  
another example  $R^2$  is B82. In another example  $R^2$  is B83. In another example  $R^2$  is B84. In

- 58 -

another example R<sup>2</sup> is B85. In another example R<sup>2</sup> is B86. In another example R<sup>2</sup> is B87. In another example R<sup>2</sup> is B88. In another example R<sup>2</sup> is B89. In another example R<sup>2</sup> is B90. In other examples R<sup>2</sup> is any one of B100-175 as if each was individually listed as a separate example.

5 In another example, R<sup>2</sup> is H.

In another example R<sup>2</sup> is selected from the group consisting of: -(C<sub>1</sub>-C<sub>3</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl), -CH(C<sub>6</sub>-C<sub>10</sub>aryl)((C<sub>1</sub>-C<sub>3</sub>alkyl)-O-(C<sub>1</sub>-C<sub>3</sub>alkyl)), -(C<sub>1</sub>-C<sub>3</sub>alkyl)heteroaryl, -heterocycloalkyl(C<sub>6</sub>-C<sub>10</sub>aryl), and -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), as these groups are described above (in any of the definitions of R<sup>2</sup>). For example, R<sup>2</sup> is selected from the group consisting of: (1) -(C<sub>1</sub>-C<sub>3</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl) (such as, for example, -(C<sub>1</sub>-C<sub>2</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>1</sub>-C<sub>3</sub>alkyl)phenyl, -CH(CH<sub>3</sub>)phenyl, -CH<sub>2</sub>CH<sub>2</sub>phenyl, and -CH<sub>2</sub>phenyl), (2) -CH(C<sub>6</sub>-C<sub>10</sub>aryl)((C<sub>1</sub>-C<sub>3</sub>alkyl)-O-(C<sub>1</sub>-C<sub>3</sub>alkyl)) (such as, for example, -CH(phenyl)-((C<sub>1</sub>-C<sub>2</sub>alkyl)-O-(C<sub>1</sub>-C<sub>2</sub>alkyl)), and -CH(phenyl)CH<sub>2</sub>OCH<sub>3</sub>), (3) -(C<sub>1</sub>-C<sub>3</sub>alkyl)heteroaryl (such as, for example, -(C<sub>1</sub>-C<sub>2</sub>alkyl)heteroaryl, -(C<sub>1</sub>-C<sub>3</sub>alkyl)pyridyl, -(C<sub>1</sub>-C<sub>2</sub>alkyl)pyridyl, and -CH(CH<sub>3</sub>)pyridyl), (4) -heterocycloalkyl(C<sub>6</sub>-C<sub>10</sub>aryl) (such as, for example, -heterocycloalkyl-phenyl, and -pyrrolidinylphenyl), (5) -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl) (such as, for example, -(C<sub>1</sub>-C<sub>3</sub>alkyl)-O-(C<sub>1</sub>-C<sub>2</sub>alkyl), -(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>, and -CH(CH<sub>3</sub>)CH<sub>2</sub>OCH<sub>3</sub>), (6) any one of the groups in (1), (2), (3), and (4) wherein the aryl, heteroaryl or heterocycloalkyl moiety is substituted with 1-3 substituents independently selected from the group consisting of halo (e.g., F, Br, and Cl, and in one example F) and -(C<sub>1</sub>-C<sub>6</sub>alkyl) (e.g., -(C<sub>1</sub>-C<sub>4</sub>alkyl), -(C<sub>1</sub>-C<sub>3</sub>alkyl), and -(C<sub>1</sub>-C<sub>2</sub>alkyl), and in one example methyl), (7) any one of the groups in (1), (2), (3), and (4) wherein the aryl, heteroaryl or heterocycloalkyl moiety is substituted with 1 substituent selected from the group consisting of halo (e.g., F, Br, and Cl, and in one example F) and -(C<sub>1</sub>-C<sub>6</sub>alkyl) (e.g., -(C<sub>1</sub>-C<sub>4</sub>alkyl), -(C<sub>1</sub>-C<sub>3</sub>alkyl), and -(C<sub>1</sub>-C<sub>2</sub>alkyl), and in one example methyl), (8) any one of the groups in (1), (2), (3), and (4) wherein the aryl, heteroaryl or heterocycloalkyl moiety is substituted with 1 substituent selected from the group consisting of F and methyl, and (9) any one of the groups in (1), (2), (3), and (4) wherein the aryl (e.g., phenyl) is substituted with 1-3 independently selected halos (e.g., F, Br, and Cl, and in one example F) and the heteroaryl (e.g., pyridyl) or heterocycloalkyl (e.g., pyrrolidine) moiety is substituted with 1-3 substituents independently selected from -(C<sub>1</sub>-C<sub>6</sub>alkyl) (e.g., -(C<sub>1</sub>-C<sub>4</sub>alkyl), -(C<sub>1</sub>-C<sub>3</sub>alkyl), and -(C<sub>1</sub>-C<sub>2</sub>alkyl), and in one example methyl), (10) any one of the groups in (1), (2), (3), and (4) wherein the aryl (e.g., phenyl) is substituted with 1 halo (e.g., F, Br, or Cl, and in one example F) and the heteroaryl (e.g., pyridyl) or heterocycloalkyl (e.g., pyrrolidine) moiety is substituted

with 1  $-(C_1-C_6\text{alkyl})$  (e.g.,  $-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})$ , and in one example methyl), and (11) any one of the groups in (1), (2), (3), and (5) wherein the alkyl is substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Br, and Cl),  $-O-(C_1-C_6\text{alkyl})$ ,  $-OH$  and  $-CF_3$ .

5 In one example  $R^{10}$  is selected from the group consisting of: H, halo, CN,  $-CF_3$ , OH,  $NH_2$ ,  $-O-(C_1-C_6\text{alkyl})$ ,  $-(C_1-C_6\text{alkyl})$ , and  $-(C_5-C_6\text{cycloalkyl})$ .

In one example  $R^{10}$  is selected from the group consisting of: CN,  $-OH$ , and  $NH_2$ .

In one example the  $R^{10}$  or  $R^{11}$   $-O-(C_1-C_6\text{alkyl})$  is  $-O-(C_1-C_2\text{alkyl})$ .

10 In one example  $R^{10}$  is selected from the group consisting of: H, F, Cl, Br,  $-CF_3$ , methyl, ethyl, isopropyl, cyclopropyl,  $-OCH_3$ ,  $-\text{CH}(\text{OH})\text{CH}_3$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2-\text{N}(\text{CH}_3)_2$ , and  $-\text{CH}_2\text{-morpholinyl}$ . In another example  $R^{10}$  is selected from the group consisting of: H, methyl, F and OH. In another example  $R^{10}$  is selected from the group consisting of: H and methyl.

15 In one example  $R^{11}$  is selected from the group consisting of: CN, OH,  $NH_2$ , aryl and heterocycloalkyl,  $-\text{NHR}^{12}$ ,  $-\text{NR}^{12}\text{R}^{13}$ , and  $-\text{NHC}(\text{O})\text{R}^8$ .

In one example  $R^{11}$  is selected from the group consisting of: H, F, Cl, Br,  $-CF_3$  methyl, ethyl, isopropyl, cyclopropyl,  $-OCH_3$ ,  $-\text{CH}(\text{OH})\text{CH}_3$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2-\text{N}(\text{CH}_3)_2$ , and  $-\text{CH}_2\text{-morpholinyl}$ . In another example  $R^{11}$  is selected from the group consisting of: H and  $-\text{CH}_2\text{OH}$ .

20 In one example  $R^{10}$  is selected from the group consisting of: H, Cl, F and  $-CF_3$ .

In one example  $R^{11}$  is selected from the group consisting of: H, Cl,  $-\text{CH}_3$ ,  $-\text{OCH}_3$ ,  $-\text{CH}_2\text{OH}$ , and  $-\text{CH}_2\text{OCH}_3$ .

25 In one example  $R^{10}$  is selected from the group consisting of: H, Cl, F and  $-CF_3$ , and  $R^{11}$  is selected from the group consisting of: H, Cl,  $-\text{CH}_3$ ,  $-\text{OCH}_3$ ,  $-\text{CH}_2\text{OH}$ , and  $-\text{CH}_2\text{OCH}_3$ .

In one example  $R^{10}$  is selected from the group consisting of: H, F, Cl, Br, methyl, ethyl, isopropyl, cyclopropyl,  $-\text{CH}(\text{OH})\text{CH}_3$ ,  $-\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2-\text{N}(\text{CH}_3)_2$ , and  $-\text{CH}_2\text{-morpholinyl}$ . In another example  $R^{10}$  is selected from the group consisting of: H, F and methyl.

30 In one example  $R^{11}$  is selected from the group consisting of: H, F, Cl, Br, methyl, ethyl, isopropyl, cyclopropyl,  $-\text{CH}(\text{OH})\text{CH}_3$ ,  $-\text{CH}_2\text{OCH}_3$ ,  $-\text{CH}_2-\text{N}(\text{CH}_3)_2$ , and  $-\text{CH}_2\text{-morpholinyl}$ . In another example  $R^{11}$  is selected from the group consisting of: H and methyl.

In one example  $R^{10}$  is H. In another example  $R^{10}$  is halo. In another example  $R^{10}$  is halo selected from the group consisting of: F, Cl and Br. In another example  $R^{10}$  is F. In

- 60 -

another example R<sup>10</sup> is Br, and in another example Cl. In another example R<sup>10</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>6</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>4</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>3</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl). In another example R<sup>10</sup> is methyl. In another example R<sup>10</sup> is ethyl. In another example R<sup>10</sup> is isopropyl. In another example R<sup>10</sup> is -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl). In another example R<sup>10</sup> is cyclopropyl. In another example R<sup>10</sup> is hydroxy substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl), and in another example hydroxy substituted -(C<sub>1</sub>-C<sub>3</sub>alkyl), and in another example hydroxy substituted -(C<sub>1</sub>-C<sub>3</sub>alkyl). In another example R<sup>10</sup> is -CH(OH)CH<sub>3</sub>. In another example R<sup>10</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>4</sub>alkyl)-O-(C<sub>1</sub>-C<sub>4</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl)-O-(C<sub>1</sub>-C<sub>2</sub>alkyl). In another example R<sup>10</sup> is -CH<sub>2</sub>OCH<sub>3</sub>. In another example R<sup>10</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl)-N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, and in another example -(C<sub>1</sub>-C<sub>4</sub>alkyl)-N(C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl)-N(C<sub>1</sub>-C<sub>2</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected. In another example R<sup>10</sup> is -CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>. In another example R<sup>10</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl)-heterocycloalkyl, and in another example -(C<sub>1</sub>-C<sub>4</sub>alkyl)-heterocycloalkyl, and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl)-heterocycloalkyl, and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl)-(6 membered heterocycloalkyl). In another example R<sup>10</sup> is -CH<sub>2</sub>-morpholinyl.

In one example R<sup>11</sup> is H. In another example R<sup>11</sup> is halo. In another example R<sup>11</sup> is halo selected from the group consisting of: F, Cl and Br. In another example R<sup>11</sup> is F. In another example R<sup>11</sup> is Br, and in another example Cl. In another example R<sup>11</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>6</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>4</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>3</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl). In another example R<sup>11</sup> is methyl. In another example R<sup>11</sup> is ethyl. In another example R<sup>11</sup> is isopropyl. In another example R<sup>11</sup> is -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl). In another example R<sup>11</sup> is cyclopropyl. In another example R<sup>11</sup> is hydroxyl substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl), and in another example hydroxy substituted -(C<sub>1</sub>-C<sub>3</sub>alkyl), and in another example hydroxy substituted -(C<sub>1</sub>-C<sub>3</sub>alkyl). In another example R<sup>11</sup> is -CH(OH)CH<sub>3</sub>. In another example R<sup>11</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>4</sub>alkyl)-O-(C<sub>1</sub>-C<sub>4</sub>alkyl), and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl)-O-(C<sub>1</sub>-C<sub>2</sub>alkyl). In another example R<sup>11</sup> is -CH<sub>2</sub>OCH<sub>3</sub>. In another example R<sup>11</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl)-N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, and in another example -(C<sub>1</sub>-C<sub>4</sub>alkyl)-N(C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, and in another example -(C<sub>1</sub>-C<sub>2</sub>alkyl)-N(C<sub>1</sub>-C<sub>2</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected. In another example R<sup>11</sup>

- 61 -

is  $-\text{CH}_2\text{-N}(\text{CH}_3)_2$ . In another example  $\text{R}^{11}$  is  $-(\text{C}_1\text{-C}_6\text{alkyl})\text{-heterocycloalkyl}$ , and in another example  $-(\text{C}_1\text{-C}_4\text{alkyl})\text{-heterocycloalkyl}$ , and in another example  $-(\text{C}_1\text{-C}_2\text{alkyl})\text{-heterocycloalkyl}$ , and in another example  $-(\text{C}_1\text{-C}_2\text{alkyl})\text{-(6 membered heterocycloalkyl)}$ . In another example  $\text{R}^{11}$  is

5  $-\text{CH}_2\text{-morpholinyl}$ . In other examples  $\text{R}^{10}$  is selected from the group consisting of: H, Br, Cl, F and  $-(\text{C}_1\text{-C}_3\text{alkyl})$  (and in one example methyl, and in another example ethyl), and  $\text{R}^{11}$  is as defined in any one of the examples described in this paragraph. In other examples  $\text{R}^{10}$  is selected from the group consisting of: H, F and methyl, and  $\text{R}^{11}$  is as defined in any one of the examples described in this paragraph.

10 In another example  $\text{R}^{10}$  is H and  $\text{R}^{11}$  is H.  $\text{R}^{10}$  is halo and  $\text{R}^{11}$  is H. In another example  $\text{R}^{10}$  is F and  $\text{R}^{11}$  is H. In another example  $\text{R}^{10}$  is Br and  $\text{R}^{11}$  is H. In another example  $\text{R}^{10}$  is Cl and  $\text{R}^{11}$  is H. In another example  $\text{R}^{10}$  is  $-(\text{C}_1\text{-C}_6\text{alkyl})$  and  $\text{R}^{11}$  is H. In another example  $\text{R}^{10}$  is  $-(\text{C}_1\text{-C}_4\text{alkyl})$  and  $\text{R}^{11}$  is H. In another example  $\text{R}^{10}$  is  $-(\text{C}_1\text{-C}_3\text{alkyl})$  and  $\text{R}^{11}$  is H. In another example  $\text{R}^{10}$  is  $-(\text{C}_1\text{-C}_2\text{alkyl})$  and  $\text{R}^{11}$  is H. In another example  $\text{R}^{10}$  is methyl and  $\text{R}^{11}$  is H. In another example  $\text{R}^{10}$  is ethyl and  $\text{R}^{11}$  is H. In other examples  $\text{R}^{10}$  and  $\text{R}^{11}$  are as defined in any one of the examples in this paragraph, and  $\text{R}^1$  and  $\text{R}^2$  are as defined in any one of the examples given above.

15 In another example  $\text{R}^{10}$  is H and  $\text{R}^{11}$  is  $-(\text{C}_1\text{-C}_3\text{alkyl})$  (and in one example methyl, and in another example ethyl, and in another example isopropyl). In another example  $\text{R}^{10}$  is H and  $\text{R}^{11}$  is  $-(\text{C}_3\text{-C}_6\text{ cycloalkyl})$  (and in another example cyclopropyl). In another example  $\text{R}^{10}$  is H and  $\text{R}^{11}$  is  $-(\text{C}_1\text{-C}_2\text{alkyl})\text{-O}\text{-(C}_1\text{-C}_2\text{alkyl)}$  (and in another example  $-\text{CH}_2\text{OCH}_3$ ). In another example  $\text{R}^{10}$  is H and  $\text{R}^{11}$  is  $-(\text{C}_1\text{-C}_2\text{alkyl})\text{-N}(\text{C}_1\text{-C}_2\text{alkyl})_2$  wherein each alkyl is independently selected (and in another example  $-\text{CH}_2\text{-N}(\text{CH}_3)_2$ ). In another example  $\text{R}^{10}$  is H and  $\text{R}^{11}$  is  $-(\text{C}_1\text{-C}_2\text{alkyl})\text{-heterocycloalkyl}$  (and in another example  $-\text{CH}_2\text{-morpholinyl}$ ). In another example  $\text{R}^{10}$  is H and  $\text{R}^{11}$  is hydroxy substituted  $-(\text{C}_1\text{-C}_3\text{alkyl})$  (and in another example  $-\text{CH}(\text{OH})\text{CH}_3$ ). In other examples  $\text{R}^{10}$  and  $\text{R}^{11}$  are as defined in any one of the examples in this paragraph, and  $\text{R}^1$  and  $\text{R}^2$  are as defined in any one of the examples given above.

20 In other examples  $\text{R}^{10}$  is selected from the group consisting of: H, halo (for example, F, or Br, or Cl), and  $-(\text{C}_1\text{-C}_6\text{alkyl})$  (for example, a  $-(\text{C}_1\text{-C}_4\text{alkyl})$ , or  $-(\text{C}_1\text{-C}_3\text{alkyl})$  or  $-(\text{C}_1\text{-C}_2\text{alkyl}$ , and in one example methyl and in another ethyl), and  $\text{R}^{11}$  is selected from the group consisting of: halo (for example, F or Br or Cl), and  $-(\text{C}_1\text{-C}_6\text{alkyl})$  (for example, a  $-(\text{C}_1\text{-C}_4\text{alkyl})$ , or  $-(\text{C}_1\text{-C}_3\text{alkyl})$  or  $-(\text{C}_1\text{-C}_2\text{alkyl})$ , and in one example methyl and in another ethyl). In other examples  $\text{R}^{10}$  is selected from the group consisting of: H, F, Br, Cl, methyl and ethyl,

- 62 -

and R<sup>11</sup> is selected from the group consisting of: F, Br, Cl, methyl and ethyl. In other examples R<sup>10</sup> is selected from the group consisting of: H, F, methyl and ethyl, and R<sup>11</sup> is selected from the group consisting of: F, methyl and ethyl. In other examples R<sup>10</sup> is selected from the group consisting of: H, F, and methyl, and R<sup>11</sup> is selected from the group consisting of: F, and methyl. In other examples R<sup>10</sup> is H and R<sup>11</sup> is selected from the group consisting of: F, methyl and ethyl. In other examples R<sup>10</sup> is H and R<sup>11</sup> is selected from the group consisting of: F, and methyl. In other examples R<sup>10</sup> and R<sup>11</sup> are as defined in any one of the examples in this paragraph, and R<sup>1</sup> and R<sup>2</sup> are as defined in any one of the examples given above.

In other examples of this invention, R<sup>1</sup>, R<sup>10</sup> and R<sup>11</sup> are as defined for formula (1), and R<sup>4</sup> and R<sup>5</sup> are each independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>4</sub>alkyl), and R<sup>2</sup> is selected from the group consisting of: B1 to B9, and B29 to B44. In other examples of this invention R<sup>1</sup>, R<sup>10</sup> and R<sup>11</sup> are as defined for formula (1), and R<sup>4</sup> and R<sup>5</sup> are each independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>4</sub>alkyl), and R<sup>2</sup> is, in one example, B1, and in another example B2, and in another example B3, and in another example B9, and in another example B29, and in another example B30, and in another example B31, and in another example B32, and in another example B33, and in another example B34, and in another example B35, and in another example B36, and in another example B37, and in another example B38, and in another example B39, and in another example B40, and in another example B41, and in another example B42, and in another example B43, and in another example B44. In other examples of this invention, R<sup>1</sup>, R<sup>10</sup> and R<sup>11</sup> are as defined for formula (1), and R<sup>4</sup> and R<sup>5</sup> are each independently selected from the group consisting of: methyl and ethyl, and R<sup>2</sup> is selected from the group consisting of: B1 to B9, and B29 to B44. In other examples of this invention R<sup>1</sup>, R<sup>10</sup> and R<sup>11</sup> are as defined for formula (1), and R<sup>4</sup> and R<sup>5</sup> are each independently selected from the group consisting of: methyl and ethyl, and R<sup>2</sup> is, in one example, B1, and in another example B2, and in another example B3, and in another example B9, and in another example B29, and in another example B30, and in another example B31, and in another example B32, and in another example B33, and in another example B34, and in another example B35, and in another example B36, and in another example B37, and in another example B38, and in another example B39, and in another example B40, and in another example B41, and in another example B42, and in another example B43, and in another example B44. Other examples include any one of the examples in this paragraph wherein R<sup>4</sup> and R<sup>5</sup> are the same. Other examples include any one of examples in this paragraph wherein R<sup>10</sup> is selected from the group consisting of H, F, and

- 63 -

methyl, and R<sup>11</sup> is selected from the group consisting of: H, F and methyl. Other examples include any one of the examples in this paragraph wherein R<sup>10</sup> is H, and R<sup>11</sup> is selected from the group consisting of: H, F and methyl. Other examples include any one of the examples in this paragraph wherein R<sup>10</sup> is F, and R<sup>11</sup> is selected from the group consisting of: H, F and methyl. Other examples include any one of the examples in this paragraph wherein R<sup>10</sup> is F, and R<sup>11</sup> is selected from the group consisting of: H, F and methyl. Other examples include any one of the examples in this paragraph wherein R<sup>10</sup> is methyl, and R<sup>11</sup> is selected from the group consisting of: H, F and methyl. Other examples include any one of the examples in this paragraph wherein R<sup>10</sup> is H, and R<sup>11</sup> is H. Other examples include any one of the examples in this paragraph wherein R<sup>10</sup> is F, and R<sup>11</sup> is H. Other examples include any one of the examples in this paragraph wherein R<sup>10</sup> is methyl, and R<sup>11</sup> is H.

In another example R<sup>4</sup> and R<sup>5</sup> are independently selected from the group consisting of: H, methyl, ethyl, propyl, isopropyl, and -(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>; R<sup>2</sup> is selected from the group consisting of: (1) -(C<sub>1</sub>-C<sub>3</sub>alkyl)aryl (such as, for example, -(C<sub>1</sub>-C<sub>2</sub>alkyl)aryl, -(C<sub>1</sub>-C<sub>3</sub>alkyl)phenyl, -CH(CH<sub>3</sub>)phenyl, -CH<sub>2</sub>CH<sub>2</sub>phenyl, and -CH<sub>2</sub>phenyl), (2) -CH(aryl)((C<sub>1</sub>-C<sub>3</sub>alkyl)-O-(C<sub>1</sub>-C<sub>3</sub>alkyl)) (such as, for example, -CH(phenyl)((C<sub>1</sub>-C<sub>2</sub>alkyl)-O-(C<sub>1</sub>-C<sub>2</sub>alkyl)), and -CH(phenyl)CH<sub>2</sub>OCH<sub>3</sub>), (3) -(C<sub>1</sub>-C<sub>3</sub>alkyl)heteroaryl (such as, for example, -(C<sub>1</sub>-C<sub>2</sub>alkyl)heteroaryl, -(C<sub>1</sub>-C<sub>3</sub>alkyl)pyridyl, -(C<sub>1</sub>-C<sub>2</sub>alkyl)pyridyl, and -CH(CH<sub>3</sub>)pyridyl), (4) -heterocycloalkylaryl (such as, for example, -heterocycloalkylphenyl, and -pyrrolidinylphenyl), (5) -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl) (such as, for example, -(C<sub>1</sub>-C<sub>3</sub>alkyl)-O-(C<sub>1</sub>-C<sub>2</sub>alkyl), -(CH<sub>2</sub>)<sub>2</sub>-O-CH<sub>3</sub>, and -CH(CH<sub>3</sub>)CH<sub>2</sub>OCH<sub>3</sub>), (6) any one of the groups in (1), (2), (3), and (4) wherein the aryl, heteroaryl or heterocycloalkyl moiety is substituted with 1-3 substituents independently selected from the group consisting of halo (e.g., F, Br, and Cl, and in one example F) and -(C<sub>1</sub>-C<sub>6</sub>alkyl) (e.g., -(C<sub>1</sub>-C<sub>4</sub>alkyl), -(C<sub>1</sub>-C<sub>3</sub>alkyl), and -(C<sub>1</sub>-C<sub>2</sub>alkyl), and in one example methyl), (7) any one of the groups in (1), (2), (3), and (4) wherein the aryl, heteroaryl or heterocycloalkyl moiety is substituted with 1 substituent selected from the group consisting of halo (e.g., F, Br, and Cl, and in one example F) and -(C<sub>1</sub>-C<sub>6</sub>alkyl) (e.g., -(C<sub>1</sub>-C<sub>4</sub>alkyl), -(C<sub>1</sub>-C<sub>3</sub>alkyl), and -(C<sub>1</sub>-C<sub>2</sub>alkyl), and in one example methyl), (8) any one of the groups in (1), (2), (3), and (4) wherein the aryl, heteroaryl or heterocycloalkyl moiety is substituted with 1 substituent selected from the group consisting of F and methyl, and (9) any one of the groups in (1), (2), (3), and (4) wherein the aryl (e.g., phenyl) is substituted with 1-3 independently selected halos (e.g., F, Br, and Cl, and in one example F) and the heteroaryl (e.g., pyridyl) or heterocycloalkyl (e.g., pyrrolidine) moiety is substituted with 1-3 substituents independently

- 64 -

selected from  $-(C_1-C_6\text{alkyl})$  (e.g.,  $-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})$ ), and in one example methyl), and (10) any one of the groups in (1), (2), (3), and (4) wherein the aryl (e.g., phenyl) is substituted with 1 halo (e.g., F, Br, or Cl, and in one example F) and the heteroaryl (e.g., pyridyl) or heterocycloalkyl (e.g., pyrrolidine) moiety is substituted with 1  $-(C_1-C_6\text{alkyl})$  (e.g.,  $-(C_1-C_4\text{alkyl})$ ,  $-(C_1-C_3\text{alkyl})$ , and  $-(C_1-C_2\text{alkyl})$ ), and in one example methyl). Other examples include any one of the examples described in this paragraph wherein  $R^{10}$  is selected from the group consisting of H, F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. Other examples include any one of the examples described in this paragraph wherein  $R^{10}$  is selected from the group consisting of H, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. Other examples include any one of the examples described in this paragraph wherein  $R^{10}$  is F, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. Other examples include any one of the examples described in this paragraph wherein  $R^{10}$  is methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. Other examples include any one of the examples described in this paragraph wherein  $R^{10}$  is H, and  $R^{11}$  is H. Other examples include any one of the examples described in this paragraph wherein  $R^{10}$  is F, and  $R^{11}$  is H. Other examples include any one of the examples described in this paragraph wherein  $R^{10}$  is methyl, and  $R^{11}$  is H.

In another example  $R^4$  and  $R^5$  are independently selected from the group consisting of: H, methyl, ethyl, propyl, isopropyl, and  $-(CH_2)_2-O-CH_3$ ;  $R^2$  is selected from the group consisting of: B1, B2, B3, B4, B5, B6, B7, B8, and B9,  $R^{10}$  is selected from the group consisting of: H, F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is H and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is F and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is methyl and  $R^{11}$  is H.

In another example  $R^4$  and  $R^5$  are independently selected from the group consisting of: H, methyl, ethyl, propyl, isopropyl, and  $-(CH_2)_2-O-CH_3$ ;  $R^2$  is selected from the group consisting of: B29, B30, B31, B32, B33, B34, B35, B36, B37, B38, B39, B40, B41, B42, B43, and B44,  $R^{10}$  is selected from the group consisting of: H, F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is H and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is F and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is methyl and  $R^{11}$  is H.

- 65 -

In another example,  $R^4$  is H,  $R^5$  is selected from the group consisting of: methyl, ethyl, propyl, isopropyl, and  $-(CH_2)_2-O-CH_3$ ,  $R^2$  is selected from the group consisting of: B1, B2, B3, B4, B5, B6, B7, B8, and B9,  $R^{10}$  is selected from the group consisting of: H, F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is H and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is F and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is methyl and  $R^{11}$  is H.

In another example,  $R^4$  is H,  $R^5$  is selected from the group consisting of: methyl, ethyl, propyl, isopropyl, and  $-(CH_2)_2-O-CH_3$ ,  $R^2$  is selected from the group consisting of: B29, B30, B31, B32, B33, B34, B35, B36, B37, B38, B39, B40, B41, B42, B43, and B44,  $R^{10}$  is selected from the group consisting of: H, F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is H and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is F and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is methyl and  $R^{11}$  is H.

In another example,  $R^4$  is H,  $R^5$  is selected from the group consisting of: methyl, ethyl, propyl, and isopropyl,  $R^2$  is selected from the group consisting of: B1, B2, B3, B4, B5, B6, B7, B8, and B9,  $R^{10}$  is selected from the group consisting of: H, F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is H and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is F and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is methyl and  $R^{11}$  is H.

In another example,  $R^4$  is H,  $R^5$  is selected from the group consisting of: methyl, ethyl, propyl, and isopropyl,  $R^2$  is selected from the group consisting of: B29, B30, B31, B32, B33, B34, B35, B36, B37, B38, B39, B40, B41, B42, B43, and B44,  $R^{10}$  is selected from the group consisting of: H, F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is H and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is F and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is methyl and  $R^{11}$  is H.

In other examples of this invention,  $R^1$ ,  $R^{10}$  and  $R^{11}$  are as defined for formula (1), and  $R^4$  is H, and  $R^5$  is selected from the group consisting of: methyl, ethyl, propyl, and isopropyl, and  $R^2$  is selected from the group consisting of: B1 to B9, and B29 to B44. In other examples

- 66 -

of this invention,  $R^1$ ,  $R^{10}$  and  $R^{11}$  are as defined for formula (1), and  $R^4$  is H, and  $R^5$  is selected from the group consisting of: methyl, ethyl, propyl, and isopropyl, and  $R^2$  is, in one example, B1, and in another example B2, and in another example B3, and in another example B9, and in another example B29, and in another example B30, and in another example B31, and in another example B32, and in another example B33, and in another example B34, and in another example B35, and in another example B36, and in another example B37, and in another example B38, and in another example B39, and in another example B40, and in another example B41, and in another example B42, and in another example B43, and in another example B44. For ease of identification, the examples in this paragraph are the examples of Group 1.

In other examples of this invention,  $R^1$ ,  $R^{10}$  and  $R^{11}$  are as defined for formula (1), and  $R^4$  is H, and  $R^5$  is selected from the group consisting of: methyl and ethyl, and  $R^2$  is selected from the group consisting of: B1 to B9, and B29 to B44. In other examples of this invention,  $R^1$ ,  $R^{10}$  and  $R^{11}$  are as defined for formula (1), and  $R^4$  is H, and  $R^5$  is selected from the group consisting of: methyl and ethyl, and  $R^2$  is, in one example, B1, and in another example B2, and in another example B3, and in another example B9, and in another example B29, and in another example B30, and in another example B31, and in another example B32, and in another example B33, and in another example B34, and in another example B35, and in another example B36, and in another example B37, and in another example B38, and in another example B39, and in another example B40, and in another example B41, and in another example B42, and in another example B43, and in another example B44. For ease of identification, the examples in this paragraph are the examples of Group 2.

In another example  $R^4$  and  $R^5$  are independently selected from the group consisting of: H, methyl, and ethyl,  $R^2$  is selected from the group consisting of: B1, B2, B3, B4, B5, B6, B7, B8, and B9,  $R^{10}$  is selected from the group consisting of: H, F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is H and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is F and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is methyl and  $R^{11}$  is H.

In another example  $R^4$  and  $R^5$  are independently selected from the group consisting of: H, methyl, and ethyl,  $R^2$  is selected from the group consisting of: B29, B30, B31, B32, B33, B34, B35, B36, B37, B38, B39, B40, B41, B42, B43, and B44,  $R^{10}$  is selected from the group consisting of: H, F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and

- 67 -

methyl. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is H and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is F and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is methyl and  $R^{11}$  is H. .

5           In another example,  $R^4$  is H,  $R^5$  is selected from the group consisting of: methyl and ethyl,  $R^2$  is selected from the group consisting of: B1, B2, B3, B4, B5, B6, B7, B8, and B9,  $R^{10}$  is selected from the group consisting of: H, F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is H and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this  
10          paragraph and  $R^{10}$  is F and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is methyl and  $R^{11}$  is H.

          In another example,  $R^4$  is H,  $R^5$  is selected from the group consisting of: methyl and ethyl,  $R^2$  is selected from the group consisting of: B29, B30, B31, B32, B33, B34, B35, B36, B37, B38, B39, B40, B41, B42, B43, and B44,  $R^{10}$  is selected from the group consisting of: H,  
15          F, and methyl, and  $R^{11}$  is selected from the group consisting of: H, F and methyl. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is H and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is F and  $R^{11}$  is H. In another example,  $R^2$ ,  $R^4$ , and  $R^5$  are as defined in this paragraph and  $R^{10}$  is methyl and  $R^{11}$  is H.

          In another example,  $R^1$  is selected from the group consisting of:  $-NH_2$ , A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17 and A18, and  $R^2$  is selected  
20          from the group consisting of: B1, B2, B3, B4, B5, B6, B7, B8, and B9. In another example,  $R^1$  is selected from the group consisting of:  $-NH_2$ , A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17 and A18, and  $R^2$  is selected from the group consisting of: B29, B30, B31, B32, B33, B34, B35, B36, B37, B38, B39, B40, B41, B42, B43, and B44.

25          In another example,  $R^1$  is selected from the group consisting of: A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17 and A18, and  $R^2$  is selected from the group consisting of: B1, B2, B3, B4, B5, B6, B7, B8, and B9.

          In another example,  $R^1$  is selected from the group consisting of: A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17 and A18, and  $R^2$  is selected from  
30          the group consisting of: B29, B30, B31, B32, B33, B34, B35, B36, B37, B38, B39, B40, B41, B42, B43, and B44.

          In other examples of this invention,  $R^{10}$  and  $R^{11}$  are as defined for formula (1),  $R^1$  is selected from the group consisting of: A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12,

- 68 -

A13, A14, A15, A16, A17 and A18, and R<sup>2</sup> is, in one example, B1, and in another example B2, and in another example B3, and in another example B9, and in another example B29, and in another example B30, and in another example B31, and in another example B32, and in another example B33, and in another example B34, and in another example B35, and in  
5 another example B36, and in another example B37, and in another example B38, and in another example B39, and in another example B40, and in another example B41, and in another example B42, and in another example B43, and in another example B44. In other examples of this invention, R<sup>10</sup> and R<sup>11</sup> are as defined for formula (1), R<sup>1</sup> is selected from the group consisting of: A1, A2, A3, A4, A5, A6, A8, A9, A10, A11, A12, A13, A14, A15, A16,  
10 A17 and A18, and R<sup>2</sup> is, in one example, B1, and in another example B2, and in another example B3, and in another example B9, and in another example B29, and in another example B30, and in another example B31, and in another example B32, and in another example B33, and in another example B34, and in another example B35, and in another example B36, and in another example B37, and in another example B38, and in another example B39, and in  
15 another example B40, and in another example B41, and in another example B42, and in another example B43, and in another example B44. For ease of identification, the examples in this paragraph are the examples of Group 3.

Other examples include any example in anyone of Groups 1, 2 and 3 above, wherein R<sup>10</sup> is selected from the group consisting of: H, F, and methyl, and R<sup>11</sup> is selected from the  
20 group consisting of: H, F and methyl. Other examples include any example in anyone of Groups 1, 2 and 3 above, wherein R<sup>10</sup> is H and R<sup>11</sup> is H, and in another example R<sup>10</sup> is F and R<sup>11</sup> is H, and in another example R<sup>10</sup> is methyl and R<sup>11</sup> is H.

Representative compounds of the invention include, but are not limited to, the final compounds of Examples 1 to 60. Representative compounds of this invention also include,  
25 but are not limited to, the final compounds of Examples 61-458. Thus, one example of this invention is the compound of Ex. 1, another is the compound of Ex. 2, another is the compound of Ex. 3, another is the compound of Ex. 4, another is the compound of Ex. 5, another is the compound of Ex. 6, another is the compound of Ex. 7, another is the compound of Ex. 8, another is the compound of Ex. 9, another is the compound of Ex. 10, another is the  
30 compound of Ex. 11, another is the compound of Ex. 12, another is the compound of Ex. 13, another is the compound of Ex. 14, another is the compound of Ex. 15, another is the compound of Ex. 16, another is the compound of Ex. 17, another is the compound of Ex. 18, another is the compound of Ex. 19, another is the compound of Ex. 20, another is the

- 69 -

compound of Ex. 21, another is the compound of Ex. 22, another is the compound of Ex. 23,  
another is the compound of Ex. 24, another is the compound of Ex. 25, another is the  
compound of Ex. 26, another is the compound of Ex. 27, another is the compound of Ex. 28,  
another is the compound of Ex. 29, another is the compound of Ex. 30, another is the  
5 compound of Ex. 31, another is the compound of Ex. 32, another is the compound of Ex. 33,  
another is the compound of Ex. 34, another is the compound of Ex. 35, another is the  
compound of Ex. 36, another is the compound of Ex. 37, another is the compound of Ex. 38,  
another is the compound of Ex. 39, another is the compound of Ex. 40, another is the  
compound of Ex. 41, another is the compound of Ex. 42, another is the compound of Ex. 43,  
10 another is the compound of Ex. 44, another is the compound of Ex. 45, another is the  
compound of Ex. 46, another is the compound of Ex. 47, another is the compound of Ex. 48,  
another is the compound of Ex. 49, another is the compound of Ex. 50, another is the  
compound of Ex. 51, another is the compound of Ex. 52, another is the compound of Ex. 53,  
another is the compound of Ex. 54, another is the compound of Ex. 55, another is the  
15 compound of Ex. 56, another is the compound of Ex. 57, another is the compound of Ex. 58,  
another is the compound of Ex. 59, another is the compound of Ex. 60. Other examples  
include any one of the final compounds of Examples 61-458 as if each was listed individually  
as a separate example.

Other examples of this invention include pharmaceutically acceptable salts of the  
20 compounds of formula (1).

Other examples include the pharmaceutically acceptable salts of any one of the final  
compounds of Examples 1 to 60, and in other examples the pharmaceutically acceptable salts  
of any one of the final compounds of Examples 61-458.

Other examples of this invention include pharmaceutically acceptable esters of the  
25 compounds of formula (1). Other examples of this invention include pharmaceutically  
acceptable esters of any one of the final compounds of Examples 1 to 60, and in other  
examples the pharmaceutically acceptable esters of any one of the final compounds of  
Examples 61-458.

Other examples of this invention include solvates of the compounds of formula (1).  
30 Other examples of this invention include the solvates of any one of the final compounds of  
Examples 1 to 60, and in other examples the solvates of any one of the final compounds of  
Examples 61-458.

- 70 -

Other examples of this invention include pharmaceutical compositions comprising at least one compound of formula (1), and a pharmaceutically acceptable carrier.

Other examples of this invention include pharmaceutical compositions comprising at least one compound selected from the group consisting of the final compounds of Examples 1  
5 to 60, and a pharmaceutically acceptable carrier, and in other examples at least one compound selected from the group consisting of the final compounds of Examples 61-458, and a pharmaceutically acceptable carrier.

Other examples of this invention include pharmaceutical compositions comprising one  
10 compound of formula (1), and a pharmaceutically acceptable carrier.

Other examples of this invention include pharmaceutical compositions comprising one  
10 compound selected from the group consisting of the final compounds of Examples 1 to 60, and a pharmaceutically acceptable carrier, and in other examples one compound selected from the group consisting of the final compounds of Examples 61-458, and a pharmaceutically acceptable carrier.

15 Other examples of this invention include pharmaceutical compositions comprising at least one pharmaceutically acceptable salt of at least one compound of formula (1), and a pharmaceutically acceptable carrier.

20 Other examples of this invention include pharmaceutical compositions comprising at least one pharmaceutically acceptable salt of one compound selected from the group consisting of the final compounds of Examples 1 to 60, and a pharmaceutically acceptable carrier, and in other examples at least one pharmaceutically acceptable salt of one compound selected from the group consisting of the final compounds of Examples 61-458, and a pharmaceutically acceptable carrier.

25 Other examples of this invention include pharmaceutical compositions comprising one pharmaceutically acceptable salt of one compound of formula (1), and a pharmaceutically acceptable carrier.

30 Other examples of this invention include pharmaceutical compositions comprising one pharmaceutically acceptable salt of one compound selected from the group consisting of the final compounds of Examples 1 to 60, and a pharmaceutically acceptable carrier, and in other examples one pharmaceutically acceptable salt of one compound selected from the group consisting of the final compounds of Examples 61-458, and a pharmaceutically acceptable carrier.

- 71 -

Other examples of this invention include the compounds of formula (1) in pure and isolate form.

Other examples of this invention include any one of the final compounds of Examples 1 to 60 in pure and isolated form, and in other examples at least one pharmaceutically  
5 acceptable salt of one compound selected from the group consisting of the final compounds of Examples 61-458, and a pharmaceutically acceptable carrier.

Another example of this invention is a pharmaceutical composition comprising an effective amount of a compound of formula (1) (e.g., a final compound of Examples 1 to 60), a  
10 chemotherapeutic agent, and a pharmaceutically acceptable carrier.

The compounds of the invention are useful in preparing a medicament that is useful in  
15 treating cancer.

The compounds of this invention inhibit the activity of ERK2. Thus, this invention further provides a method of inhibiting ERK in mammals, especially humans, by the administration of an effective amount of one or more (e.g., one) compounds of this invention.  
20 The administration of the compounds of this invention to patients, to inhibit ERK2, is useful in the treatment of cancer.

In any of the methods of treating cancer described herein, unless stated otherwise, the methods can optionally include the administration of an effective amount of one or more (e.g., 1, 2 or 3, or 1 or 2, or 1) chemotherapeutic agents. The chemotherapeutic agents can be  
25 administered currently or sequentially with the compounds of this invention. In the treatment of breast cancer, the compounds of formula (1) can be administered in a treatment protocol which also includes the administration of an effective amount of at least one (e.g., 1-3, or 1-2, or 1) antihormonal agent (i.e., the methods of treating breast cancer can include hormonal therapies).

The methods of treating cancer described herein include methods wherein a combination of drugs (i.e., compounds, or pharmaceutically active ingredients, or pharmaceutical compositions) are used (i.e., the methods of treating cancer of this invention include combination therapies). Those skilled in the art will appreciate that the drugs are generally administered individually as a pharmaceutical composition. The use of a  
30 pharmaceutical composition comprising more than one drug is within the scope of this invention.

The methods of treating cancer described herein include methods comprising administering a therapeutically effective amount of a compound of the instant invention in

- 72 -

combination with radiation therapy and/or in combination with a second compound selected from the group consisting of: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxicostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a  
5 reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR- $\gamma$  agonists, PPAR- $\delta$  agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic,  $\gamma$ -secretase and/or NOTCH inhibitors, agents that  
10 interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint, and any of the therapeutic agents listed herein.

In any of the methods of treating cancer described herein, unless stated otherwise, the methods can optionally include the administration of an effective amount of radiation therapy. For radiation therapy,  $\gamma$ -radiation is preferred.

15 Thus, another example of this invention is a method of treating cancer in a patient in need of such treatment, said method comprising administering an effective amount of a compound of formula (1). Another example of this invention is a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a compound of formula (1), and an effective amount of at least one (e.g.,  
20 1-3, 1-2, or 1) chemotherapeutic agent.

The compounds, compositions and methods provided herein are useful for the treatment of cancer. Cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: (1) Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; (2) Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma, non-small cell; (3)  
25 Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal  
30 adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colorectal, rectal; (4)

- 73 -

Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); (5) Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; (6) Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; (7) Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); (8) Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; (9) Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelomonocytic (CMML), myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; (10) Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and (11) Adrenal glands: neuroblastoma. Examples of cancer that may be treated by the compounds, compositions and methods of the invention include thyroid cancer, anaplastic thyroid carcinoma, epidermal cancer, head and neck cancer (e.g., squamous cell cancer of the head and neck), sarcoma, tetracarcinoma, hepatoma and multiple myeloma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

- 74 -

In the treatment of breast cancer (e.g., postmenopausal and premenopausal breast cancer, e.g., hormone-dependent breast cancer) the compound of formula (1) may be used with an effective amount of at least one antihormonal agent selected from the group consisting of: (a) aromatase inhibitors, (b) antiestrogens, and (c) LHRH analogues; and optionally an effective amount of at least one chemotherapeutic agent. Examples of aromatase inhibitors include but are not limited to: Anastrozole (e.g., Arimidex), Letrozole (e.g., Femara), Exemestane (Aromasin), Fadrozole and Formestane (e.g., Lentaron). Examples of antiestrogens include but are not limited to: Tamoxifen (e.g., Nolvadex), Fulvestrant (e.g., Faslodex), Raloxifene (e.g., Evista), and Acolbifene. Examples of LHRH analogues include but are not limited to: Goserelin (e.g., Zoladex) and Leuprolide (e.g., Leuprolide Acetate, such as Lupron or Lupron Depot). Examples of chemotherapeutic agents include but are not limited to: Trastuzumab (e.g., Herceptin), Gefitinib (e.g., Iressa), Erlotinib (e.g., Erlotinib HCl, such as Tarceva), Bevacizumab (e.g., Avastin), Cetuximab (e.g., Erbitux), and Bortezomib (e.g., Velcade).

In one example of this invention the cancer treated is colo-rectal cancer (such as, for example, colon adenocarcinoma and colon adenoma). Thus, another example of this invention is a method of treating colo-rectal cancer in a patient in need of such treatment, said method comprising administering an effective amount of a compound of formula (1) (e.g., a final compound of Examples 1 to 60, and in another example the final compounds of Examples 61-458), or a pharmaceutically acceptable salt thereof, to said patient. Another example is a method of treating colo-rectal cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a compound selected from the group consisting of: the final compounds of Examples 2, 5, 27-35, 39-40, 42, 43, 46-49, 68-70, 109-110, 113-115, 123-127, 129, 130, 220-222, 229, 272-273, 287-289, 366-367, 385-386 and 389-390, and in another example the final compounds of Examples 2, 5, 27-35, 39-40, 42, 43, and 47-49, or a pharmaceutically acceptable salt thereof. Another example of this invention is a method of treating colo-rectal cancer in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a compound of formula (1) (e.g., a final compound of Examples 1 to 60, and in another example the final compounds of Examples 61-458), or a pharmaceutically acceptable salt thereof, and an effective amount of at least one (e.g., 1-3, or 1-2, or 1) chemotherapeutic agent.

In one example of this invention the cancer treated is melanoma. Thus, another example of this invention is directed to a method of treating melanoma in a patient in need of

- 75 -

such treatment, said method comprising administering an effective amount of a compound of formula (1) (e.g. a final compound of Examples 1 to 60, and in another example the final compounds of Examples 61-458), or a pharmaceutically acceptable salt thereof, to said patient. Another example is a method of treating melanoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a compound selected from the group consisting of: the final compounds of Examples 2, 5, 27-35, 39-40, 42, 43, 46-49, 68-70, 109-110, 113-115, 123-127, 129, 130, 220-222, 229, 272-273, 287-289, 366-367, 385-386 and 389-390, and in another example the final compounds of Examples 2, 5, 27-35, 39-40, 42, 43, and 47-49, or a pharmaceutically acceptable carrier thereof. Another example of this invention is a method of treating melanoma in a patient in need of such treatment, said method comprising administering to said patient an effective amount of a compound of formula (1) (e.g., a final compound of Examples 1 to 60, and in another example the final compounds of Examples 61-458), or a pharmaceutically acceptable salt thereof, and an effective amount of at least one (e.g., 1-3, or 1-2, or 1) chemotherapeutic agent.

The compounds of the invention are also useful in preparing a medicament that is useful in treating cancer.

The compounds of this invention may be administered to mammals, including humans, either alone or, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic

- 76 -

acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a  
5 sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium  
10 phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for  
15 example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example  
20 heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-  
25 hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid  
30 paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

- 77 -

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional  
5 excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents  
10 may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

15 Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water,  
20 Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a  
25 microemulsion.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous  
30 intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension

- 78 -

may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, 5 fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of the instant invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by 10 mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

15 For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of the instant invention are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, 20 using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of 25 polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

When a composition according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

30 The dosage regimen utilizing the compounds of the instant invention can be selected in accordance with a variety of factors including type, species, age, weight, sex and the type of cancer being treated; the severity (i.e., stage) of the cancer to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or

- 79 -

salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to treat, for example, to prevent, inhibit (fully or partially) or arrest the progress of the disease. Compounds of this invention can be administered in a total daily dose of 10 mg to 3000 mg. For example, compounds of the  
5 instant invention can be administered in a total daily dose of up to 3000 mg. Compounds of the instant invention can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). Compounds of the instant invention can be administered at a total daily dosage of up to 3000 mg, e.g., 200 mg, 300 mg, 400 mg, 600 mg, 800 mg, 1000 mg, 2000mg or 3000mg, which can be administered in one daily dose  
10 or can be divided into multiple daily doses as described above.

In addition, the administration can be continuous, i.e., every day, or intermittently. The terms "intermittent" or "intermittently" as used herein means stopping and starting at either regular or irregular intervals. For example, intermittent administration of a compound of the  
15 instant invention may be administration one to six days per week or it may mean administration in cycles (e.g. daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week) or it may mean administration on alternate days. The compounds of this invention may be administered discontinuously rather than continuously during the treatment cycle. Thus, the compounds of this invention may be administered daily for one or more weeks during the cycle and discontinued for one or more  
20 weeks during the cycle, with this pattern of administration repeating during the treatment cycle (e.g., administration for a week and then discontinued for a week). This discontinuous treatment may also be based upon numbers of days rather than a full week. The number of days (or weeks) that the compounds of this invention are not dosed do not have to equal the number of days (or weeks) wherein the compounds of this invention are dosed. Usually, if a  
25 discontinuous dosing protocol is used, the number of days or weeks that the compounds of this invention are dosed is at least equal to or greater than the number of days or weeks that the compounds of this invention are not dosed.

In addition, the compounds of the instant invention may be administered according to any of the schedules described above, consecutively for a few weeks, followed by a rest  
30 period. For example, the compounds of the instant invention may be administered according to any one of the schedules described above from two to eight weeks, followed by a rest period of one week, or twice daily at a dose of 100 - 500 mg for three to five days a week. In another

- 80 -

particular embodiment, the compounds of the instant invention may be administered three times daily for two consecutive weeks, followed by one week of rest.

Any one or more of the specific dosages and dosage schedules of the compounds of the instant invention, may also be applicable to any one or more of the therapeutic agents to be  
5 used in the combination treatment (hereinafter referred to as the "second therapeutic agent").

Moreover, the specific dosage and dosage schedule of this second therapeutic agent can further vary, and the optimal dose, dosing schedule and route of administration will be determined based upon the specific second therapeutic agent that is being used.

Of course, the route of administration of the compounds of the instant invention is  
10 independent of the route of administration of the second therapeutic agent. In an embodiment, the administration for a compound of the instant invention is oral administration. In another embodiment, the administration for a compound of the instant invention is intravenous administration. Thus, in accordance with these embodiments, a compound of the instant invention is administered orally or intravenously, and the second therapeutic agent can be  
15 administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form.

In addition, a compound of the instant invention and second therapeutic agent may be  
20 administered by the same mode of administration, i.e. both agents administered e.g. orally, by IV. However, it is also within the scope of the present invention to administer a compound of the instant invention by one mode of administration, e.g. oral, and to administer the second therapeutic agent by another mode of administration, e.g. IV or any other ones of the administration modes described hereinabove.

25 The first treatment procedure, administration of a compound of the instant invention, can take place prior to the second treatment procedure, i.e., the second therapeutic agent, after the treatment with the second therapeutic agent, at the same time as the treatment with the second therapeutic agent, or a combination thereof. For example, a total treatment period can be decided for a compound of the instant invention. The second therapeutic agent can be  
30 administered prior to onset of treatment with a compound of the instant invention or following treatment with a compound of the instant invention. In addition, anti-cancer treatment can be administered during the period of administration of a compound of the instant invention but does not need to occur over the entire treatment period of a compound of the instant invention.

- 81 -

The instant compounds are also useful in combination with therapeutic, chemotherapeutic and anti-cancer agents. Combinations of the presently disclosed compounds with therapeutic, chemotherapeutic and anti-cancer agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of*  
5 *Oncology* by V.T. Devita and S. Hellman (editors), 6<sup>th</sup> edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such agents include the following: estrogen receptor  
10 modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, inhibitors of cell proliferation and survival signaling, bisphosphonates, aromatase inhibitors, siRNA therapeutics,  $\gamma$ -secretase inhibitors, agents that interfere with receptor  
15 tyrosine kinases (RTKs) and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy.

“Estrogen receptor modulators” refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-  
20 piperidinyloxy)phenyl]-2H-1-benzopyran-3-yl]-phenyl)-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

“Androgen receptor modulators” refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 $\alpha$ -reductase inhibitors, nilutamide,  
25 flutamide, bicalutamide, liarozole, and abiraterone acetate.

“Retinoid receptor modulators” refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid,  $\alpha$ -difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-  
30 carboxyphenyl retinamide.

“Cytotoxic/cytostatic agents” refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia

- 82 -

activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, histone deacetylase inhibitors, inhibitors of kinases involved in mitotic progression, inhibitors of kinases involved in growth factor and cytokine signal transduction pathways, antimetabolites, biological response modifiers, hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors, ubiquitin ligase inhibitors, and aurora kinase inhibitors.

Examples of cytotoxic/cytostatic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxy-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032), Raf kinase inhibitors (such as Bay43-9006) and mTOR inhibitors (such as Wyeth's CCI-779).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin and MLN-341 (Velcade).

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincal leukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797. In an embodiment the epothilones are not included in the microtubule inhibitors/microtubule-stabilising agents.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrzolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in Publications WO03/039460, WO03/050064, WO03/050122, WO03/049527, WO03/049679, WO03/049678, WO04/039774, WO03/079973, WO03/099211, WO03/105855, WO03/106417, WO04/037171, WO04/058148, WO04/058700, WO04/126699, WO05/018638, WO05/019206, WO05/019205, WO05/018547, WO05/017190, US2005/0176776. In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK and inhibitors of Rab6-KIFL.

Examples of "histone deacetylase inhibitors" include, but are not limited to, SAHA, TSA, oxamflatin, PDX101, MG98 and scriptaid. Further reference to other histone deacetylase inhibitors may be found in the following manuscript; Miller, T.A. et al. *J. Med. Chem.* 46(24):5097-5116 (2003).

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK; in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1. An example of an "aurora kinase inhibitor" is VX-680.

“Antiproliferative agents” includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazoferin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone and trastuzumab.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

“HMG-CoA reductase inhibitors” refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR<sup>®</sup>; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR<sup>®</sup>; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL<sup>®</sup>; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL<sup>®</sup>; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR<sup>®</sup>; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL<sup>®</sup>; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefore the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

- 85 -

“Prenyl-protein transferase inhibitor” refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

5           Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, 10           WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 15           WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer*, Vol. 35, No. 9, pp.1394-1401 (1999).

“Angiogenesis inhibitors” refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 25           (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon- $\alpha$ , interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (*PNAS*, Vol. 89, p. 7384 (1992); 30           *JNCI*, Vol. 69, p. 475 (1982); *Arch. Ophthalmol.*, Vol. 108, p.573 (1990); *Anat. Rec.*, Vol. 238, p. 68 (1994); *FEBS Letters*, Vol. 372, p. 83 (1995); *Clin. Orthop.* Vol. 313, p. 76 (1995); *J. Mol. Endocrinol.*, Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, Vol. 75, p. 105 (1997); *Cancer Res.*, Vol. 57, p. 1625 (1997); *Cell*, Vol. 93, p. 705 (1998); *Intl. J. Mol. Med.*, Vol. 2, p. 715

- 86 -

(1998); *J. Biol. Chem.*, Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see  
5 Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature*, 362, 841-844 (1993); WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or  
10 inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354  
15 (2001)). TAFIa inhibitors have been described in U.S. Ser. Nos. 60/310,927 (filed August 8, 2001) and 60/349,925 (filed January 18, 2002).

“Agents that interfere with cell cycle checkpoints” refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the CHK1 and  
20 CHK2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

“Agents that interfere with receptor tyrosine kinases (RTKs)” refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met. Further agents include  
25 inhibitors of RTKs as described by Bume-Jensen and Hunter, *Nature*, 411:355-365, 2001.

“Inhibitors of cell proliferation and survival signalling pathway” refer to compounds that inhibit signal transduction cascades downstream of cell surface receptors. Such agents include inhibitors of serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO  
30 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469), inhibitors of Raf kinase (for

- 87 -

example BAY-43-9006 ), inhibitors of MEK (for example CI-1040 and PD-098059), inhibitors of mTOR (for example Wyeth CCI-779), and inhibitors of PI3K (for example LY294002).

As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an  
5 NSAID is potent if it possesses an IC<sub>50</sub> for the inhibition of COX-2 of 1μM or less as measured by cell or microsomal assays.

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1  
10 of at least 100 fold as measured by the ratio of IC<sub>50</sub> for COX-2 over IC<sub>50</sub> for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Patent 5,474,995, U.S. Patent 5,861,419, U.S. Patent 6,001,843, U.S. Patent 6,020,343, U.S. Patent 5,409,944, U.S. Patent 5,436,265, U.S. Patent 5,536,752, U.S. Patent 5,550,142, U.S. Patent 5,604,260, U.S. 5,698,584, U.S. Patent 5,710,140, WO 94/15932, U.S.  
15 Patent 5,344,991, U.S. Patent 5,134,142, U.S. Patent 5,380,738, U.S. Patent 5,393,790, U.S. Patent 5,466,823, U.S. Patent 5,633,272 and U.S. Patent 5,932,598, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are:  
20 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5*H*)-furanone; and 5-chloro-3-(4-methylsulfonyl)-phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following: parecoxib, BEXTRA® and CELEBREX® or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin,  
25 ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1*H*-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-*N*-methyl-4,2-pyrrolocarbonylimino[*N*-methyl-4,2-pyrrole]-carbonylimino]-bis-  
30 (1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the α<sub>v</sub>β<sub>3</sub> integrin, to compounds

- 88 -

which selectively antagonize, inhibit or counteract binding of a physiological ligand to the  $\alpha_v\beta_5$  integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the  $\alpha_v\beta_3$  integrin and the  $\alpha_v\beta_5$  integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the  $\alpha_v\beta_6$ ,  $\alpha_v\beta_8$ ,  $\alpha_1\beta_1$ ,  $\alpha_2\beta_1$ ,  $\alpha_5\beta_1$ ,  $\alpha_6\beta_1$  and  $\alpha_6\beta_4$  integrins. The term also refers to antagonists of any combination of  $\alpha_v\beta_3$ ,  $\alpha_v\beta_5$ ,  $\alpha_v\beta_6$ ,  $\alpha_v\beta_8$ ,  $\alpha_1\beta_1$ ,  $\alpha_2\beta_1$ ,  $\alpha_5\beta_1$ ,  $\alpha_6\beta_1$  and  $\alpha_6\beta_4$  integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidene]indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxy]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR- $\gamma$  (i.e., PPAR-gamma) agonists and PPAR- $\delta$  (i.e., PPAR-delta) agonists are useful in the treatment of certain malignancies. PPAR- $\gamma$  and PPAR- $\delta$  are the nuclear peroxisome proliferator-activated receptors  $\gamma$  and  $\delta$ . The expression of PPAR- $\gamma$  on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999; 274:9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR- $\gamma$  agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthalmol.* 2001; 119:709-717). Examples of PPAR- $\gamma$  agonists and PPAR- $\gamma/\alpha$  agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622,

GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

5           Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (*Am. J. Hum. Genet.* 61:785-789, 1997) and Kufe et al (*Cancer Medicine*, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are  
10           not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," *Gene Therapy*, August 1998;5(8):1105-13), and interferon gamma (*J. Immunol.* 2000;164:217-222).

15           The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valsopodar).

20           A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor  
25           antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S. Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for  
30           example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In another embodiment, conjunctive therapy with an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is

- 90 -

disclosed for the treatment or prevention of emesis that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; 5 European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913, 0 590 152, 10 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 15 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 20 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 25 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the 30 compounds of the present invention is selected from: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Patent No. 5,719,147.

- 91 -

A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous erythropoiesis receptor activator (such as epoetin alfa).

5 A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

10 A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with P450 inhibitors including: xenobiotics, quinidine, tyramine, ketoconazole, testosterone, quinine, methyrapone, caffeine, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin, cocaine, furafyline, cimetidine,  
15 dextromethorphan, ritonavir, indinavir, amprenavir, diltiazem, terfenadine, verapamil, cortisol, itraconazole, mibefradil, nefazodone and nelfinavir.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with Pgp and/or BCRP inhibitors including: cyclosporin A, PSC833, GF120918, cremophorEL, fumitremorgin C, Ko132, Ko134, Iressa, Imatinib mesylate, EKI-  
20 785, C11033, novobiocin, diethylstilbestrol, tamoxifen, reserpine, VX-710, tryprostatin A, flavonoids, ritonavir, saquinavir, nelfinavir, omeprazole, quinidine, verapamil, terfenadine, ketoconazole, nifedipine, FK506, amiodarone, XR9576, indinavir, amprenavir, cortisol, testosterone, LY335979, OC144-093, erythromycin, vincristine, digoxin and talinolol.

25 A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and  
30 tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

- 92 -

A compound of the instant invention may also be useful for treating or preventing breast cancer in combination with aromatase inhibitors. Examples of aromatase inhibitors include but are not limited to: anastrozole, letrozole and exemestane.

5 A compound of the instant invention may also be useful for treating or preventing cancer in combination with siRNA therapeutics.

The compounds of the instant invention may also be administered in combination with  $\gamma$ -secretase inhibitors and/or inhibitors of NOTCH signaling. Such inhibitors include compounds described in WO 01/90084, WO 02/30912, WO 01/70677, WO 03/013506, WO 02/36555, WO 03/093252, WO 03/093264, WO 03/093251, WO 03/093253, WO 10 2004/039800, WO 2004/039370, WO 2005/030731, WO 2005/014553, USSN 10/957,251, WO 2004/089911, WO 02/081435, WO 02/081433, WO 03/018543, WO 2004/031137, WO 2004/031139, WO 2004/031138, WO 2004/101538, WO 2004/101539 and WO 02/47671 (including LY-450139).

15 A compound of the instant invention may also be useful for treating or preventing cancer in combination with PARP inhibitors.

A compound of the instant invention may also be useful for treating cancer in combination with the following therapeutic agents: abarelix (Plenaxis depot<sup>®</sup>); aldesleukin (Prokine<sup>®</sup>); Aldesleukin (Proleukin<sup>®</sup>); Alemtuzumab (Campath<sup>®</sup>); alitretinoin (Panretin<sup>®</sup>); allopurinol (Zyloprim<sup>®</sup>); altretamine (Hexalen<sup>®</sup>); amifostine (Ethyol<sup>®</sup>); anastrozole (Arimidex<sup>®</sup>); arsenic trioxide (Trisenox<sup>®</sup>); asparaginase (Elspar<sup>®</sup>); azacitidine (Vidaza<sup>®</sup>); 20 bevacuzimab (Avastin<sup>®</sup>); bexarotene capsules (Targretin<sup>®</sup>); bexarotene gel (Targretin<sup>®</sup>); bleomycin (Blenoxane<sup>®</sup>); bortezomib (Velcade<sup>®</sup>); busulfan intravenous (Busulfex<sup>®</sup>); busulfan oral (Myleran<sup>®</sup>); calusterone (Methosarb<sup>®</sup>); capecitabine (Xeloda<sup>®</sup>); carboplatin (Paraplatin<sup>®</sup>); carmustine (BCNU<sup>®</sup>, BiCNU<sup>®</sup>); carmustine (Gliadel<sup>®</sup>); carmustine with Polifeprosan 20 Implant (Gliadel Wafer<sup>®</sup>); celecoxib (Celebrex<sup>®</sup>); cetuximab (Erbix<sup>®</sup>); 25 chlorambucil (Leukeran<sup>®</sup>); cisplatin (Platinol<sup>®</sup>); cladribine (Leustatin<sup>®</sup>, 2-CdA<sup>®</sup>); clofarabine (Clolar<sup>®</sup>); cyclophosphamide (Cytosan<sup>®</sup>, Neosar<sup>®</sup>); cyclophosphamide (Cytosan Injection<sup>®</sup>); cyclophosphamide (Cytosan Tablet<sup>®</sup>); cytarabine (Cytosar-U<sup>®</sup>); cytarabine liposomal (DepoCyt<sup>®</sup>); dacarbazine (DTIC-Dome<sup>®</sup>); dactinomycin, actinomycin D 30 (Cosmegen<sup>®</sup>); Darbepoetin alfa (Aranesp<sup>®</sup>); daunorubicin liposomal (DanuoXome<sup>®</sup>); daunorubicin, daunomycin (Daunorubicin<sup>®</sup>); daunorubicin, daunomycin (Cerubidine<sup>®</sup>); Denileukin diftitox (Ontak<sup>®</sup>); dexrazoxane (Zinecard<sup>®</sup>); docetaxel (Taxotere<sup>®</sup>); doxorubicin

- 93 -

(Adriamycin PFS<sup>®</sup>); doxorubicin (Adriamycin<sup>®</sup>, Rubex<sup>®</sup>); doxorubicin (Adriamycin PFS Injection<sup>®</sup>); doxorubicin liposomal (Doxil<sup>®</sup>); DROMOSTANOLONE PROPIONATE (DROMOSTANOLONE<sup>®</sup>); DROMOSTANOLONE PROPIONATE (MASTERONE INJECTION<sup>®</sup>); Elliott's B Solution (Elliott's B Solution<sup>®</sup>); epirubicin (Ellence<sup>®</sup>); Epoetin alfa (epogen<sup>®</sup>); erlotinib (Tarceva<sup>®</sup>); estramustine (Emcyt<sup>®</sup>); etoposide phosphate (Etopophos<sup>®</sup>); etoposide, VP-16 (Vepesid<sup>®</sup>); exemestane (Aromasin<sup>®</sup>); Filgrastim (Neupogen<sup>®</sup>); floxuridine (intraarterial) (FU DR<sup>®</sup>); fludarabine (Fludara<sup>®</sup>); fluorouracil, 5-FU (Adrucil<sup>®</sup>); fulvestrant (Faslodex<sup>®</sup>); gefitinib (Iressa<sup>®</sup>); gemcitabine (Gemzar<sup>®</sup>); gemtuzumab ozogamicin (Mylotarg<sup>®</sup>); goserelin acetate (Zoladex Implant<sup>®</sup>); goserelin acetate (Zoladex<sup>®</sup>); histrelin acetate (Histrelin implant<sup>®</sup>); hydroxyurea (Hydrea<sup>®</sup>); Ibritumomab Tiuxetan (Zevalin<sup>®</sup>); idarubicin (Idamycin<sup>®</sup>); ifosfamide (IFEX<sup>®</sup>); imatinib mesylate (Gleevec<sup>®</sup>); interferon alfa 2a (Roferon A<sup>®</sup>); Interferon alfa-2b (Intron A<sup>®</sup>); irinotecan (Camptosar<sup>®</sup>); lenalidomide (Revlimid<sup>®</sup>); letrozole (Femara<sup>®</sup>); leucovorin (Wellcovorin<sup>®</sup>, Leucovorin<sup>®</sup>); Leuprolide Acetate (Eligard<sup>®</sup>); levamisole (Ergamisol<sup>®</sup>); lomustine, CCNU (CeeBU<sup>®</sup>); meclorethamine, nitrogen mustard (Mustargen<sup>®</sup>); megestrol acetate (Megace<sup>®</sup>); melphalan, L-PAM (Alkeran<sup>®</sup>); mercaptopurine, 6-MP (Purinethol<sup>®</sup>); mesna (Mesnex<sup>®</sup>); mesna (Mesnex tabs<sup>®</sup>); methotrexate (Methotrexate<sup>®</sup>); methoxsalen (Uvadex<sup>®</sup>); mitomycin C (Mutamycin<sup>®</sup>); mitotane (Lysodren<sup>®</sup>); mitoxantrone (Novantrone<sup>®</sup>); nandrolone phenpropionate (Durabolin-50<sup>®</sup>); nelarabine (Arranon<sup>®</sup>); Nofetumomab (Verluma<sup>®</sup>); Oprelvekin (Neumega<sup>®</sup>); oxaliplatin (Eloxatin<sup>®</sup>); paclitaxel (Paxene<sup>®</sup>); paclitaxel (Taxol<sup>®</sup>); paclitaxel protein-bound particles (Abraxane<sup>®</sup>); palifermin (Kepivance<sup>®</sup>); pamidronate (Aredia<sup>®</sup>); pegademase (Adagen (Pegademase Bovine)<sup>®</sup>); pegaspargase (Oncaspar<sup>®</sup>); Pegfilgrastim (Neulasta<sup>®</sup>); pemetrexed disodium (Alimta<sup>®</sup>); pentostatin (Nipent<sup>®</sup>); pipobroman (Vercyte<sup>®</sup>); plicamycin, mithramycin (Mithracin<sup>®</sup>); porfimer sodium (Photofrin<sup>®</sup>); procarbazine (Matulane<sup>®</sup>); quinacrine (Atabrine<sup>®</sup>); Rasburicase (Elitek<sup>®</sup>); Rituximab (Rituxan<sup>®</sup>); Ridaforolimus; sargramostim (Leukine<sup>®</sup>); Sargramostim (Prokine<sup>®</sup>); sorafenib (Nexavar<sup>®</sup>); streptozocin (Zanosar<sup>®</sup>); sunitinib maleate (Sutent<sup>®</sup>); talc (Sclerosol<sup>®</sup>); tamoxifen (Nolvadex<sup>®</sup>); temozolomide (Temodar<sup>®</sup>); teniposide, VM-26 (Vumon<sup>®</sup>); testolactone (Teslac<sup>®</sup>); thioguanine, 6-TG (Thioguanine<sup>®</sup>); thiotepa (Thioplex<sup>®</sup>); topotecan (Hycamtin<sup>®</sup>); toremifene (Fareston<sup>®</sup>); Tositumomab (Bexxar<sup>®</sup>);

- 94 -

Tositumomab/I-131 tositumomab (Bexxar<sup>®</sup>); Trastuzumab (Herceptin<sup>®</sup>); tretinoin, ATRA (Vesanoid<sup>®</sup>); Uracil Mustard (Uracil Mustard Capsules<sup>®</sup>); valrubicin (Valstar<sup>®</sup>); vinblastine (Velban<sup>®</sup>); vincristine (Oncovin<sup>®</sup>); vinorelbine (Navelbine<sup>®</sup>); vorinostat (Zolinza<sup>®</sup>) and zoledronate (Zometa<sup>®</sup>).

5           In one example, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon- $\alpha$ , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, 10           squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

          Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from: an estrogen receptor 15           modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR- $\gamma$  agonists, PPAR- $\delta$  agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in 20           the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic,  $\gamma$ -secretase and/or NOTCH inhibitors, agents that interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint, and any of the therapeutic agents listed above.

25           Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of the instant invention in combination with radiation therapy and/or in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor 30           modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR- $\gamma$  agonists, PPAR- $\delta$  agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor

- 95 -

of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic,  $\gamma$ -secretase and/or NOTCH inhibitors, agents that interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint, and any of the therapeutic agents listed above.

5           And yet another example of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of the instant invention in combination with paclitaxel or trastuzumab.

10           The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of the instant invention in combination with a COX-2 inhibitor.

15           The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of the instant invention and a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR- $\gamma$  agonist, a PPAR- $\delta$  agonist, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic,  $\gamma$ -secretase and/or NOTCH inhibitors, agents that interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint, and any of the therapeutic agents listed above.

20           Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA), the Physicians' Desk Reference, 56<sup>th</sup> Edition, 2002 (published by Medical Economics company, Inc. Montvale, NJ 07645-1742), the Physicians' Desk Reference, 57<sup>th</sup> Edition, 2003 (published by Thompson PDR, Montvale, NJ 07645-1742), the Physicians' Desk Reference, 60<sup>th</sup> Edition, 2006 (published by Thompson PDR, Montvale, NJ 07645-1742), and the Physicians' Desk Reference, 64<sup>th</sup> Edition, 2010 (published by PDR Network, LLC at Montvale, NJ 07645-1725); the disclosures of which are incorporated herein by reference thereto.

30           If the patient is responding, or is stable, after completion of the therapy cycle, the therapy cycle can be repeated according to the judgment of the skilled clinician. Upon

- 96 -

completion of the therapy cycles, the patient can be continued on the compounds of this invention at the same dose that was administered in the treatment protocol. This maintenance dose can be continued until the patient progresses or can no longer tolerate the dose (in which case the dose can be reduced and the patient can be continued on the reduced dose).

5           Those skilled in the art will recognize that the actual dosages and protocols for administration employed in the methods of this invention may be varied according to the judgment of the skilled clinician. The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. A determination to vary the dosages and protocols for administration may be made after the skilled clinician takes into account such factors as the patient's age, condition and size, as well as the severity of the cancer being treated and the response of the patient to the treatment.

10           The amount and frequency of administration of the compound of formula (1) and the chemotherapeutic agents will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the cancer being treated.

15           The chemotherapeutic agent can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent can be varied depending on the cancer being treated and the known effects of the chemotherapeutic agent on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents on the patient, and in view of the observed responses of the cancer to the administered therapeutic agents.

20           The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

25           The particular choice of chemotherapeutic agent will depend upon the diagnosis of the attending physicians and their judgement of the condition of the patient and the appropriate treatment protocol.

30           The determination of the order of administration, and the number of repetitions of administration of the chemotherapeutic agent during a treatment protocol, is well within the

- 97 -

knowledge of the skilled physician after evaluation of the cancer being treated and the condition of the patient.

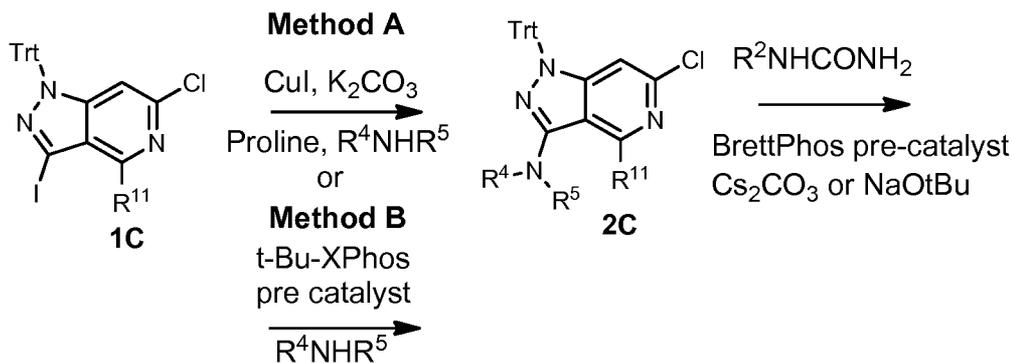
Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a chemotherapeutic agent according to the individual patient's needs, as the treatment proceeds. All such modifications are within the scope of the present invention.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of cancer-related symptoms (e.g., pain), inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

The compounds of this invention may be prepared by employing reactions as shown in the following Reaction Schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. The illustrative Reaction Schemes below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the Reaction Schemes do not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are optionally allowed under the definitions of formula (1) hereinabove.

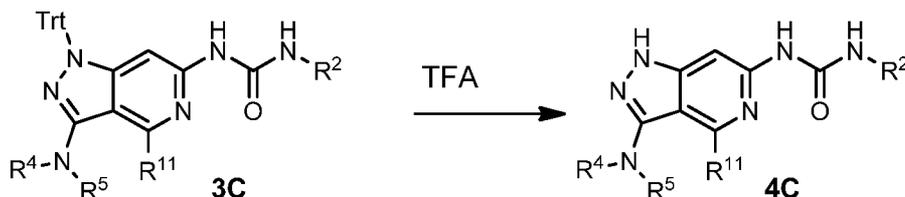
### General Schemes

#### Scheme 1



25

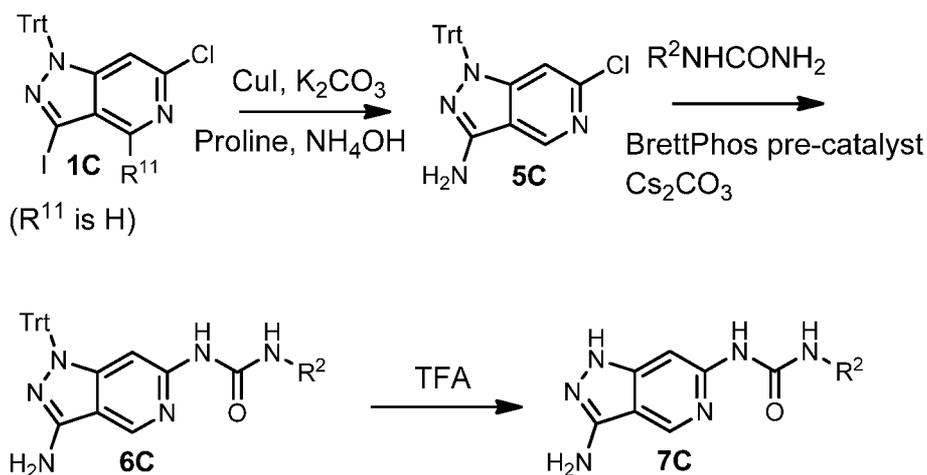
- 98 -



**Step 1:** Amine derivatives have been prepared by treating various 6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine intermediates **1C** with the appropriate amine in the presence of CuI, proline, and a suitable base (i.e.  $K_2CO_3$ ) in DMSO at 70 °C to afford **2C**.

**Step 2:** Aryl urea derivatives have been prepared by heating **2C** to 100 °C (from 1 to 16 h) with the appropriate primary urea (commercial or synthesized by heating the appropriate amine in the presence of HCl and potassium cyanate),  $Cs_2CO_3$ , and BrettPhos pre-catalyst in 1,4-dioxane. The residue was treated with TFA and triethylsilane (with or without DCM) to yield the desired product **4C**.

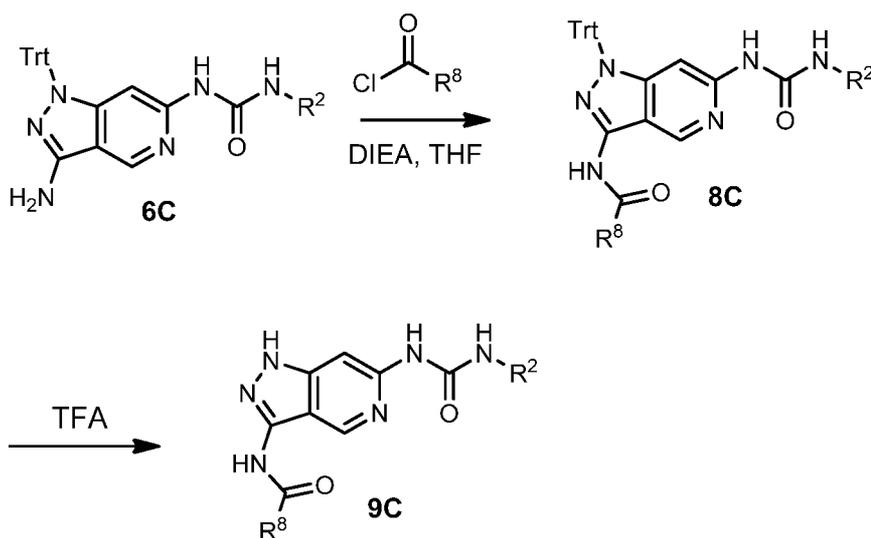
## Scheme 2



Aryl urea derivatives have been prepared by heating **5C** to 100 °C (from 1 to 16 h) 6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine with the appropriate primary urea (commercial or synthesized by heating the appropriate amine in the presence of HCl and potassium cyanate),  $Cs_2CO_3$ , and BrettPhos pre-catalyst in 1,4-dioxane. The residue was treated with TFA and triethylsilane (with or without DCM) to yield the desired product **7C**.

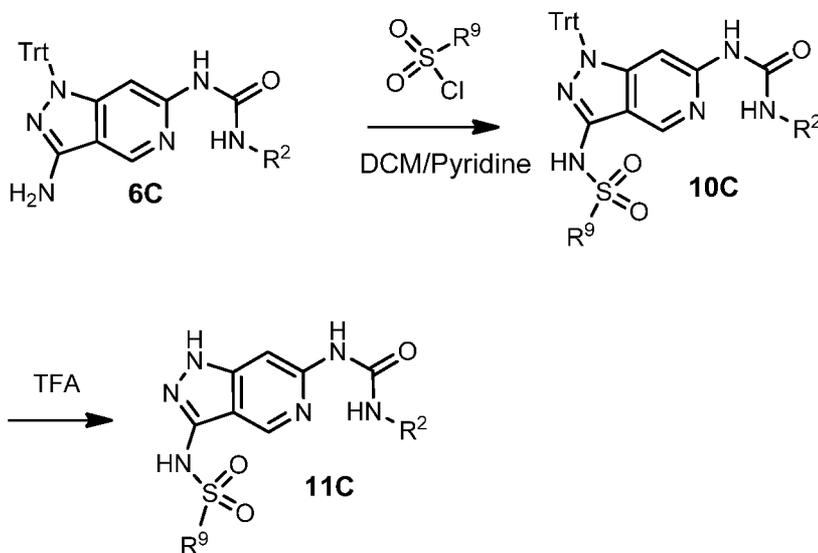
- 99 -

## Scheme 3



- 5 Amide derivatives have been prepared by treating **6C** (Scheme 2) with the appropriate acid chloride in the presence of DIEA in THF at ambient temperature. The residue was treated with TFA and triethylsilane to yield the desired product **9C**.

## Scheme 4



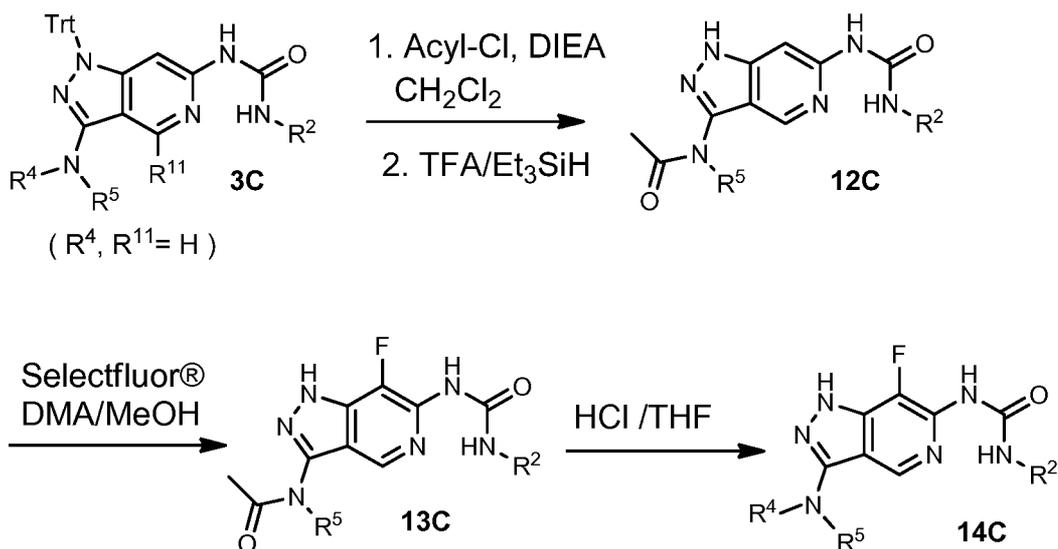
10

- 10 Sulfonamide derivatives have been prepared by treating **6C** (Scheme 2) with the appropriate sulfonyl chloride in DCM/pyridine at ambient temperature. The residue was treated with TFA and triethylsilane to yield the desired product **11C**.

15

- 100 -

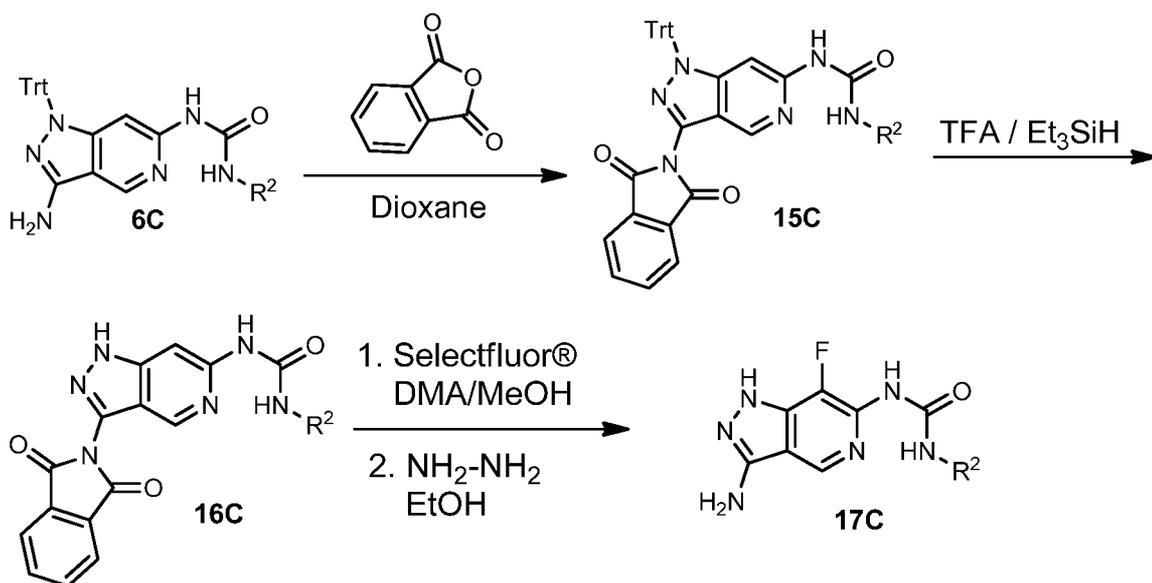
## Scheme 5



5 **Step 1:** Acyl derivatives have been prepared by treating **3C** (Scheme 1) with acetyl chloride in the presence of DIEA in DCM at 0 °C. The residue was treated with TFA and triethylsilane to yield the desired product **12C**.

**Step 2:** Fluorinated compounds have been prepared by heating **12C** to 60 °C (from 2 to 8 h) with Selectfluor® in DMA/MeOH to afford **13C**. The residue was treated with HCl in THF at 60 °C to yield the desired product **14C**.

## Scheme 6

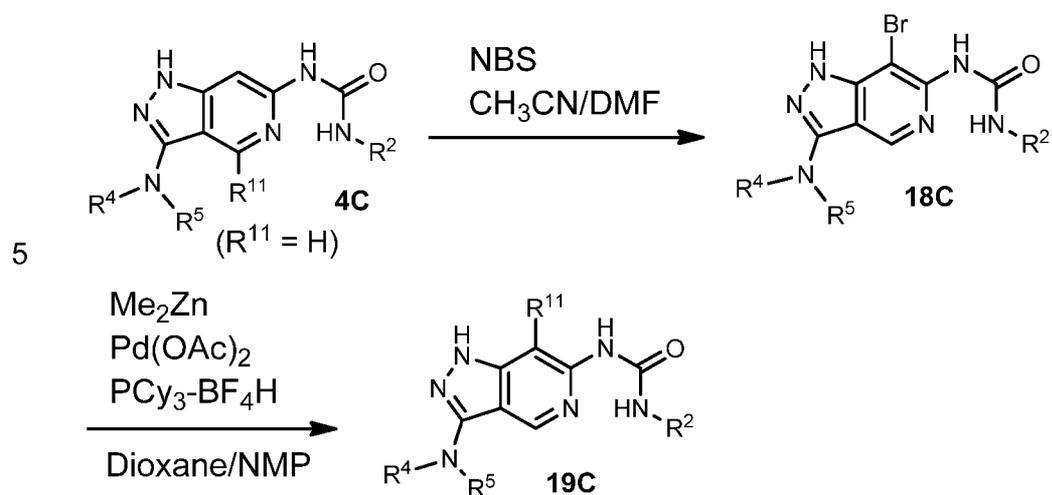


15 **Step 1:** Protected amine aryl urea derivatives have been prepared by treating **6C** (Scheme 2) with isobenzofuran-1,3-dione in dioxane at 110 °C followed by TFA and triethylsilane to yield the desired product **16C**.

- 101 -

**Step 2:** Fluorinated compounds have been prepared by heating **16C** to 60 °C (from 2 to 8 h) with Selectfluor® in DMA/MeOH. The residue was treated with hydrazine hydrate in ethanol at 85 °C to yield the desired product **17C**.

Scheme 7

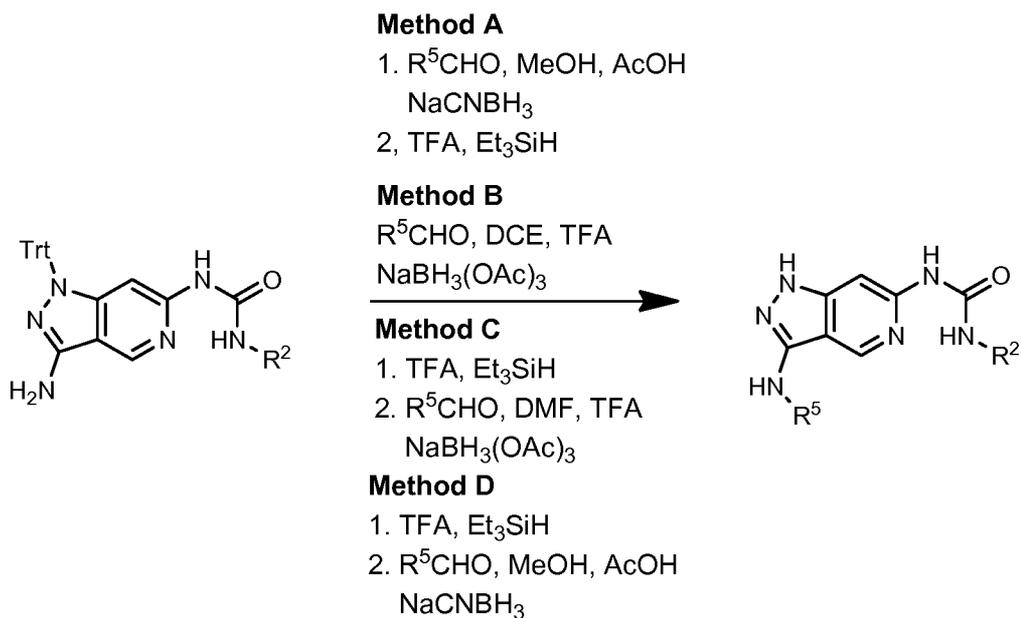


**Step 1:** Brominated compounds have been prepared by treating **4C** (Scheme 1) with NBS in acetonitrile and DMF at ambient temperature.

10 **Step 2:** Alkyl derivatives have been prepared by heating **18C** to 100 °C for 17 h with the appropriate zinc reagent,  $Pd(OAc)_2$ , and  $PCy_3-BF_4H$  in dioxane/NMP to yield the desired product **19C**.

- 102 -

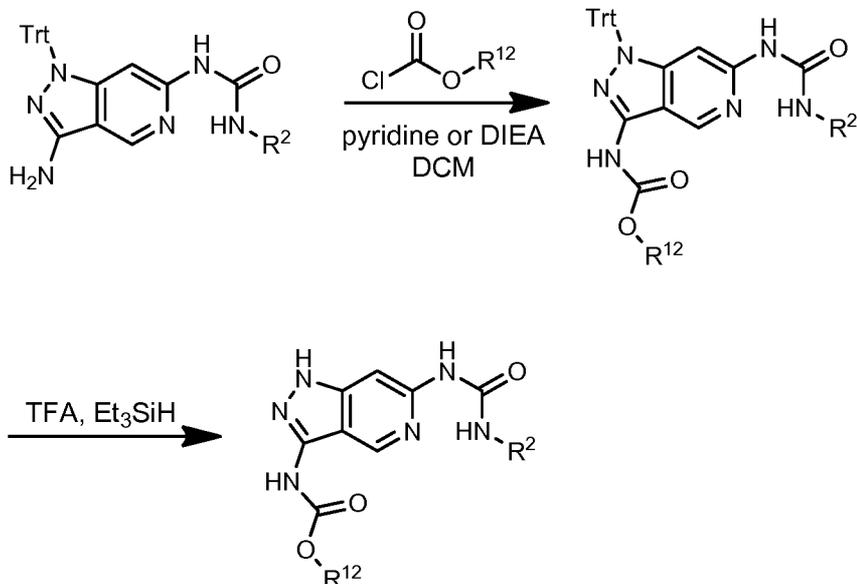
## Scheme 8



In Scheme 8  $R^5$  is as defined for formula 1, except that  $R^5$  is not  $-\text{C}(\text{O})\text{R}^8$ ,  $-\text{S}(\text{O})_2\text{R}^9$ ,  $-\text{C}(\text{O})(\text{substituted C}_1\text{-C}_6\text{alkyl})\text{NHC}(\text{O})\text{O}(\text{C}_1\text{-C}_6\text{alkyl})$ , and  $-\text{C}(\text{O})(\text{C}_1\text{-C}_6\text{alkyl})\text{NHC}(\text{O})\text{O}(\text{C}_1\text{-C}_6\text{alkyl})$ .

5

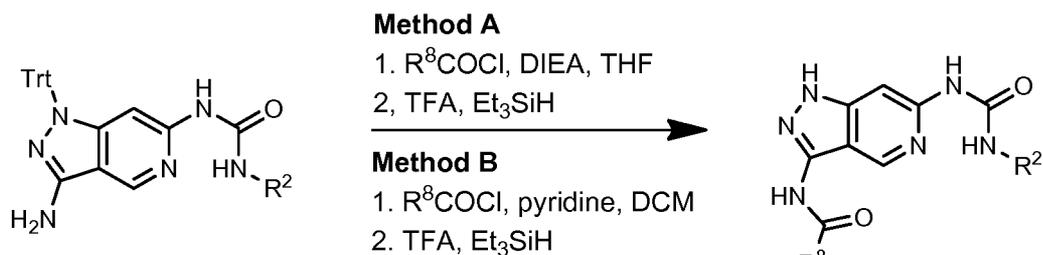
## Scheme 9



10

- 103 -

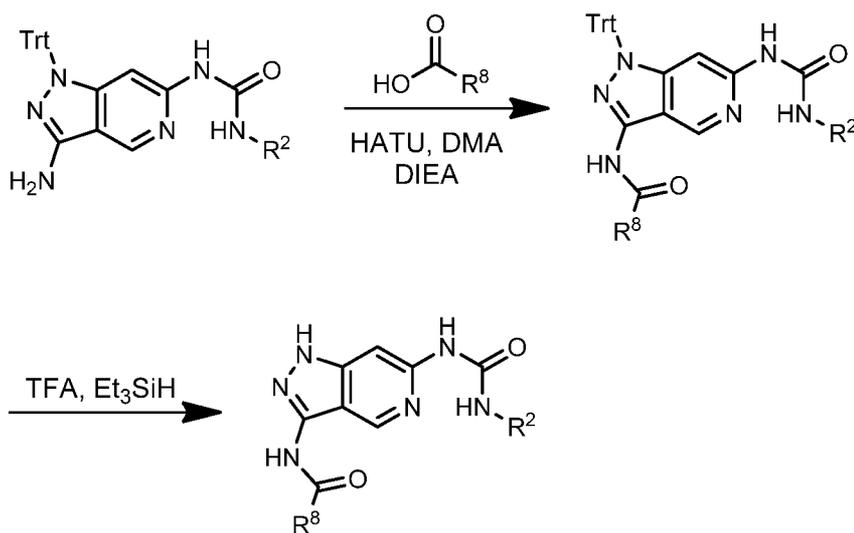
## Scheme 10



In Scheme 10  $R^8$  is as defined for formula 1, except that  $R^8$  is not  $-OR^{12}$ ,  $-NHR^{12}$  and  $-NR^{12}R^{13}$ .

5

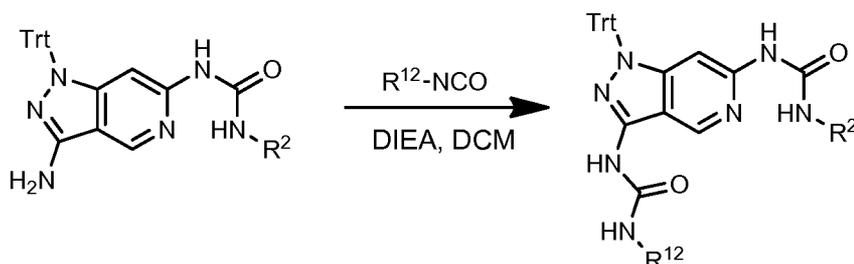
## Scheme 11



10

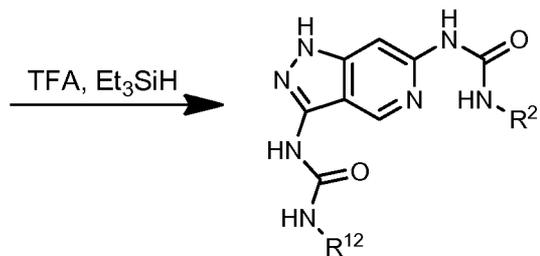
In Scheme 11  $R^8$  is as defined for formula 1, except that  $R^8$  is not  $-OR^{12}$ ,  $-NHR^{12}$  and  $-NR^{12}R^{13}$ .

## Scheme 12

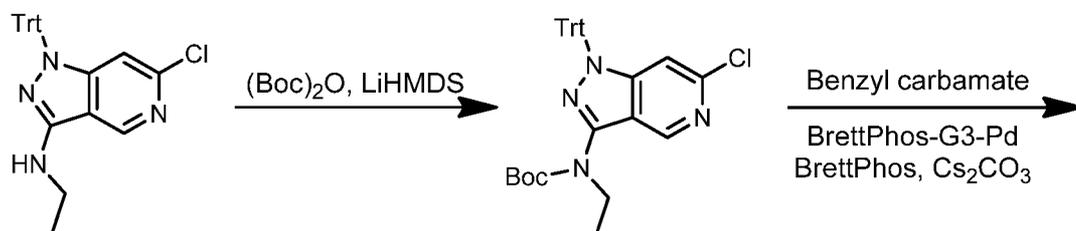


15

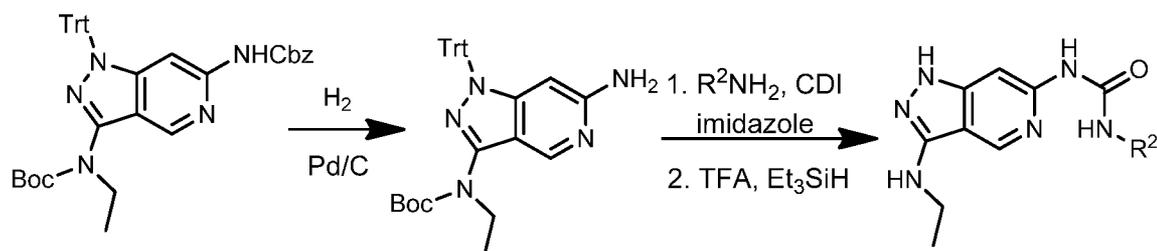
- 104 -



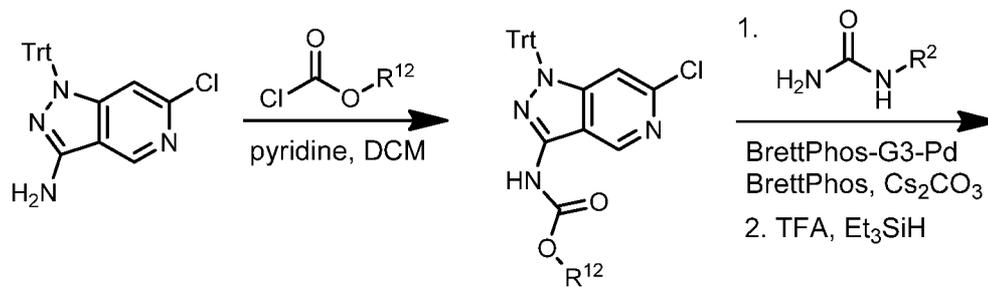
**Scheme 13**



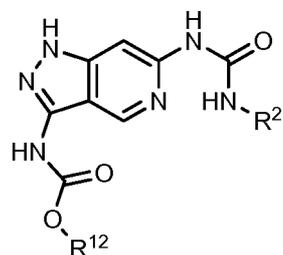
5



**Scheme 14**

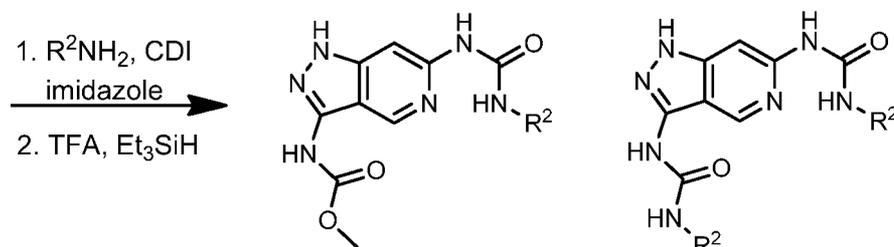
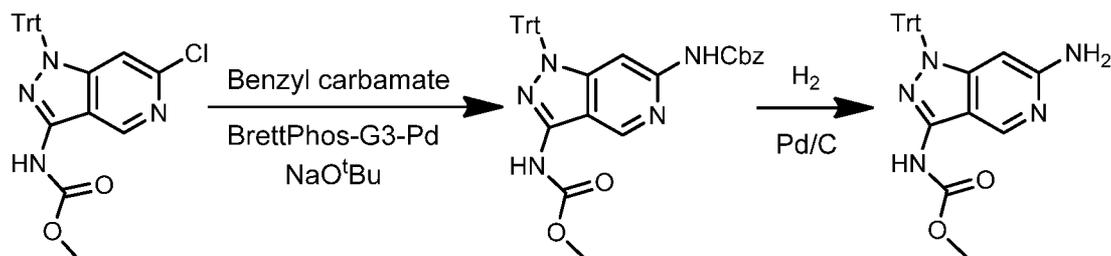


10

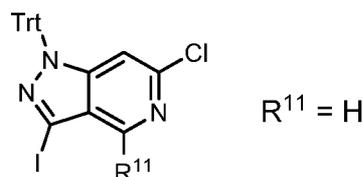


- 105 -

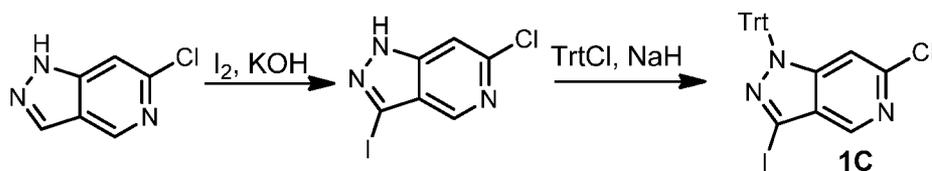
## Scheme 15



5

Intermediates  
Intermediate 1C**6-Chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine**

10 6-Chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine was synthesized according to the following scheme and procedures.

**Step 1: 6-Chloro-3-iodo-1H-pyrazolo[4,3-c]pyridine**

15 A flask was charged with 6-chloro-1H-pyrazolo[4,3-c]pyridine (3.0 g, 19.54 mmol), iodine (13.11 g, 51.7 mmol), KOH (3.29 g, 58.6 mmol) and DMF (60 mL). The mixture was heated at 40 °C for 16 h and then additional iodine (7.8 g, 30.7 mmol) and KOH (1.6 g, 28.4 mmol) were added. The mixture was heated at 70 °C for 3 h then quenched with 1N Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with EtOAc. The organic phase was washed with water, brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of volatiles DCM was added. A solid precipitated and filtered to

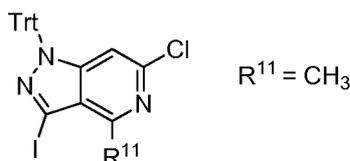
- 106 -

yield 6-chloro-3-iodo-1H-pyrazolo[4,3-c]pyridine, which was carried onto the next step without further purification. MS ESI calc'd. for  $C_6H_4ClIN_3$   $[M+1]^+$  280, found 280.

### Step 2: 6-Chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine

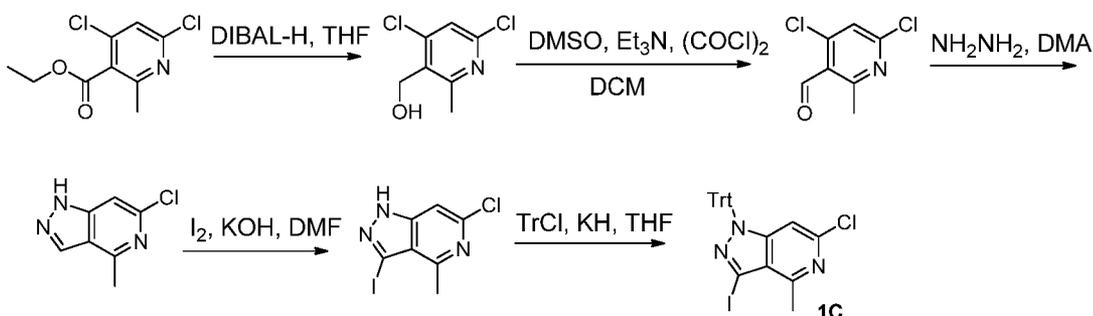
A solution of 6-chloro-3-iodo-1H-pyrazolo[4,3-c]pyridine (1.874 g, 6.71 mmol) in THF (20 mL) was treated with NaH (60% in mineral oil; 0.402 g, 10.06 mmol) at 0 °C and the mixture was stirred for 50 min. Trityl chloride (2.244 g, 8.05 mmol) was added at 0 °C and the mixture was stirred for 16 h at room temperature, quenched with saturated  $NH_4Cl$ , and extracted with EtOAc. The organic phase was washed with water, brine, dried over  $Na_2SO_4$ , and concentrated *in vacuo*. The residue was purified via flash chromatography (0-10% EtOAc-hexanes) to yield 6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine. MS ESI calc'd. for  $C_{25}H_{18}ClIN_3$   $[M+1]^+$  522, found 522.

#### Intermediate 1C



### 6-Chloro-3-iodo-4-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridine

6-Chloro-3-iodo-4-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridine was synthesized according to the following scheme and procedures.



### Step 1: (4,6-Dichloro-2-methylpyridin-3-yl)methanol

THF (52.3 mL) was cooled to 0 °C in a dry round bottomed flask under an atmosphere of  $N_2$ . Ethyl 4,6-dichloro-2-methylnicotinate (4.60 mL, 26.1 mmol) was then added followed by diisobutylaluminum hydride (57.5 mL, 57.5 mmol). The reaction was stirred at 0 °C for 3 h. The reaction was then poured into cold saturated sodium potassium tartrate solution. The mixture was stirred for several hours to allow the precipitate to dissolve, then the aqueous phase was extracted with EtOAc. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (0-50%

- 107 -

EtOAc/hexanes) to give (4,6-dichloro-2-methylpyridin-3-yl)methanol. MS ESI calc'd. for  $C_7H_7Cl_2NO$   $[M+1]^+$  192, found 192.

**Step 2: 4,6-Dichloro-2-methylnicotinaldehyde**

A dry flask was charged with DCM (59.9 mL) and oxalyl chloride (3.15 mL, 35.9 mmol) and cooled to -78 °C. Dimethyl sulfoxide (3.40 mL, 47.9 mmol) was added and the reaction was stirred for 30 min. A solution of (4,6-dichloro-2-methylpyridin-3-yl)methanol (4.60 g, 23.95 mmol) in DCM (2 mL) was then added. The reaction was stirred for 30 min then triethylamine (6.74 mL, 71.9 mmol) was added and the reaction mixture was stirred at -78 °C for 30 min. The reaction was warmed to 0 °C and stirred for 1 h. The reaction was then quenched with sodium bicarbonate, diluted with water, and the aqueous layer extracted with EtOAc. The organic phase was washed with sat. sodium bicarbonate, dried over  $MgSO_4$ , filtered, and concentrated *in vacuo* to afford 4,6-dichloro-2-methylnicotinaldehyde, which was carried onto the next step without further purification.  $^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  10.60 (s, 1H), 7.37 (s, 1H), 2.80 (s, 3H).

**Step 3: 6-Chloro-4-methyl-1H-pyrazolo[4,3-c]pyridine**

A solution of 4,6-dichloro-2-methylnicotinaldehyde (5.25 g, 23.48 mmol) in DMA (50 mL) was treated with hydrazine (7.37 mL, 235 mmol) at 0 °C. The reaction was stirred for 15 min and then warmed to 80 °C for 2 h. The reaction was cooled and diluted with EtOAc and washed with water. The organic phase was dried over  $MgSO_4$ , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (0-100% EtOAc/hexanes) to give 6-chloro-4-methyl-1H-pyrazolo[4,3-c]pyridine. MS ESI calc'd. for  $C_7H_6ClN_3$   $[M+1]^+$  168, found 168.

**Step 4: 6-Chloro-3-iodo-4-methyl-1H-pyrazolo[4,3-c]pyridine**

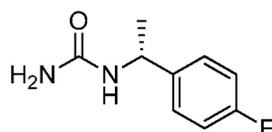
A 100 mL round bottom flask was charged with 6-chloro-4-methyl-1H-pyrazolo[4,3-c]pyridine (1.20 g, 7.16 mmol) and DMF (28.5 mL). The reaction flask was warmed to 70 °C and KOH (1.2 g, 21.48 mmol) was added. Iodine (5.45 g, 21.48 mmol) was added gradually over 1 h. The reaction mixture was stirred for 3 h then additional KOH (3.2 g, 57.0 mmol) and iodine (15.6 g, 61.5 mmol) were added. The reaction was heated at 70 °C for 2 h. The reaction was poured into saturated sodium thiosulfate (500 mL) and diluted with EtOAc (200 mL). The aqueous phase was extracted with EtOAc (200 mL, x2). The combined organic phase was washed with water (200 mL) and brine (200 mL), dried over  $MgSO_4$ , filtered, and concentrated *in vacuo* to give 6-chloro-3-iodo-4-methyl-1H-pyrazolo[4,3-c]pyridine. MS ESI calc'd. for  $C_7H_5ClIN_3$   $[M+1]^+$  294, found 294.

- 108 -

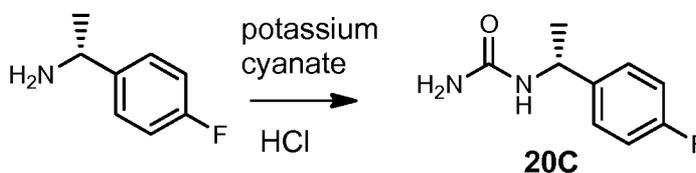
**Step 5: 6-Chloro-3-iodo-4-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridine**

A flask containing 6-chloro-3-iodo-4-methyl-1H-pyrazolo[4,3-c]pyridine (2.06 g, 7.02 mmol) in THF (60 mL) was cooled to 0 °C and potassium hydride (1.126 g, 14.04 mmol) was added. The reaction was stirred for 30 min followed by addition of trityl chloride (2.94 g, 10.53 mmol). The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction was poured into sat. sodium bicarbonate and extracted with EtOAc. The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (0-10% DCM/EtOAc) to give 6-chloro-3-iodo-4-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridine. MS ESI calc'd. for C<sub>26</sub>H<sub>19</sub>ClIIN<sub>3</sub> [M+1]<sup>+</sup> 536, found 536.

10

**Intermediate 20C****(R)-1-(1-(4-Fluorophenyl)ethyl)urea**

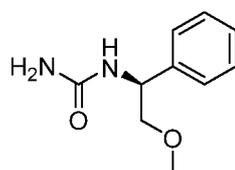
(R)-1-(1-(4-Fluorophenyl)ethyl)urea was prepared according to the following scheme and procedure.



15

(R)-1-(4-Fluorophenyl)ethanamine (5.15 g, 37.0 mmol) was taken up in HCl (2N, 40 mL) and potassium cyanate (15.01 g, 185 mmol) was added. The mixture was stirred at 80 °C for 3 h. Upon cooling to room temperature, a precipitate formed which was collected by filtration and washed with water. The solid was partitioned between water and EtOAc, and the aqueous phase extracted once more with EtOAc. The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give (R)-1-(1-(4-fluorophenyl)ethyl)urea. MS ESI calc'd. for C<sub>9</sub>H<sub>11</sub>FN<sub>2</sub>O [M+1]<sup>+</sup> 183, found 183.

20

**Intermediate 21C**

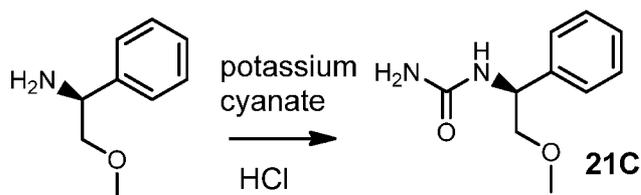
25

**(S)-1-(2-Methoxy-1-phenylethyl)urea**

(S)-1-(2-Methoxy-1-phenylethyl)urea was prepared according to the following scheme and

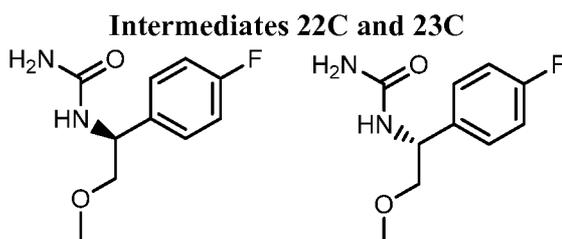
- 109 -

procedure.



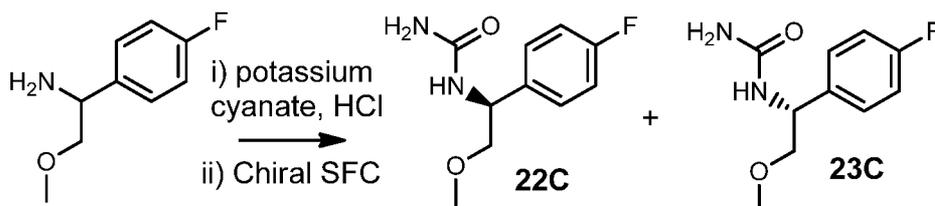
(S)-2-Methoxy-1-phenylethanamine (5.6 g, 37.0 mmol) and potassium cyanate (8.12 g, 100 mmol) were taken up in HCl (1 N, 40 mL, 40.0 mmol) and water (40 mL). The reaction mixture was heated to 100 °C for 3 h. Room temperature was attained, water was added, and the products extracted into EtOAc (x3) followed by 10% MeOH-DCM (x2). The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was triturated in Et<sub>2</sub>O to give (S)-1-(2-methoxy-1-phenylethyl)urea. MS ESI calc'd. for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> [M+1]<sup>+</sup> 195, found 195.

10



**(S)-1-(1-(4-Fluorophenyl)-2-methoxyethyl)urea (Intermediate 22C) and (R)-1-(1-(4-fluorophenyl)-2-methoxyethyl)urea (Intermediate 23C)**

(S)-1-(1-(4-Fluorophenyl)-2-methoxyethyl)urea and (R)-1-(1-(4-fluorophenyl)-2-methoxyethyl)urea were prepared according to the following scheme and procedures.



### Step 1: 1-(1-(4-Fluorophenyl)-2-methoxyethyl)urea

To a microwave vial equipped with a stir bar was added 1-(4-fluorophenyl)-2-methoxyethanamine (1.2 g, 7.09 mmol) and water (10 mL). To this mixture was added HCl (1N, 7.23 mL, 7.23 mmol) and potassium cyanate (2.88 g, 35.5 mmol). The mixture was heated in a microwave reactor to 80 °C for 1 h. Saturated sodium bicarbonate was added and the products extracted into EtOAc (x4). The organic layers were combined, washed with brine (x2), and dried over MgSO<sub>4</sub>. The material was concentrated *in vacuo* while loading onto silica

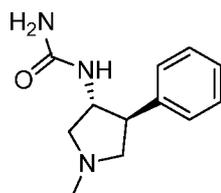
- 110 -

gel. Purification by flash chromatography (0-10% EtOAc-Hexanes) gave 1-(1-(4-fluorophenyl)-2-methoxyethyl)urea. MS ESI calc'd. for  $C_{10}H_{13}FN_2O_2$   $[M+1]^+$  213, found 213.

**Step 2: (S)-1-(1-(4-Fluorophenyl)-2-methoxyethyl)urea and (R)-1-(1-(4-fluorophenyl)-2-methoxyethyl)urea**

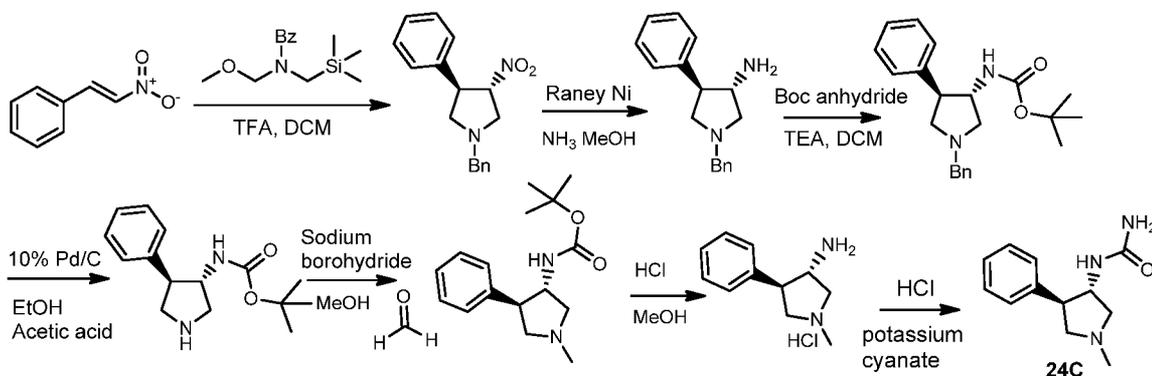
- 5 The enantiomers of 1-(1-(4-fluorophenyl)-2-methoxyethyl)urea (1.411 g, 6.65 mmol) were separated by SFC (Berger Multigram II SFC, column: Chiral Technology IC-H 2.1 X 25cm, 5  $\mu$ M, mobile phase: 20% to 80% MeOH in  $CO_{2(l)}$ , flow rate: 70 mL/min, 4 min run time). The fractions were collected and the solvent evaporated *in vacuo* to afford (S)-1-(1-(4-fluorophenyl)-2-methoxyethyl)urea and (R)-1-(1-(4-fluorophenyl)-2-methoxyethyl)urea. MS  
10 ESI calc'd. for  $C_{10}H_{13}FN_2O_2$   $[M+1]^+$  213, found 213 (Intermediate 22C) and MS ESI calc'd. for  $C_{10}H_{13}FN_2O_2$   $[M+1]^+$  213, found 213 (Intermediate 23C).

**Intermediate 24C**



**1-((3R and S, 4S and R)-1-Methyl-4-phenylpyrrolidin-3-yl)urea**

- 15 1-((3R and S, 4S and R)-1-Methyl-4-phenylpyrrolidin-3-yl)urea was prepared according to the following scheme and procedures.



**Step 1: (3S and R, 4R and S)-1-Benzyl-3-nitro-4-phenylpyrrolidine**

- 20 To a solution of (E)-(2-nitrovinyl)benzene (110 g, 0.738 mol) and TFA (8.42 g, 0.073 mol) in DCM (500 mL) was added N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)-methanamine (351.4 g, 1.476 mol) in DCM (500 mL) drop-wise at 0 °C for a period of 30 min. Then the reaction mixture was stirred at room temperature for 48 h. After completion of the reaction, the mixture was concentrated *in vacuo*, dissolved in water, and extracted into EtOAc (x2, 1.0 L). The organic layer was separated, dried over anhydrous sodium sulfate, and

- 111 -

concentrated *in vacuo*. The residue was purified via flash chromatography (20-80% petroleum ether/EtOAc) to afford (3S and R, 4R and S)-1-benzyl-3-nitro-4-phenylpyrrolidine. MS ESI calc'd. For  $C_{17}H_{18}N_2O_2$   $[M+1]^+$  283, found 283.

**Step 2: (3S and R, 4R and S)-1-Benzyl-4-phenylpyrrolidin-3-amine**

5 To a stirred solution of (3S and R, 4R and S)-1-benzyl-3-nitro-4-phenylpyrrolidine (100 g, 0.354 mol) in methanolic ammonia (1 L) was added Raney Ni (20 g) at room temperature in a 2.0 L hydrogenation flask. The reaction was hydrogenated at 100 psi for 12 h at room temperature. After completion of the reaction, the mixture was filtered through Celite and the filtrate was concentrated *in vacuo* to afford (3S and R, 4R and S)-1-benzyl-4-phenylpyrrolidin-3-amine, which was carried onto the next step without further purification. MS ESI calc'd. For  $C_{17}H_{20}N_2$   $[M+1]^+$  253, found 253.

**Step 3: tert-Butyl ((3S and R, 4R and S)-1-benzyl-4-phenylpyrrolidin-3-yl)carbamate**

15 To a stirred solution of (3S and R, 4R and S)-1-benzyl-4-phenylpyrrolidin-3-amine (120.5 g, 0.476 mol) in DCM (1.2 L) was added triethylamine (48.1 g, 0.476 mol) and the reaction mixture was cooled to 0 °C. Boc anhydride (103.84 g, 0.476 mol) was added dropwise over a period of 30 min at 0 °C. The resulting reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the mixture was diluted with water (3.0 L), the separated organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford *tert*-butyl ((3S and R, 4R and S)-1-benzyl-4-phenylpyrrolidin-3-yl)carbamate, which was carried onto the next step without further purification. MS ESI calc'd. For  $C_{22}H_{28}N_2O_2$   $[M+1]^+$  353, found 353.

**Step 4: tert-Butyl ((3S and R, 4R and S)-4-phenylpyrrolidin-3-yl)carbamate**

25 To a stirred solution of ((3S and R, 4R and S)-1-benzyl-4-phenylpyrrolidin-3-yl)carbamate (115 g, 0.325 mol) and acetic acid (5 mL, 0.097 mol) in ethanol (1.5 L) was added 10 % Pd-C (20 g) in a hydrogenation flask. The reaction was hydrogenated at 150 psi at 50 °C for 12 h. After completion of the reaction, the mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The crude compound was triturated with a minimum amount of EtOAc and dried under vacuum to afford *tert*-butyl ((3S and R, 4R and S)-4-phenylpyrrolidin-3-yl)carbamate. MS ESI calc'd. For  $C_{15}H_{22}N_2O_2$   $[M+1]^+$  263, found 263.

30 **Step 5: tert-Butyl ((3R and S, 4S and R)-1-methyl-4-phenylpyrrolidin-3-yl)carbamate**

*tert*-Butyl ((3R and S, 4S and R)-4-phenylpyrrolidin-3-yl)carbamate (1 g, 3.81 mmol) and formaldehyde (0.795 mL, 10.67 mmol) were dissolved in MeOH (15.25 mL) and treated with sodium borohydride (0.433 g, 11.44 mmol) at 0 °C. The reaction was warmed to room

- 112 -

temperature and stirred overnight. The crude reaction mixture was diluted with EtOAc and washed with water and brine. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford *tert*-butyl ((3R and S, 4S and R)-1-methyl-4-phenylpyrrolidin-3-yl)carbamate, which was carried onto the next step without further purification. MS ESI calc'd. For C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> [M+1]<sup>+</sup> 277, found 277.

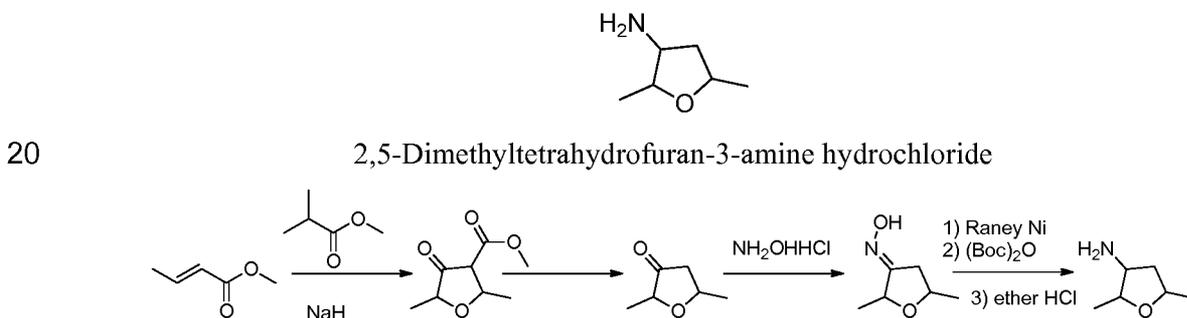
**Step 6: (3R and S, 4S and R)-1-Methyl-4-phenylpyrrolidin-3-amine hydrochloride**

*tert*-Butyl ((3R and S, 4S and R)-1-methyl-4-phenylpyrrolidin-3-yl)carbamate (860 mg, 3.11 mmol) was dissolved in methanolic HCl, (3N, 20 mL) and heated to 50 °C for 2 h. The reaction mixture was concentrated *in vacuo* to afford (3R and S,4S and R)-1-methyl-4-phenylpyrrolidin-3-amine hydrochloride as a white solid, which was carried onto the next step without further purification. MS ESI calc'd. For C<sub>11</sub>H<sub>16</sub>N<sub>2</sub> [M+1]<sup>+</sup> 177, found 177.

**Step 7: 1-((3R and S, 4S and R)-1-Methyl-4-phenylpyrrolidin-3-yl)urea**

1-((3R and S, 4S and R)-1-Methyl-4-phenylpyrrolidin-3-yl)urea was prepared using the same procedure described for (R)-1-(1-(4-fluorophenyl)ethyl)urea (**Intermediate 20C**). MS ESI calc'd. For C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O [M+1]<sup>+</sup> 220, found 220.

**Intermediate 78A**



**Step 1: Methyl 2,5-dimethyl-4-oxotetrahydrofuran-3-carboxylate**

Methyl lactate (20.8 g, 0.2 mol) was added to a suspension of NaH (4.8 g, 0.2 mol) in ether (200 mL). After the cessation of hydrogen evolution the solvent was evaporated in vacuum and replaced by dry DMSO (100 mL). Methyl crotonate (22 g, 0.22 mol) was then added at 0 °C and allowed to warm up to 20 °C. The mixture was poured into diluted H<sub>2</sub>SO<sub>4</sub> and extracted with ether (x3, 150 mL). The organic phase was extracted with brine (x3) and dried over magnesium sulfate to give methyl 2,5-dimethyl-4-oxotetrahydrofuran-3-carboxylate.

25

30

- 113 -

**Step 2: 2,5-Dimethyldihydrofuran-3(2H)-one**

Methyl 2,5-dimethyl-4-oxotetrahydrofuran-3-carboxylate was refluxed in H<sub>2</sub>SO<sub>4</sub> (10%, 100 mL) for 2 hours. After extraction with ether and washing with aqueous sodium bicarbonate solution, the organic layer was dried over magnesium sulfate. Distillation affords 2,5-dimethyldihydrofuran-3(2H)-one. <sup>1</sup>H NMR (ppm, 300 MHz, CDCl<sub>3</sub>): δ 4.4-4.6(m, 1H), 4.0-4.2(m, 2H), 3.7-3.8 (m, 1H), 2.5-2.7 (m, 2H), 2.2-2.3 (m, 2H), 1.2-1.5 (4d, 12H).

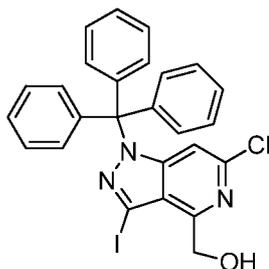
**Step 3: 2,5-Dimethyldihydrofuran-3(2H)-one oxime**

To a solution of 2,5-dimethyldihydrofuran-3(2H)-one (20 g, 0.175 mol) and NaOAc (43 g, 0.526 mol) in EtOH (300 mL), NH<sub>2</sub>OH.HCl (15.8 g, 0.228 mol) was added portion in the mixture at 0 °C. After addition, the reaction was stirred at rt for 3h. Filtered, the filtrate was concentrated and the residue was dissolved in DCM, filtered, the filtrate was concentrated to give 2,5-dimethyldihydrofuran-3(2H)-one oxime. <sup>1</sup>H NMR (ppm, 300 MHz, CDCl<sub>3</sub>) δ 3.7-4.9 (m, 2H), 2.0-3.0(m, 2H), 1.2-1.4(m, 6H).

**Step 4: 2,5-Dimethyltetrahydrofuran-3-amine hydrochloride**

To a mixture of 2,5-dimethyldihydrofuran-3(2H)-one oxime (23 g, 0.175 mol) and Raney Ni (4 g) in THF/NH<sub>3</sub>.H<sub>2</sub>O (1:1, 200 mL) was stirred at 60 °C under 4 MPa for overnight. The mixture was cooled and filtered, the filtrate was concentrated to give 2,5-dimethyltetrahydrofuran-3-amine. To a mixture of 2,5-dimethyltetrahydrofuran-3-amine and Et<sub>3</sub>N (53.2 g, 0.526 mol) in DCM (300 mL), (Boc)<sub>2</sub>O (42 g, 0.193 mol) was dissolved in DCM (100 mL) and dropwise added in the mixture at 0 °C. After addition, the reaction mixture was stirred at rt. for 4 hours before water was added in the reaction. The aqueous phase was extracted with DCM, the organic layer was washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated. The residue was purified by column to give tert-butyl (2,5-dimethyltetrahydrofuran-3-yl)carbamate hydrochloride. To a solution of tert-butyl (2,5-dimethyltetrahydrofuran-3-yl)carbamate hydrochloride in ether, ether.HCl was added dropwise at 0 °C. After addition, the mixture was filtered to give 2,5-dimethyltetrahydrofuran-3-amine hydrochloride. <sup>1</sup>H NMR (ppm, 300 MHz, D<sub>2</sub>O) δ 3.5-4.4(m, 3H), 1.5-2.7(m, 2H), 1.2-1.3(m, 6H).

- 114 -

**Intermediate 101A****(6-Chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)methanol****Step 1: 6-Chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine-4-carbaldehyde**

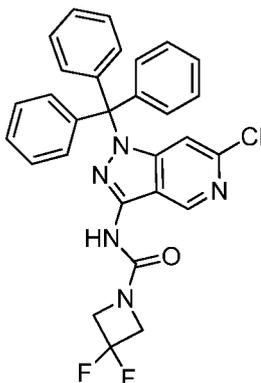
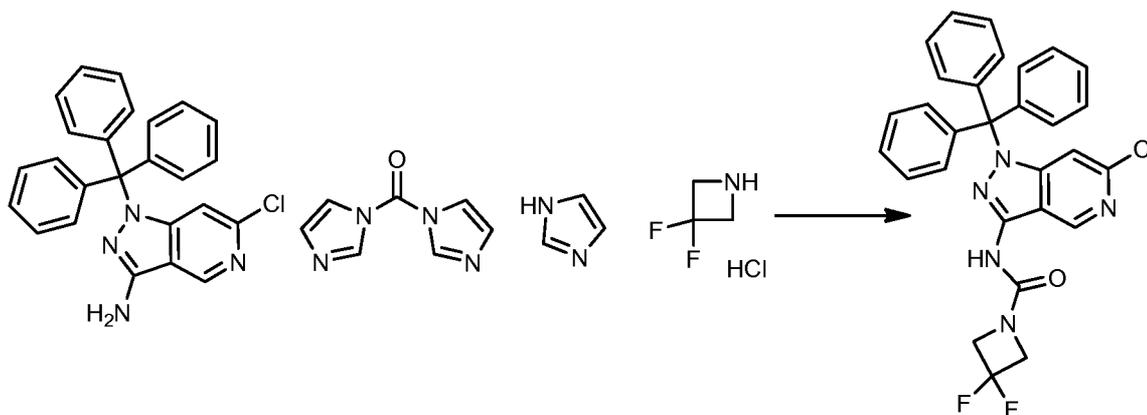
5           6-Chloro-3-iodo-4-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridine (20 g, 37.3 mmol) was dissolved in dioxane (400 mL) and selenium dioxide (12.43 g, 112 mmol) was added. The reaction mixture was stirred at 100 °C for 6 hrs. Selenium dioxide (4.14 g, 37.3 mmol) was added and the reaction mixture continued stirring at 100 °C overnight. The reaction was filtered over celite, rinsed with DCM, and concentrated *in vacuo*. The residue was dissolved in DCM (1.0 L) and filtered over celite. The material was concentrated *in vacuo* while loading on silica gel. Purification by flash chromatography (0-5% DCM/EtOAc) gave 6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine-4-carbaldehyde (10.88 g, 19.79 mmol, 53.0 %). <sup>1</sup>H NMR (ppm, 500 MHz, DMSO-*d*<sub>6</sub>) δ 10.54 (s, 1H), 7.39-7.35 (m, 10H), 7.17-7.11 (m, 5H), 6.29 (s, 1H).

**Step 2: (6-Chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)methanol**

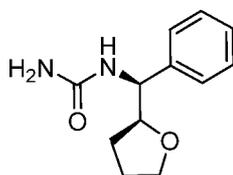
15           6-Chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine-4-carbaldehyde (10.26 g, 18.66 mmol) was dissolved in DCM (250 mL) and methanol (125 mL). The reaction mixture was then cooled to 0 °C and sodium borohydride (0.706 g, 18.66 mmol) was added. The reaction mixture was stirred at room temperature for 15 min. The reaction was quenched with water and extracted with DCM. The combined organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* while loading on silica gel. Purification by flash chromatography (2-10% DCM/EtOAc) gave (6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)methanol (7.09 g, 12.85 mmol, 69 %). MS ESI calc'd. for C<sub>26</sub>H<sub>19</sub>ClI<sub>2</sub>N<sub>3</sub>O [M+H]<sup>+</sup> 552, found 552.

25

- 115 -

**Intermediate 128A****N-(6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)-3,3-difluoroazetidine-1-carboxamide**

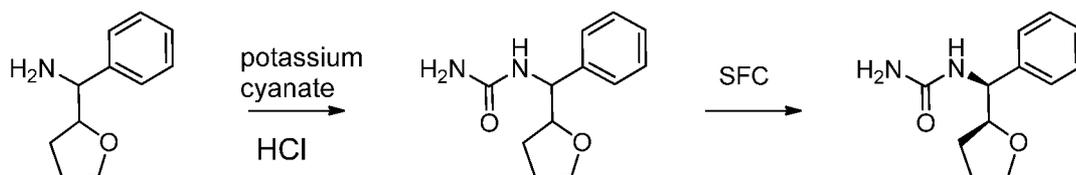
- 5 Di(1H-imidazol-1-yl)methanone (197 mg, 1.217 mmol) was added to a stirred mixture of 1H-imidazole (166 mg, 2.434 mmol) and 6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (250 mg, 0.608 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 ml) and the mixture was stirred at room temperature for overnight. The second day, 3,3-difluoroazetidine hydrochloride (190 mg) was added and the mixture was heated at 50 °C for 3 hours, LCMS and TLC showed clean reaction. The mixture
- 10 was directly loaded to a silica gel column eluting with EtOAc/Hexane = 0% to 100% gradient to give N-(6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)-3,3-difluoroazetidine-1-carboxamide (320 mg, 0.604 mmol, 99 % yield).

**Intermediate 148A**

15

**1-((S)-phenyl((S)-tetrahydrofuran-2-yl)methyl)urea**

- 116 -

**Step 1: 1-(phenyl(tetrahydrofuran-2-yl)methyl)urea**

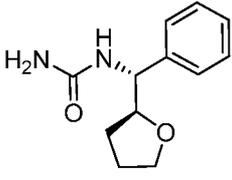
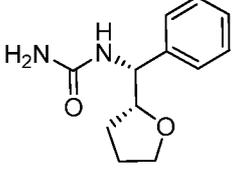
Phenyl(tetrahydrofuran-2-yl)methanamine.HCl (640 mg, 2.99 mmol) was taken up in water (3 ml). Potassium cyanate (1215 mg, 14.97 mmol) and HCl (3 ml, 36.5 mmol) were then added. The reaction mixture was allowed to stir under microwave irradiation at 80 °C for 1 hr. Saturated NaHCO<sub>3</sub> and EtOAc were added. The products were extracted into EtOAc (3x). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo* to give 1-(phenyl(tetrahydrofuran-2-yl)methyl)urea. <sup>1</sup>H NMR (ppm, 500 MHz, DMSO-d<sub>6</sub>) δ 7.23 (m, 4H), 7.18 (m, 1H), 6.43 (d, J= 9.5, 1H), 5.57 (br s, 2H), 4.68-4.47 (dd, J= 3.5, J= 5.5, 1H), 3.97 (m, 1H), 3.76 (q, J= 8.0 1H), 3.56 (q, J= 7.0, 1H), 1.79-1.75 (m, 3H), 1.73 (m, 1H).

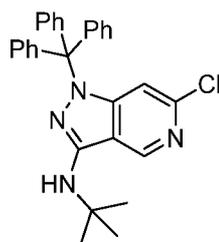
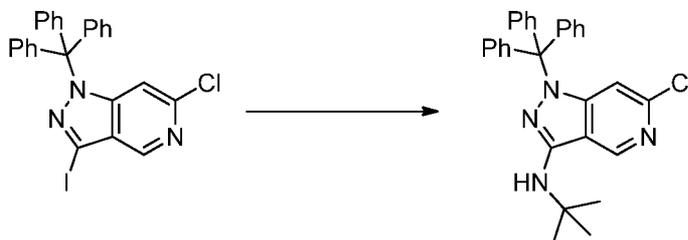
**Step 2: 1-((S)-phenyl((S)-tetrahydrofuran-2-yl)methyl)urea**

The enantiomers of 1-(phenyl(tetrahydrofuran-2-yl)methyl)urea (150 mg, 0.681 mmol) were separated by SFC (Berger Multigram II, Column: Chiral Technology OZ-H 2.1 X 25cm, 5μM, UV wavelength: 220 nm, mobile phase: 40% / 60% Methanol + 0.25% dimethyl ethylamine/CO<sub>2(l)</sub>, flow rate: 70 mL/Min, 7 min run time). Elution was observed at 2.46 min. The fractions were collected and the solvent evaporated *in vacuo* to afford 1-((S)-phenyl((S)-tetrahydrofuran-2-yl)methyl)urea and Intermediates 149A-151A. <sup>1</sup>H NMR (ppm, 500 MHz, DMSO-d<sub>6</sub>) δ 7.23 (m, 4H), 7.18 (m, 1H), 6.43 (d, J= 9.5, 1H), 5.57 (br s, 2H), 4.68-4.47 (dd, J= 3.5, J= 5.5, 1H), 3.97 (m, 1H), 3.76 (q, J= 8.0 1H), 3.56 (q, J= 7.0, 1H), 1.79-1.75 (m, 3H), 1.73 (m, 1H).

Intermediate	Structure	IUPAC Name	Exact Mass [M+H] <sup>+</sup>
149A		1-((S)-phenyl((R)-tetrahydrofuran-2-yl)methyl)urea	Calc'd 221, found 221

- 117 -

150A		1-((R)-phenyl((S)-tetrahydrofuran-2-yl)methyl)urea	Calc'd 221, found 221
151A		1-((R)-phenyl((R)-tetrahydrofuran-2-yl)methyl)urea	Calc'd 221, found 221

**Intermediate 351A****N-(tert-butyl)-6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine**

5

**Step 1: N-(tert-butyl)-6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine:**

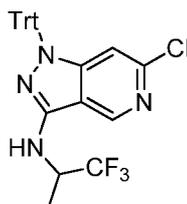
A mixture of 6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine (1000 mg, 1.917 mmol), tert-butylamine (565  $\mu$ l, 5.75 mmol), brettphos palladacycle (77 mg, 0.096 mmol), 2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl (44.7 mg, 0.096 mmol) and sodium tert-butoxide (553 mg, 5.75 mmol) were degassed. Toluene (9583  $\mu$ l) was added to and reaction system was degassed and heated at 110  $^{\circ}$ C for 8 h. Solvent was evaporated in vacuo and partitioned between water and EtOAc. Aqueous layer was extracted with EtOAc (2x) and combined organics were washed with water and saturated aqueous Brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* on silica. Material was purified by normal phase column chromatography eluting with EtOAc/Hex (0-15 %) affording N-(tert-butyl)-6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (219 mg, 0.469 mmol, 24.47 % yield) as a white solid. <sup>1</sup>H NMR (ppm, 500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.81 (s, 1H), 7.52 – 7.13 (m, 15H), 6.30 (s, 1H), 5.76 (s,

15

- 118 -

1H), 1.24 (s, 9H). MS ESI calc'd. For  $C_{29}H_{27}ClN_4[M+H]^+$  467, found 467.

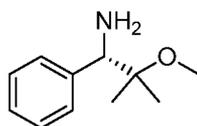
### Intermediate 419A



### 6-chloro-N-(1,1,1-trifluoropropan-2-yl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine

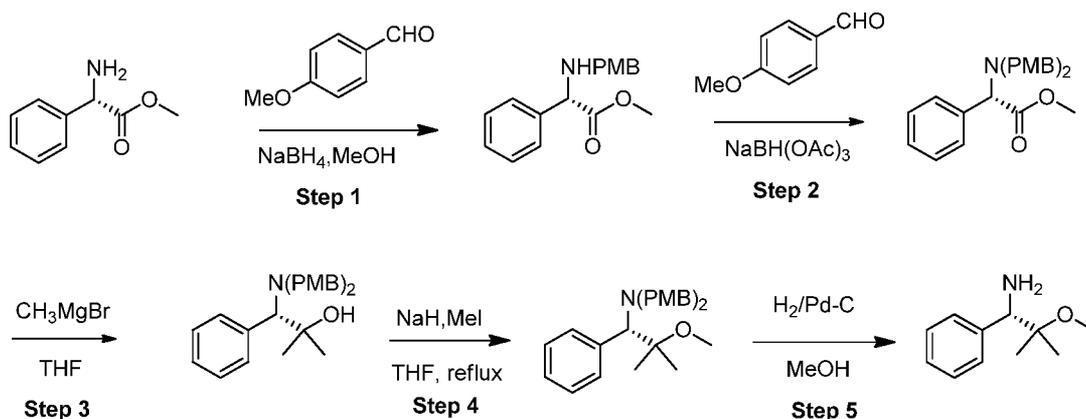
5 To a solution of 6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine (0.5 g, 0.96 mmol) in *anhydrous* THF (5 mL) was added 1,1,1-trifluoropropan-2-amine (0.13 g, 1.2 mmol), t-Bu-X-Phos precatalyst (0.1 g, 0.14 mmol) and sodium-t-Butoxide (0.27 g, 2.8 mmol). The contents were heated to 80 °C in a sealed reaction vessel under inert atmosphere. After 4 h, the reaction mixture was brought back to ambient temperature, the reaction was quenched with  
 10 H<sub>2</sub>O (10 mL) and the organic contents were extracted with EtOAc (2 x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue thus obtained was purified by flash column chromatography, to afford the title compound (0.32 g, 67% yield). MS ESI calc'd. for  $C_{28}H_{22}ClF_3N_4 [M+H]^+$  507; Found 507.

### Intermediate 431A



15

### (S)-2-methoxy-2-methyl-1-phenylpropan-1-amine



### Step 1: Synthesis of (S)-methyl 2-((4-methoxybenzyl)amino)-2-phenylacetate:

20 To a solution of (S)-methyl 2-amino-2-phenylacetate (1.0 g, 6.06 mmol) in *anhydrous* MeOH (20 mL) was added 4-methoxy benzaldehyde (0.82 g, 6.06 mmol) and few drops of HOAc. After 30 min, the reaction mixture was cooled to 0 °C, NaBH<sub>4</sub> (0.69 g, 12.12 mmol)

- 119 -

was added and the contents were stirred at ambient temperature. After 2h, the reaction was quenched with ice cold H<sub>2</sub>O (10 mL), MeOH was removed under reduced pressure and the organic contents were extracted with EtOAc (3x25 mL). The combined organic extracts were washed with brine (1x20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and the residue thus obtained was taken directly for step 2. MS ES+APCI calc'd. for C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 286; Found 286.

**Step 2: Synthesis of (S)-methyl 2-(bis(4-methoxybenzyl)amino)-2-phenylacetate:**

To a solution of (S)-methyl 2-((4-methoxybenzyl)amino)-2-phenylacetate (1.6 g, 5.61 mmol) in *anhydrous* dichloroethane (20 mL) was added 4-methoxy benzaldehyde (0.76g, 5.61mmol) and few drops of HOAc. After 30 min, the reaction mixture was cooled to 0 °C, sodium triacetoxy borohydride (2.38 g, 11.22 mmol) was added and the contents were allowed to stir at ambient temperature. After 2h, the reaction was quenched with ice cold H<sub>2</sub>O (10 mL), and the organic contents were extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x25 mL). The combined organic extracts were washed with brine (1x20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and the residue thus obtained was purified by flash column chromatography to afford the title compound as pale yellow liquid (1.5 g, 66%). MS ES+APCI calc'd. for C<sub>25</sub>H<sub>27</sub>NO<sub>4</sub> [M+H]<sup>+</sup> 406; Found 406.

**Step 3: Synthesis of (S)-1-(bis(4-methoxybenzyl)amino)-2-methyl-1-phenylpropan-2-ol:**

At 0 °C, to a solution of (S)-methyl 2-(bis(4-methoxybenzyl)amino)-2-phenylacetate (1.5 g, 3.7 mmol) in *anhydrous* THF (15 mL), was added MeMgBr (3M solution in Et<sub>2</sub>O, 12.3 mL, 37.0 mmol) and resultant mixture was allowed to warm and stirred at ambient temperature. After 10 h, the reaction was carefully quenched with saturated aqueous NH<sub>4</sub>Cl solution (25 mL), and the organic contents were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The volatiles were removed under reduced pressure and the residue thus obtained was further purified by flash column chromatography to afford the title compound. MS ES+APCI calc'd. for C<sub>26</sub>H<sub>31</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 406; Found 406.

**Step 4: Synthesis of (S)-2-methoxy-N,N-bis(4-methoxybenzyl)-2-methyl-1-phenylpropan-1-amine:**

At 0 °C, to a suspension of NaH (0.13 g, 2.96 mmol) in *anhydrous* THF (5 mL), was added a solution of (S)-1-(bis(4-methoxybenzyl)amino)-2-methyl-1-phenylpropan-2-ol (1.0 g, 2.47 mmol) in *anhydrous* THF (10 mL). After 15 min, MeI (0.55 g, 3.71 mmol) was added and the contents were heated to reflux. After 8 h, the reaction was brought back to ambient temperature, quenched carefully with ice cold H<sub>2</sub>O (10 mL), and the organic contents were extracted with EtOAc (3x25 mL). The combined organic extracts were washed with brine (1x20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated to afford the title compound. H<sup>1</sup>NMR (ppm,

- 120 -

400MHz, CD<sub>3</sub>OD)  $\delta$  7.45-7.44 (m, 2H), 7.37-7.34 (m, 2H), 7.33-7.28 (m, 5H), 6.88-6.86 (m, 4H), 4.20(s, 1H), 3.78 (s, 6H), 3.25 (s, 4H), 2.81 (s, 3H), 1.4 (s, 3H), 0.81 (s, 3H). MS ES+APCI calc'd. for C<sub>27</sub>H<sub>33</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 420; Found 420.

**Step 5: Synthesis of (S)-2-methoxy-2-methyl-1-phenylpropan-1-amine:**

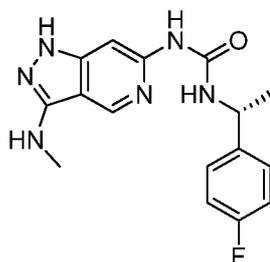
- 5 A solution of (S)-2-methoxy-N,N-bis(4-methoxybenzyl)-2-methyl-1-phenylpropan-1-amine (0.7 g, 1.67 mmol) in *anhydrous* MeOH was added Pd on C (0.1 g) and the contents were stirred at ambient temperature in H<sub>2</sub> atmosphere. After 14 h, the reaction mixture was filtered through a pad of celite and the volatiles were removed under reduced pressure. The residue thus obtained was further purified by preparative HPLC to afford the title compound .
- 10 <sup>1</sup>H NMR (ppm, 400MHz, CDCl<sub>3</sub>)  $\delta$  7.45-7.44 (m, 2H), 7.35-7.33 (m, 3H), 4.1 (s, 1H), 3.32 (s, 3H), 1.2 (s, 3H), 1.12 (s, 3H).

**Examples**

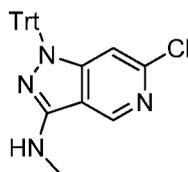
Examples 1-42 were prepared according to scheme 1.

15

**Example 1**



**1-[(1R)-1-(4-Fluorophenyl)ethyl]-3-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea**

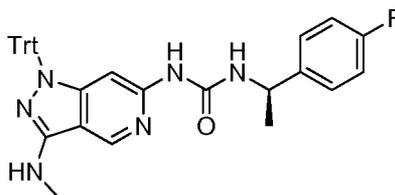


**20 Step 1: 6-Chloro-N-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine**

- 6-Chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine (**Intermediate 1C**; 6.08 g, 11.65 mmol), proline (0.42 g, 3.65 mmol), copper(I) iodide (0.24 g, 1.260 mmol), potassium carbonate (9.83 g, 71.1 mmol), and methylamine hydrochloride (3.26 g, 48.3 mmol) were stirred in DMSO (45 mL) at 70 °C for 24 h. Room temperature was attained, ammonium hydroxide was added, and the products extracted into DCM (x2). The combined organic
- 25 extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*.

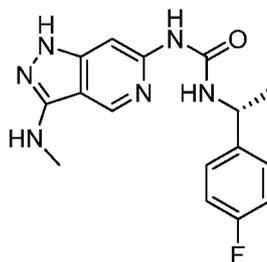
- 121 -

Purification of the residue by flash chromatography (6-50% EtOAc-hexanes) gave 6-chloro-N-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine. MS ESI calc'd. For  $C_{26}H_{21}ClN_4$   $[M+1]^+$  425, found 425.



5 **Step 2: (R)-1-(1-(4-Fluorophenyl)ethyl)-3-(3-(methylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

6-Chloro-N-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (332 mg, 0.781 mmol), (R)-1-(1-(4-fluorophenyl)ethyl)urea (**Intermediate 20C**; 193 mg, 1.059 mmol), BrettPhos pre-catalyst (48.0 mg, 0.060 mmol), and cesium carbonate (759 mg, 2.330 mmol) were taken up in 1,4-dioxane (6 mL) in a 20 mL microwave vial. The vial was evacuated and back-filled with  $N_2$  (x3) and the reaction was stirred at 100 °C for 3 h. Room temperature was attained, the reaction mixture was filtered through Celite, eluting with MeOH, and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (0-100% EtOAc-DCM) gave (R)-1-(1-(4-fluorophenyl)ethyl)-3-(3-(methylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea. MS ESI calc'd. For  $C_{35}H_{31}FN_6O$   $[M+1]^+$  571, found 571.

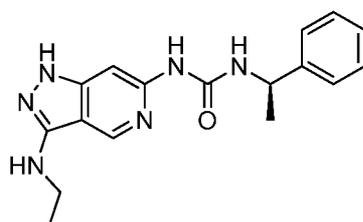


20 **Step 3: 1-[(1R)-1-(4-Fluorophenyl)ethyl]-3-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea**

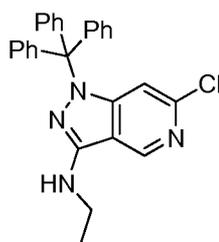
(R)-1-(1-(4-Fluorophenyl)ethyl)-3-(3-(methylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (404 mg, 0.708 mmol) and triethylsilane (0.170 mL, 1.062 mmol) were stirred in TFA (5 mL) at room temperature for 30 min. The solvent was removed *in vacuo*, saturated  $NaHCO_3$  was added, and the products extracted into EtOAc (x2). The combined organic extracts were washed with brine, dried over  $Na_2SO_4$ , filtered through Celite, and concentrated *in vacuo*. Purification of the residue by flash chromatography (0-15% MeOH-EtOAc) gave 1-[(1R)-1-(4-fluorophenyl)ethyl]-3-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea. MS ESI calc'd. For  $C_{16}H_{17}FN_6O$   $[M+1]^+$  329, found 329.  $^1H$  NMR (500

- 122 -

MHz, DMSO- $d_6$ )  $\delta$  11.48 (s, 1H), 8.86 (s, 1H), 8.54 (s, 1H), 8.05 (br s, 1H), 7.36 (dd,  $J = 8.5, 5.5$  Hz, 2H), 7.24 (s, 1H), 7.14 (t,  $J = 9.0$  Hz, 2H), 6.25 (q,  $J = 5.0$  Hz, 1H), 4.88-4.83 (m, 1H), 2.81 (d,  $J = 5.0$  Hz, 3H), 1.38 (d,  $J = 6.5$  Hz, 3H).

**Example 2**

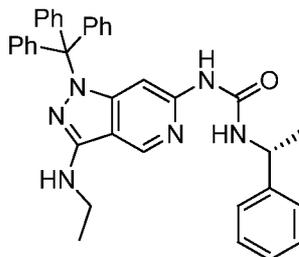
5

**(R)-1-(3-(Ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea****Step 1: 6-Chloro-N-ethyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine**

6-Chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine (**Intermediate 1C**; 5.53 g, 10.60 mmol), proline (0.42 g, 3.65 mmol), copper (I) iodide (0.21 g, 1.103 mmol), potassium carbonate (7.40 g, 53.5 mmol), and ethylamine hydrochloride (2.78 g, 34.1 mmol) were stirred in DMSO (30 mL) at 70 °C for 24 h. Room temperature was attained, ammonium hydroxide was added and the products extracted into DCM (x2). The combined organic extracts were washed with brine, dried over  $MgSO_4$ , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (6-50% EtOAc-hexanes) gave 6-chloro-N-ethyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine. MS ESI calc'd. For  $C_{27}H_{23}ClN_4$   $[M+1]^+$  439, found 439.

10

15

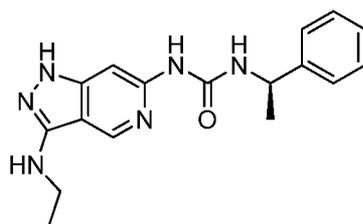
**Step 2: (R)-1-(3-(Ethylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

20

6-Chloro-N-ethyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (3 g, 6.83 mmol), (R)-1-(1-phenylethyl)urea (1.68 g, 10.25 mmol), and BrettPhos pre-catalyst (546 mg, 0.68 mmol)

- 123 -

were taken up in THF (13 mL). The resulting mixture was degassed for 5 min followed by addition of sodium *tert*-butoxide (6834  $\mu$ L, 13.67 mmol) at room temperature. After the mixture was degassed again for 5 min, the reaction was heated to 50 °C under N<sub>2</sub> for 6 h, Room temperature was attained, sat NH<sub>4</sub>Cl was added, and the mixture was extracted with  
5 EtOAc. The organic layer was washed with water, dried, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (0-100% EtOAc/Hexanes) gave (R)-1-(3-(ethylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. For C<sub>36</sub>H<sub>34</sub>N<sub>6</sub>O [M+1]<sup>+</sup> 567, found 567.

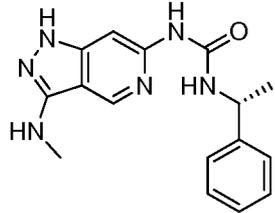
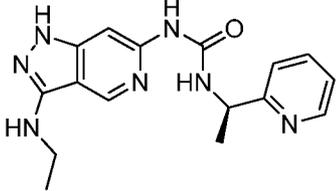
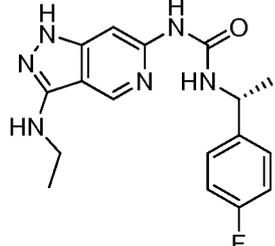
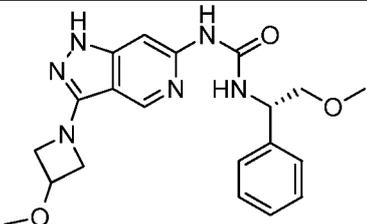
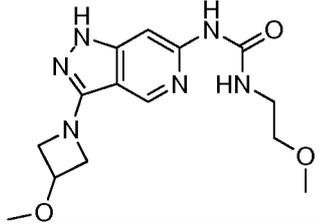
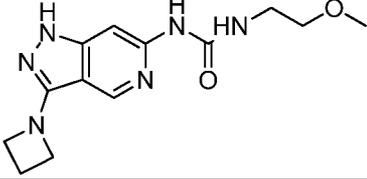
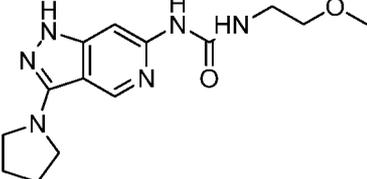


10 **Step 3: (R)-1-(3-(Ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

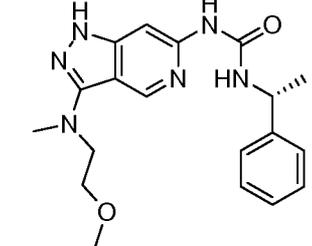
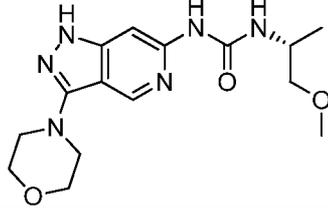
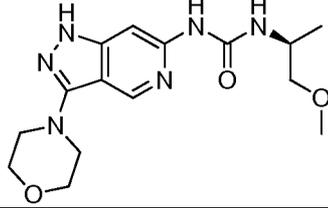
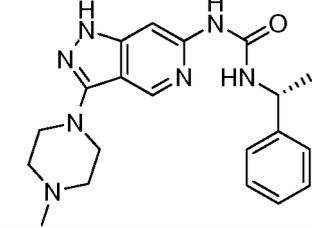
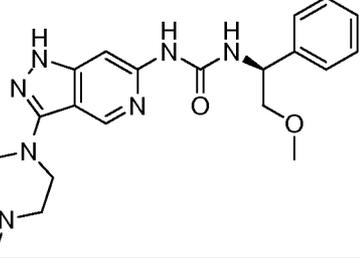
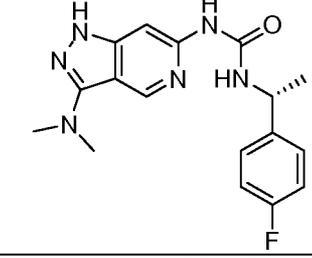
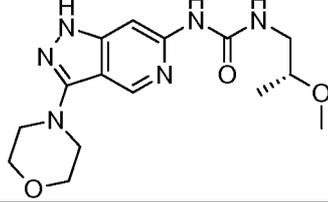
(R)-1-(3-(Ethylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (187 mg, 0.330 mmol) and triethylsilane (0.080 mL, 0.501 mmol) were stirred in TFA (2 mL) at room temperature for 30 min. The solvent was removed *in vacuo*, saturated NaHCO<sub>3</sub> was added, and the products extracted into EtOAc (x2). The combined organic extracts were  
15 washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered through Celite, and concentrated *in vacuo*. Purification of the residue by flash chromatography (0-10% MeOH-EtOAc) gave (R)-1-(3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. For C<sub>17</sub>H<sub>20</sub>N<sub>6</sub>O [M+1]<sup>+</sup> 325, found 325. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  11.45 (s, 1H), 8.86 (s, 1H), 8.57 (s, 1H), 8.09 (br s, 1H), 7.34-7.31 (m, 4H), 7.25-7.20 (m, 2H), 6.21 (t, J = 5.5 Hz,  
20 1H), 4.89-4.83 (m, 1H), 3.25-3.19 (m, 2H), 1.39 (d, J = 7.0 Hz, 3H), 1.18 (t, J = 7.0 Hz, 3H). Examples 3-38 (Table 1) were prepared according to Scheme 1 following a similar procedure to that described for Example 1 using the appropriate pyrazolopyridine (Intermediate 1C), the appropriate aryl chlorides, and commercial or synthesized ureas (prepared using the same procedure as intermediates 20C-24C), which can be achieved by those of ordinary skill in the  
25 art of organic synthesis. The compounds of examples 6, 8, 9, 11, 12, 16, 17, 18, 21, 25, 27, 28, 30, and 38 were obtained as the trifluoroacetic acid salt.

- 124 -

Table 1

Ex	Structure	IUPAC Name	Exact Mass [M+H] <sup>+</sup>
3		1-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 311, Found 311
4		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-pyridin-2-ylethyl]urea	Calc'd 326, Found 326
5		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-(4-fluorophenyl)ethyl]urea	Calc'd 343, Found 343
6		1-[3-(3-methoxyazetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 397, Found 397
7		1-[3-(3-methoxyazetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-(2-methoxyethyl)urea	Calc'd 321, Found 321
8		1-(3-azetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-methoxyethyl)urea	Calc'd 291, Found 291
9		1-(2-methoxyethyl)-3-(3-pyrrolidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 305, Found 305

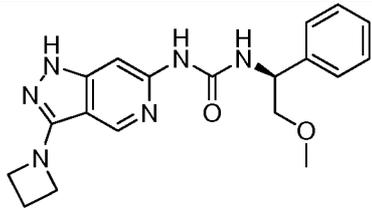
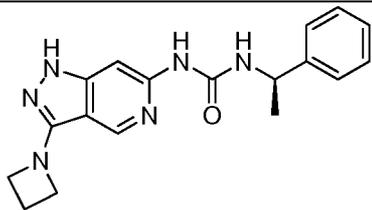
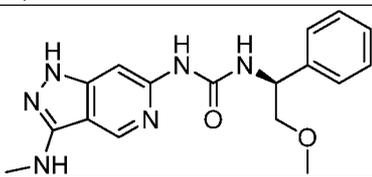
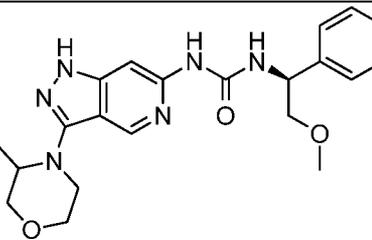
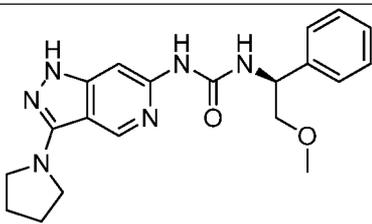
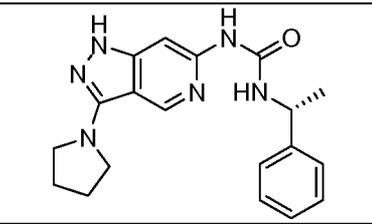
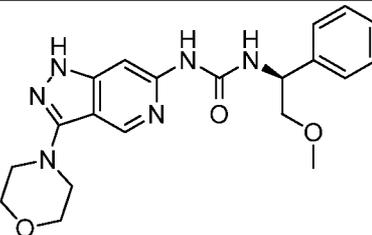
- 125 -

10		1-{3-[(2-methoxyethyl)(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 369, Found 369
11		1-[(1R)-2-methoxy-1-methylethyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 335, Found 335
12		1-[(1S)-2-methoxy-1-methylethyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 335, Found 335
13		1-[3-(4-methylpiperazin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 380, Found 380
14		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(4-methylpiperazin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 410, Found 410
15		1-[3-(dimethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-(4-fluorophenyl)ethyl]urea	Calc'd 343, Found 343
16		1-[(2R)-2-methoxypropyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 335, Found 335

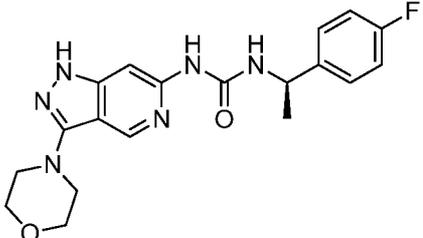
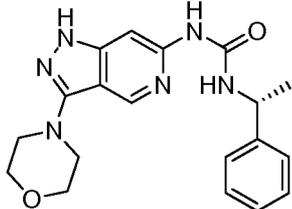
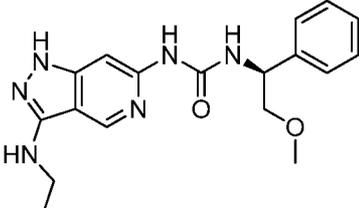
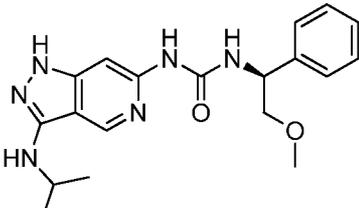
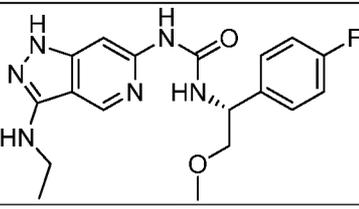
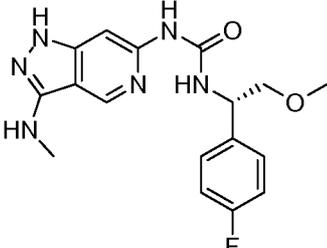
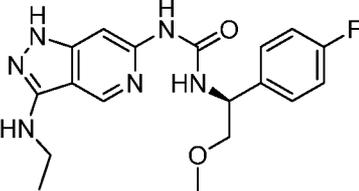
- 126 -

17		1-[(2S)-2-methoxypropyl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 335, Found 335
18		1-[3-(dimethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 355, Found 355
19		1-[3-(dimethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 325, Found 325
20		1-(2-methoxyethyl)-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 321, Found 321
21		1-[3-(diethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 383, Found 383
22		1-[3-(3-methoxyazetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 367, Found 367
23		1-[(1R)-1-(4-fluorophenyl)ethyl]-3-[3-(3-methoxyazetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 385, Found 385

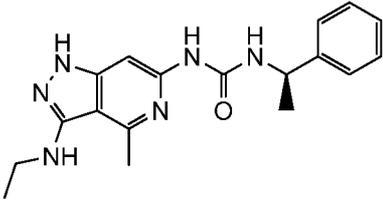
- 127 -

24		1-(3-azetidin-1-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 367, Found 367
25		1-(3-azetidin-1-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 337, Found 337
26		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 341, Found 341
27		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(3-methylmorpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 411, Found 411
28		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(3-pyrrolidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 381, Found 381
29		1-[(1R)-1-phenylethyl]-3-[3-(3-pyrrolidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 351, Found 351
30		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 397, Found 397

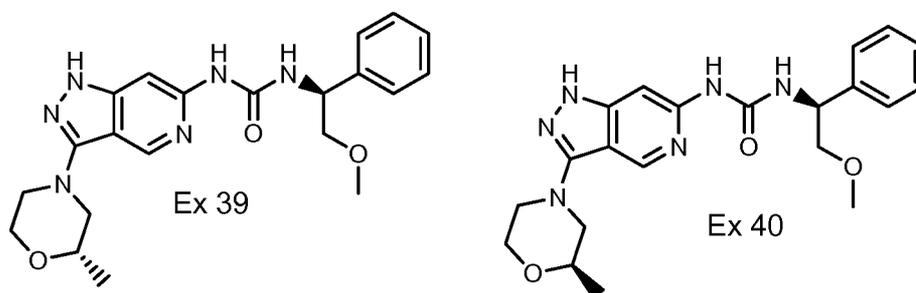
- 128 -

31		1-[(1R)-1-(4-fluorophenyl)ethyl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 385, Found 385
32		1-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 367, Found 367
33		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 355, Found 355
34		1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(1-methylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl} urea	Calc'd 369, Found 369
35		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-(4-fluorophenyl)-2-methoxyethyl]urea	Calc'd 373, Found 373
36		1-[(1S)-1-(4-fluorophenyl)-2-methoxyethyl]-3-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 359, Found 359
37		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-1-(4-fluorophenyl)-2-methoxyethyl]urea	Calc'd 373, Found 373.

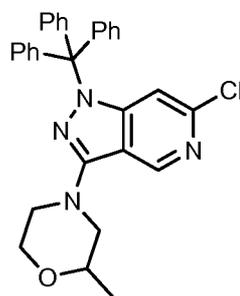
- 129 -

38		1-[3-(ethylamino)-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 339,  Found 339
----	---	---	------------------------------------

## Examples 39 and 40



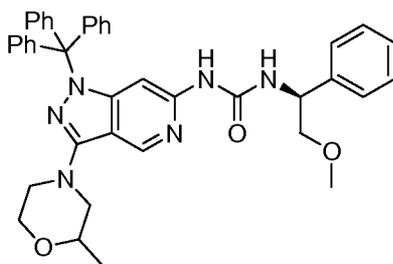
1-[(1S)-2-Methoxy-1-phenylethyl]-3-{3-[(2R)-2-methylmorpholin-4-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea (Example 39) and 1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(2S)-2-methylmorpholin-4-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea (Example 40)



## Step 1: 4-(6-Chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)-2-methylmorpholine

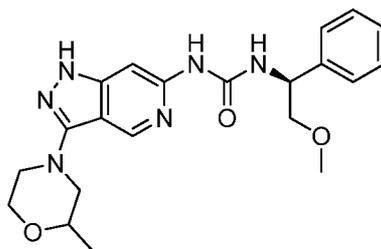
4-(6-Chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)-2-methylmorpholine was prepared using the same procedure described for 6-chloro-N-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (Example 1, Step 1). MS ESI calc'd. For  $C_{30}H_{27}ClN_4O$   $[M+1]^+$  495, found 495.

- 130 -



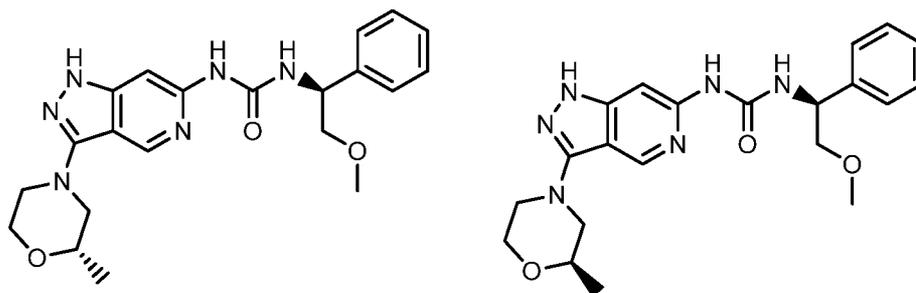
**Step 2: 1-((S)-2-Methoxy-1-phenylethyl)-3-(3-(2-methylmorpholino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

1-((S)-2-Methoxy-1-phenylethyl)-3-(3-(2-methylmorpholino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea was prepared using the same procedure described for (R)-1-(1-(4-fluorophenyl)ethyl)-3-(3-(methylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (**Example 1, Step 2**). MS ESI calc'd. For  $C_{40}H_{40}N_6O_3$   $[M+1]^+$  653, found 653.



**Step 3: 1-((S)-2-Methoxy-1-phenylethyl)-3-(3-(2-methylmorpholino)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

1-((S)-2-Methoxy-1-phenylethyl)-3-(3-(2-methylmorpholino)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea was prepared using the same procedure described for 1-[(1R)-1-(4-fluorophenyl)ethyl]-3-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea (**Example 1, Step 3**). MS ESI calc'd. For  $C_{21}H_{26}N_6O_3$   $[M+1]^+$  411, found 411.



**Step 4: 1-[(1S)-2-Methoxy-1-phenylethyl]-3-[(2R)-2-methylmorpholin-4-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl)urea and 1-[(1S)-2-methoxy-1-phenylethyl]-3-[(2S)-2-methylmorpholin-4-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

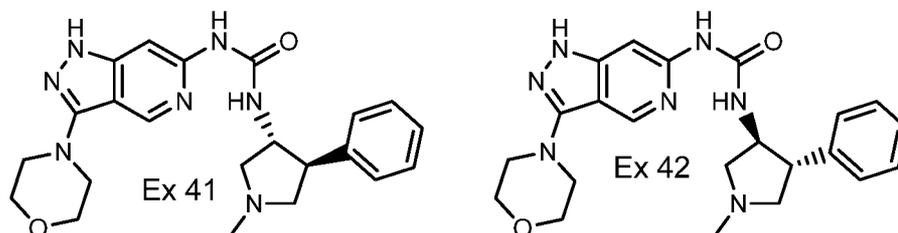
The enantiomers of 1-((S)-2-Methoxy-1-phenylethyl)-3-(3-(2-methylmorpholino)-1H-

15

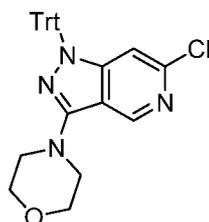
- 131 -

pyrazolo[4,3-c]pyridin-6-yl)urea (38 mg, 0.072 mmol) were separated by SFC (Berger Multigram II SFC, column: Chiral Technology IC-H 2.1 X 25cm, 5 uM, mobile phase: 39% to 61% MeOH + 0.25% dimethyl ethylamine in CO<sub>2(l)</sub>, flow rate: 70 mL/min, 6 min run time). The fractions were collected and the solvent evaporated *in vacuo* to afford 1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(2R)-2-methylmorpholin-4-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl} urea (9.91 mg, 0.024 mmol, 67%) and 1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(2S)-2-methylmorpholin-4-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl} urea. MS ESI calc'd. For C<sub>21</sub>H<sub>26</sub>N<sub>6</sub>O<sub>3</sub> [M+1]<sup>+</sup> 411, found 411. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 12.01 (s, 1H), 9.09 (s, 1H), 8.82 (s, 1H), 8.09 (br s, 1H), 7.39 (s, 1H), 7.35 – 7.31 (m, 4H), 7.26 – 7.21 (m, 1H), 5.00 – 4.93 (m, 1H), 3.91 – 3.83 (m, 1H), 3.78 (d, *J* = 12.0 Hz, 1H), 3.74 – 3.65 (m, 3H), 3.55 (d, *J* = 5.4 Hz, 2H), 3.25 (s, 3H), 2.91 – 2.82 (m, 1H), 2.59 – 2.51 (m, 1H), 1.15 (d, *J* = 6.2 Hz, 3H) (Example 39). MS ESI calc'd. For C<sub>21</sub>H<sub>26</sub>N<sub>6</sub>O<sub>3</sub> [M+1]<sup>+</sup> 411, found 411. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 12.02 (s, 1H), 9.35 – 9.16 (br s, 1H), 9.11 (s, 1H), 8.83 (s, 1H), 8.18 – 8.09 (br s, 1H), 7.38 (s, 1H), 7.35 – 7.29 (m, 4H), 7.27 – 7.20 (m, 8.7, 1H), 5.02 – 4.90 (m, 1H), 3.93 – 3.83 (m, 1H), 3.78 (d, *J* = 11.8 Hz, 1H), 3.74 – 3.64 (m, 3H), 3.55 (d, *J* = 5.4 Hz, 2H), 3.25 (s, 3H), 3.10 – 3.01 (m, 1H), 2.93 – 2.82 (m, 1H), 2.60 – 2.51 (m, 1H), 1.14 (d, *J* = 6.0 Hz, 3H) (Example 40).

## Examples 41 and 42



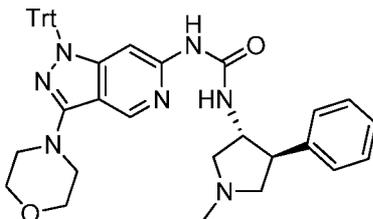
20 **1-[(3R,4S)-1-Methyl-4-phenylpyrrolidin-3-yl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (Example 41) and 1-[(3S,4R)-1-methyl-4-phenylpyrrolidin-3-yl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (Example 42)**

**Step 1: 4-(6-Chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)morpholine**

25 4-(6-Chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)morpholine was prepared using the same procedure described for 6-chloro-N-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-

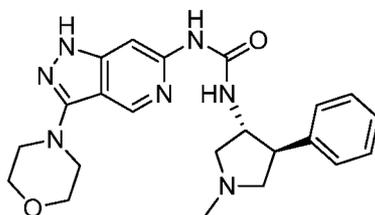
- 132 -

amine (**Example 1, Step 1**). MS ESI calc'd. For  $C_{29}H_{25}ClN_4O$   $[M+1]^+$  481, found 481.



**Step 2: 1-((3R and S, 4S and R)-1-Methyl-4-phenylpyrrolidin-3-yl)-3-(3-morpholino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

5           4-(6-Chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)morpholine (200 mg, 0.416 mmol), 1-((3R and S, 4S and R)-1-methyl-4-phenylpyrrolidin-3-yl)urea (**Intermediate 24C**; 137 mg, 0.624 mmol), BrettPhos pre-catalyst (33.2 mg, 0.042 mmol) and potassium tert-butoxide (93 mg, 0.832 mmol) were taken up in DMA (2 mL) in a 5 mL microwave vial. The vial was degassed with argon and the reaction stirred at 100 °C overnight. Room temperature  
10           was attained, the reaction mixture was filtered through Celite, eluting with EtOAc. The filtrate was concentrated *in vacuo* with silica gel. The residue was purified by flash chromatography (0-10% DCM/MeOH) to give 1-((3R and S, 4S and R)-1-methyl-4-phenylpyrrolidin-3-yl)-3-(3-morpholino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea. MS ESI calc'd. For  $C_{41}H_{41}N_7O_2$   $[M+1]^+$  664, found 664.

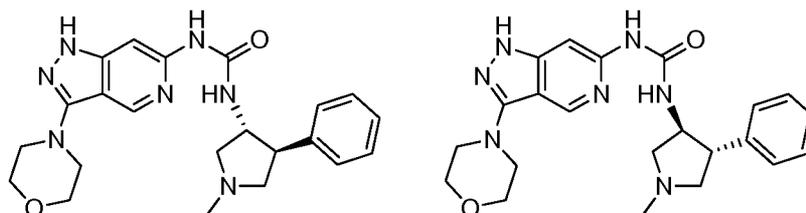


15

**Step 3: 1-[(3R and S, 4S and R)-1-Methyl-4-phenylpyrrolidin-3-yl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

20           1-((3R and S, 4S and R)-1-Methyl-4-phenylpyrrolidin-3-yl)-3-(3-morpholino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (98.5 mg, 0.148 mmol) was dissolved in TFA (1 mL) and triethylsilane (0.036 mL, 0.223 mmol) was added. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with DMF (1 mL), filtered, and purified by mass-triggered reverse-phase HPLC. Fractions containing pure compound were concentrated *in vacuo* to afford 1-[(3R and S, 4S and R)-1-methyl-4-phenylpyrrolidin-3-yl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea. MS ESI calc'd. For  $C_{22}H_{27}N_7O_2$   
25            $[M+1]^+$  422, found 422.

- 133 -



**Step 4: 1-[(3R,4S)-1-Methyl-4-phenylpyrrolidin-3-yl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea and 1-[(3S,4R)-1-methyl-4-phenylpyrrolidin-3-yl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

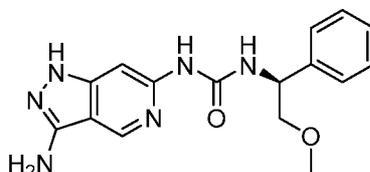
5 The enantiomers of 1-[(3R and S, 4S and R)-1-Methyl-4-phenylpyrrolidin-3-yl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (63.5 mg, 0.098 mmol) were separated by SFC (Berger Multigram II SFC, column: Chiral Technology IC 2.1 X 25cm, 5 uM, mobile phase: 40% to 60% MeOH + 0.25% dimethyl ethylamine in CO<sub>2(l)</sub>, flow rate: 70 mL/min, 12 min run time). The fractions were collected and the solvent evaporated *in vacuo*, dissolved in

10 ACN/water, and lyophilized to afford 1-[(3R,4S)-1-methyl-4-phenylpyrrolidin-3-yl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (15.6 mg, 0.037 mmol, 50%) and 1-[(3S,4R)-1-methyl-4-phenylpyrrolidin-3-yl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (Example 42 was obtained as the trifluoroacetic acid salt of the compound). MS ESI calc'd. For C<sub>22</sub>H<sub>27</sub>N<sub>7</sub>O<sub>2</sub> [M+1]<sup>+</sup> 422, found 422. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 12.0 (s, 1H), 8.90 (s, 1H), 8.79 (s, 1H), 7.88-7.80 (m, 1H), 7.35 (s, 1H), 7.35-7.23 (m, 4H), 7.23-7.14 (m, 1H), 4.21-4.18 (m, 1H), 3.82-3.69 (m, 4H), 3.36-3.30 (m, 4H), 3.13-3.01 (m, 2H), 2.82 (dd, J = 4.5, 9.4 Hz, 1H), 2.54 (dd, J = 4.5, 9.4 Hz, 1H), 2.43-2.33 (m, 1H), 2.28 (s, 3H)

15 (Example 41). MS ESI calc'd. For C<sub>22</sub>H<sub>27</sub>N<sub>7</sub>O<sub>2</sub> [M+1]<sup>+</sup> 422, found 422. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 12.02 (s, 1H), 8.97 (s, 1H), 8.79 (s, 1H), 7.88-7.80 (m, 1H), 7.32 (s, 1H), 7.35-7.23 (m, 4H), 7.23-7.14 (m, 1H), 4.21-4.18 (m, 1H), 3.81-3.70 (m, 4H), 3.36-3.30 (m, 4H), 3.13-3.01 (m, 2H), 2.82 (dd, J = 4.5, 9.4 Hz, 1H), 2.54 (dd, J = 4.5, 9.4 Hz, 1H), 2.43-2.33 (m, 1H), 2.28 (s, 3H). (Example 42).

Examples 43-46 were prepared according to scheme 2.

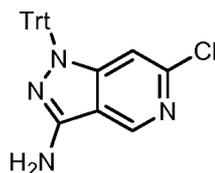
**Example 43**



**(S)-1-(3-Amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-methoxy-1-phenylethyl)urea**

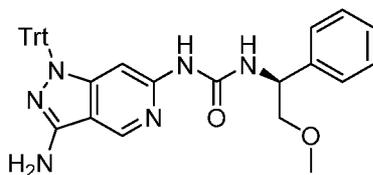
25

- 134 -



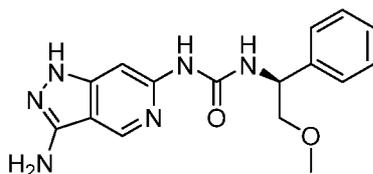
**Step 1: 6-Chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine**

A mixture of 6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine (**Intermediate 1C**; 5.0 g, 9.58 mmol), acetylacetone (0.979 mL, 9.58 mmol), cupric acetylacetonate (0.251 g, 0.958 mmol), and cesium carbonate (6.24 g, 19.17 mmol) in DMF (25.2 mL) were charged in a sealed vessel. The system was degassed and ammonium hydroxide (13.33 mL, 96 mmol) was added. The reaction was heated at 60 °C for 16 h. The reaction was then poured into a solution of 10% NH<sub>4</sub>OH aq. (150 mL), brine (50 mL), and EtOAc (75 mL). The layers were separated and the aqueous phase was extracted with EtOAc (75 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated *in vacuo*. The residue was purified by flash chromatography (0-45% EtOAc/Hexanes) to afford 6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine. MS ESI calc'd. for C<sub>25</sub>H<sub>19</sub>ClN<sub>4</sub> [M+1]<sup>+</sup> 411, found 411.



**Step 2: (S)-1-(3-Amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-methoxy-1-phenylethyl)urea**

(S)-1-(3-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-methoxy-1-phenylethyl)urea was prepared using the same procedure described for (R)-1-(1-(4-fluorophenyl)ethyl)-3-(3-(methylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (**Example 1, Step 2**). MS ESI calc'd. For C<sub>35</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub> [M+1]<sup>+</sup> 569, found 569.



20

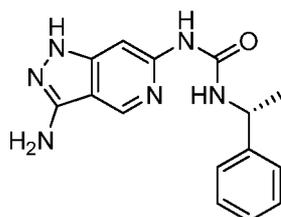
**Step 3: (S)-1-(3-Amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-methoxy-1-phenylethyl)urea**

(S)-1-(3-Amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-methoxy-1-phenylethyl)urea was prepared using the same procedure described for [(1R)-1-(4-fluorophenyl)ethyl]-3-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea (**Example 1, Step 3**). MS ESI calc'd. For C<sub>16</sub>H<sub>18</sub>N<sub>6</sub>O<sub>2</sub> [M+1]<sup>+</sup> 327, found 327. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 11.41 (s, 1H), 8.99 (s,

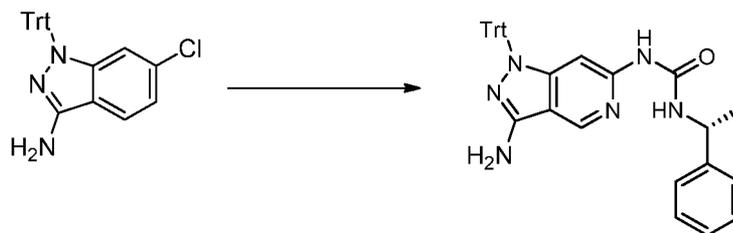
25

- 135 -

1H), 8.57 (s, 1H), 8.45 – 8.19 (br s, 1H), 7.37 – 7.25 (m, 4H), 7.24 – 7.13 (m, 1H), 5.62 (s, 2H), 4.98 – 4.90 (m, 1H), 3.54 (d,  $J = 5.1$ , 2H), 3.23 (s, 3H).

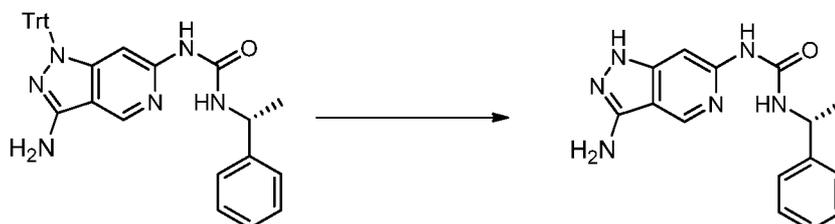
**Example 46**

5

**1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea (Example 46)****Step 1: (R)-1-(3-amino-1-(trityl)amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea:**

6-chloro-1-(trityl)amino-3-amino-1H-pyrazolo[4,3-c]pyridine (500 mg, 1.217 mmol), (R)-1-(1-phenylethyl)urea (400 mg, 2.434 mmol), cesium carbonate (1023 mg, 3.14 mmol) and chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-tri-*i*-propyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl] palladium(II) (58.3 mg, 0.073 mmol) were charge in a 40 mL vial with dioxane (11 ml). System was degassed and stirred at 100 °C for 3 hours. Reaction mixture was evaporated *in vacuo* and purified by normal phase column chromatography eluting with hexane/EtOAc(0-50%) affording (R)-1-(3-amino-1-(trityl)amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (333 mg, 0.618 mmol, 50.8 % yield) as an off white solid. 1H NMR (500 MHz, dmsO)  $\delta$  8.82 (s, 1H), 8.51 (s, 1H), 8.32 (bs, 1H), 7.38 – 7.13 (m, 19H), 6.49 (s, 1H), 5.88 (s, 2H), 4.85 – 4.75 (m, 1H), 1.35 (d, 3H). MS ESI calc'd. For  $C_{34}H_{30}N_6O[M+H]^+$  539, found 539.

20

**Step 2: (R)-1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea:**

- 136 -

A solution of (R)-1-(3-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (310 mg, 0.576 mmol) and triethylsilane (184  $\mu$ l, 1.151 mmol) in DCM (5232  $\mu$ l) were treated with trifluoroacetic acid (2660  $\mu$ l, 34.5 mmol) and stirred for 1 hr at room temperature. Reaction mixture was evaporated *in vacuo*, partitioned between EtOAc/saturated aqeous NaHCO<sub>3</sub> and extracted with EtOAc(2x). Combined organics were washed with saturated aqeous NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated *in vacuo* affording crude product which was purified by normal phase column chromatography eluting with MeOH/EtOAc (0-10 %) affording (R)-1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (145 mg, 0.489 mmol, 85 % yield) as an off white solid. <sup>1</sup>H NMR (500 MHz, dmsO)  $\delta$  11.42 (s, 1H), 8.87 (s, 1H), 8.57 (s, 1H), 8.07 (s, 1H), 7.39 – 7.27 (m, 4H), 7.27 – 7.17 (m, 1H), 5.64 (s, 2H), 4.86 (m, 1H), 1.39 (d, 3H). MS ESI calc'd. For C<sub>15</sub>H<sub>16</sub>N<sub>6</sub>O[M+H]<sup>+</sup> 297, found 297.

Examples 44-46 (Table 2) were prepared according to Scheme 2 following similar procedures described for Example 43 using the appropriate commercial or synthesized ureas (intermediates 20C and 22C).

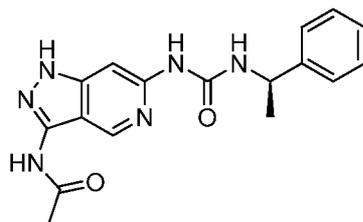
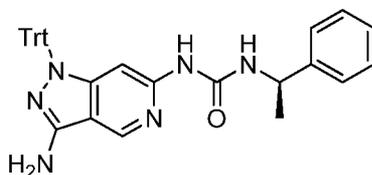
Table 2

Ex	Structure	IUPAC Name	Exact Mass [M+H] <sup>+</sup>
44		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-(4-fluorophenyl)ethyl]urea	Calc'd 315, found 315
45		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-1-(4-fluorophenyl)-2-methoxyethyl]urea	Calc'd 345, found 345
46		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 297, found 297

Examples 47-49 were prepared according to scheme 3.

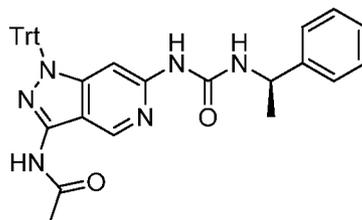
- 137 -

## Example 47

**(R)-N-(6-(3-(1-Phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide****5 Step 1: (R)-1-(3-Amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

6-Chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (**5C**; 4.0 g, 9.73 mmol), (R)-1-(1-phenylethyl)urea (2.4 g, 14.60 mmol), cesium carbonate (7.9 g, 24.34 mmol) and BrettPhos pre-catalyst (467 mg, 0.584 mmol) were charged in a 350 mL pressure vessel with 1,4-dioxane (88 mL). The system was degassed and stirred at 100 °C for 8 h. The reaction mixture was

10 filtered through Celite, evaporated *in vacuo*, dissolved in DCM, and purified by flash chromatography (0-20 % EtOAc/DCM) to afford (R)-1-(3-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. For C<sub>34</sub>H<sub>30</sub>N<sub>6</sub>O<sub>2</sub> [M+1]<sup>+</sup> 539, found 539.

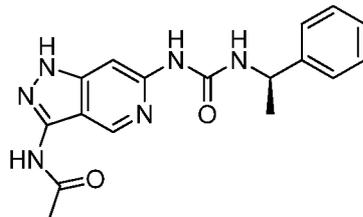
**15 Step 2: (R)-N-(6-(3-(1-Phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide**

A solution of (R)-1-(3-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (900 mg, 1.671 mmol) and DIEA (0.584 mL, 3.34 mmol) in THF (16 mL) at 0° C was treated drop-wise with a solution of acetyl chloride (0.131 mL, 1.838 mmol) in THF (0.5 mL). The reaction was stirred at 0° C for 10 min, then allowed to warm to room temperature and stirred for 1 h. The solvent was evaporated *in vacuo* and purified by flash chromatography (0-30% EtOAc/DCM) to afford (R)-N-(6-(3-(1-phenylethyl)ureido)-1-trityl-

20

- 138 -

1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide. MS ESI calc'd. For C<sub>36</sub>H<sub>32</sub>N<sub>6</sub>O<sub>2</sub> [M+1]<sup>+</sup> 581, found 581.



**Step 3: (R)-N-(6-(3-(1-Phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide**

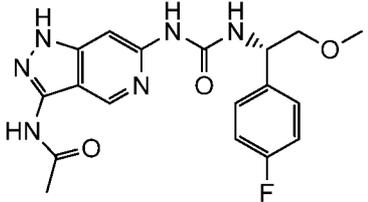
5 A solution of (R)-N-(6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide (900 mg, 1.550 mmol) and triethylsilane (0.495 mL, 3.10 mmol) in DCM (14 mL) was treated with TFA (7.16 mL, 93 mmol). The reaction was stirred at room temperature for 1 h. The reaction mixture was evaporated *in vacuo* and the residue was partitioned between EtOAc and sat. aq. NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc and the  
 10 combined organics were washed with sat. aq. NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated *in vacuo*. The residue was purified by flash chromatography (0-10% MeOH/DCM) to afford (R)-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide. MS ESI calc'd. For C<sub>17</sub>H<sub>18</sub>N<sub>6</sub>O<sub>2</sub> [M+1]<sup>+</sup> 339, found 339. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 12.56 (s, 1H), 10.71 (s, 1H), 8.99 (s, 1H), 8.94 (s, 1H), 7.80 – 7.72 (br s, 1H),  
 15 7.50 (s, 1H), 7.36 – 7.29 (m, 4H), 7.26 – 7.19 (m, 1H), 4.91 – 4.81 (m, 1H), 2.09 (s, 3H), 1.39 (d, *J* = 6.9, 3H).

Examples 48 and 49 (Table 3) were prepared according to Scheme 3 following similar procedures described for Example 47 using the appropriate synthesized ureas (intermediates 21C and 22C).

20

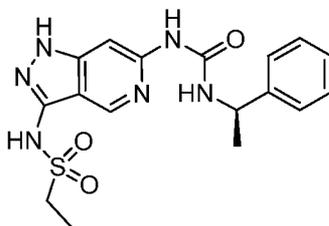
Table 3

Ex	Structure	IUPAC Name	Exact Mass [M+H] <sup>+</sup>
48		N-([6-((1S)-2-methoxy-1-phenylethyl)carbamoyl]-amino)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide	Calc'd 369, Found 369

49		N-[6-({[(1S)-1-(4-fluorophenyl)-2-methoxyethyl]carbamoyl}-amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]acetamide	Calc'd 387, Found 387
----	---	---	--------------------------------

Examples 50-56 were prepared according to scheme 4.

#### Example 50



#### (R)-N-(6-(3-(1-Phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)ethanesulfonamide

5 To an 8 mL vial charged with ethanesulfonyl chloride (10.53  $\mu$ L, 0.111 mmol) was added (R)-1-(3-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (Example 47, Step 1; 20 mg, 0.037 mmol) in DCM (1 mL) and pyridine (0.1 mL). The reaction mixture was stirred at room temperature for 2 h. Excess sulfonyl chloride was quenched by shaking with MP-Trisamine (91 mg, 0.186 mmol) for 3 h. The resin was filtered, 10 the volatiles removed *in vacuo*, and the resulting residue dissolved in TFA (1 mL) and stirred at room temperature for 1 h. Triethylsilane (5.93  $\mu$ L, 0.037 mmol) was added and the reaction mixture was stirred for an additional 5 min. The reaction mixture was concentrated *in vacuo*, the resulting crude residue dissolved in DMSO (1.5 mL), filtered, and purified by mass-triggered reverse phase HPLC to afford (R)-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3- 15 c]pyridin-3-yl)ethanesulfonamide. MS ESI calc'd. For  $C_{17}H_{20}N_6O_3S$   $[M+1]^+$  389, found 389.  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  12.74 (1 H, s), 10.63 (1 H, s), 9.20 (1H, s), 8.76 (1 H, s), 7.70 (1 H, s), 7.50 (1 H, s), 7.31 (4 H, d,  $J = 4.4$  Hz), 7.20-7.21 (1 H, m), 4.84 (1 H, t,  $J = 7.2$  Hz), 3.30 (2 H, q,  $J = 7.4$  Hz), 1.38 (3 H, d,  $J = 7.0$  Hz), 1.23 (3 H, t,  $J = 7.4$  Hz).

20 Examples 51-56 (Table 4) were prepared according to Scheme 4 following similar procedures described for Example 50 using the appropriate sulfonyl chloride. The compounds of Examples 51-56 were obtained as the trifluoroacetic acid salt.

Table 4

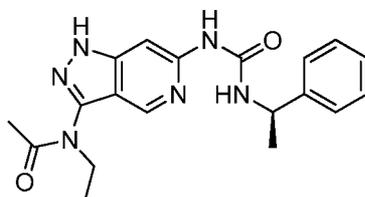
Ex	Structure	IUPAC Name	Exact Mass [M+H] <sup>+</sup>
----	-----------	------------	----------------------------------

51		N-[6-((1R)-1-phenylethyl)carbamoyl]-2-methoxy-1H-pyrazolo[4,3-c]pyridin-3-ylmethanesulfonamide	Calc'd 375, Found 375
52		N-[6-((1R)-1-phenylethyl)carbamoyl]-1H-pyrazolo[4,3-c]pyridin-3-ylcyclopropanesulfonamide	Calc'd 401, Found 401
53		N-[6-((1R)-1-phenylethyl)carbamoyl]-1H-pyrazolo[4,3-c]pyridin-3-ylcyclobutanesulfonamide	Calc'd 415, Found 415
54		2-methoxy-N-[6-((1R)-1-phenylethyl)carbamoyl]-1H-pyrazolo[4,3-c]pyridin-3-ylethanesulfonamide	Calc'd 419, Found 419
55		1-cyclopropyl-N-[6-((1R)-1-phenylethyl)carbamoyl]-1H-pyrazolo[4,3-c]pyridin-3-ylmethanesulfonamide	Calc'd 415, Found 415
56		N-[6-((1R)-1-phenylethyl)carbamoyl]-1H-pyrazolo[4,3-c]pyridin-3-ylazetidine-3-sulfonamide	Calc'd 416, Found 416

Examples 57-58 were prepared according to scheme 5.

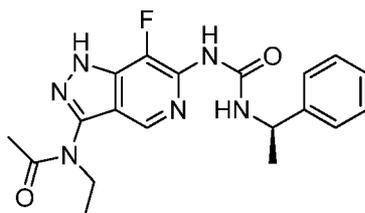
### Example 57

- 141 -

**(R)-1-(3-(Ethylamino)-7-fluoro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

5 **Step 1: (R)-N-Ethyl-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide**

(R)-1-(3-(Ethylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (**Example 2, Step 2**; 680 mg, 1.198 mmol) was dissolved in DCM (20 mL), charged with DIEA (0.42 mL, 2.396 mmol), and cooled to 0 °C. Acetyl chloride (0.095 mL, 1.318 mmol) was added drop-wise and the reaction was warmed to room temperature and stirred for 1 h. The reaction was charged with TFA (2.3 mL, 30.0 mmol) and triethylsilane (0.20 mL, 1.198 mmol) and stirred for 1 h at room temperature. The solvents were removed *in vacuo* and the residue was treated with DCM (3 mL) and triethylamine (1 mL) and stirred for 15 min. The residue was purified by flash chromatography (2-10% MeOH/DCM w/ NH<sub>3</sub>) to afford (R)-N-ethyl-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide. MS ESI calc'd. for C<sub>19</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub> [M+1]<sup>+</sup> 366, found 366.

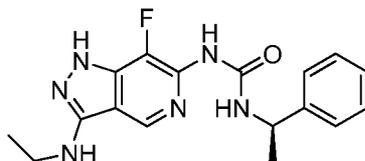


20 **Step 2: (R)-N-Ethyl-N-(7-fluoro-6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide**

(R)-N-Ethyl-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide (154 mg, 0.420 mmol) was dissolved in DMA (1 mL) and methanol (1 mL), charged with powdered Selectfluor® (164 mg, 0.462 mmol), and stirred at room temperature overnight. The reaction was then heated to 55 °C for 8 h. The resulting crude residue was purified by mass-triggered reverse phase HPLC. Fractions containing pure compound were filtered

- 142 -

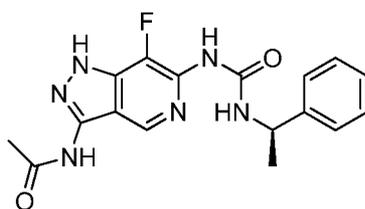
through a PS-HCO<sub>3</sub> cartridge and the filtrate was concentrated *in vacuo* to give (R)-1-(3-(ethylamino)-7-fluoro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for C<sub>19</sub>H<sub>21</sub>FN<sub>6</sub>O<sub>2</sub> [M+1]<sup>+</sup> 385, found 385.



**5 Step 3: (R)-1-(3-(Ethylamino)-7-fluoro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

(R)-N-Ethyl-N-(7-fluoro-6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide (27 mg, 0.070 mmol) was dissolved in THF (3 mL), charged with HCl (300 μL, 3.65 mmol), and heated to 60 °C for 4 h. The solvents were removed *in vacuo* and the residue  
 10 was taken up in DMF and purified by mass-triggered reverse phase HPLC. Fractions containing pure compound were filtered through a PS-HCO<sub>3</sub> cartridge and the filtrate was concentrated *in vacuo* to give (R)-1-(3-(ethylamino)-7-fluoro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for C<sub>17</sub>H<sub>19</sub>FN<sub>6</sub>O [M+1]<sup>+</sup> 343, found 343. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 12.15 (s, 1H), 8.67 (s, 1H), 8.90 (br s, 1H), 8.49 (s, 1H), 7.39 – 7.27  
 15 (m, 4H), 7.26 – 7.18 (m, 1H), 4.90 (t, *J* = 7.2 Hz, 1H), 3.25 (m, 2H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H).

**Example 58**



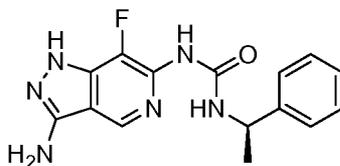
**(R)-N-(7-Fluoro-6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide**

20 (R)-N-(6-(3-(1-Phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide (Example 47; 75 mg, 0.222 mmol) was dissolved in DMA (0.5 mL) and methanol (0.5 mL), charged with powdered Selectfluor® (86 mg, 0.244 mmol), and stirred at room temperature overnight. The reaction was then heated to 65 °C for 2 h. The resulting crude residue was  
 25 purified by mass-triggered reverse phase HPLC. Fractions containing pure compound were filtered through a PS-HCO<sub>3</sub> cartridge and the filtrate was concentrated *in vacuo* to give (R)-N-(7-fluoro-6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide. MS ESI calc'd. for C<sub>17</sub>H<sub>17</sub>FN<sub>6</sub>O<sub>2</sub> [M+1]<sup>+</sup> 357, found 357. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 13.83 (s,

- 143 -

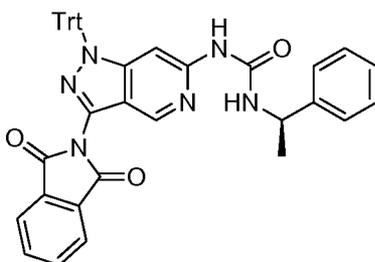
1H) 11.15 (s, 1H), 10.79 (s, 1H), 9.86 (s, 1H), 8.28 (d,  $J = 7.3$ , 1H) 7.34 (m, 4H), 7.34 (m, 1H), 4.88 (m, 1H), 2.20 (s, 3H), 1.43 (d,  $J = 6.9$ , 3H).

Example 59 was prepared according to Scheme 6.

**Example 59**

5

**(R)-1-(3-Amino-7-fluoro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

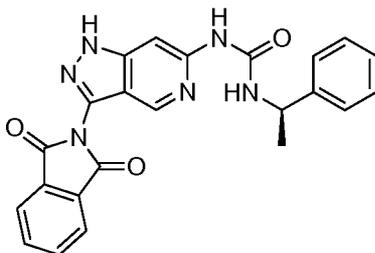


**Step 1: (R)-1-(3-(1,3-Dioxisoindolin-2-yl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

10

(R)-1-(3-Amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (**Example 47, Step 1**; 503 mg, 0.934 mmol) and isobenzofuran-1,3-dione (159 mg, 1.074 mmol) were added to a 1.5 mL microwave vial, charged with dioxane (4 mL), and heated to 110 °C for 4.5 h. The solvents were concentrated *in vacuo* and the residue was purified by flash chromatography (2-10% EtOAc/DCM) to give (R)-1-(3-(1,3-dioxisoindolin-2-yl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for  $C_{42}H_{32}N_6O_3$   $[M+1]^+$  669, found 669.

15



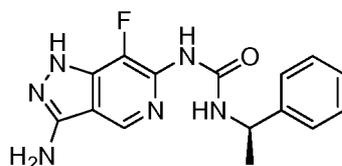
**Step 2: (R)-1-(3-(1,3-Dioxisoindolin-2-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

20

(R)-1-(3-(1,3-Dioxisoindolin-2-yl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (229 mg, 0.342 mmol) was dissolved in DCM (2 mL), charged with TFA (660  $\mu$ L, 8.56 mmol) and triethylsilane (54.7  $\mu$ L, 0.342 mmol), and stirred at room

- 144 -

temperature for 30 min. The solvents were concentrated *in vacuo* and the residue was treated with triethylamine (1 mL). Purification via flash chromatography (10-100% EtOAc/DCM) afforded (R)-1-(3-(1,3-dioxoisindolin-2-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for C<sub>23</sub>H<sub>18</sub>N<sub>6</sub>O<sub>3</sub> [M+1]<sup>+</sup> 427, found 427.



5

**Step 3: (R)-1-(3-Amino-7-fluoro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

(R)-1-(3-(1,3-Dioxoisindolin-2-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (114 mg, 0.267 mmol) was dissolved in DMA (1 mL) and methanol (1 mL), charged with powdered Selectfluor® (108 mg, 0.305 mmol), and stirred at room temperature for 20 h. The solvents were concentrated *in vacuo* and the residue was purified by flash chromatography (3-15% MeOH/DCM). The crude mixture obtained was then dissolved in EtOH (3 mL), charged with hydrazine hydrate (0.130 mL, 2.67 mmol), and heated to 85 °C for 30 min. The solvents were concentrated *in vacuo* and the residue was purified by mass-triggered reverse phase HPLC followed by purification via flash chromatography (2-10% MeOH/DCM) to give (R)-1-(3-amino-7-fluoro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for C<sub>15</sub>H<sub>15</sub>FN<sub>6</sub>O [M+1]<sup>+</sup> 315, found 315. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.55 (s, 1H), 7.42-7.34 (m, 4H), 7.27 (m, 1H) 5.07 (q, *J* = 6.7 Hz, 1H), 1.58 (d, *J* = 7.0 Hz, 4H).

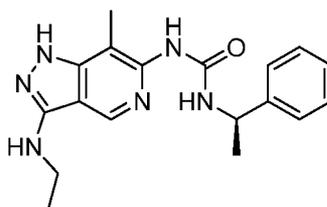
10

15

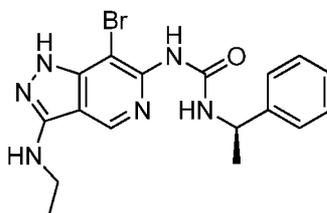
Example 60 was prepared according to scheme 7.

20

**Example 60**



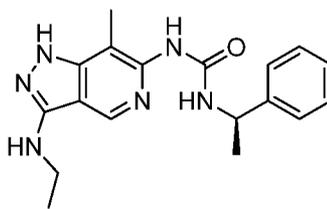
**(R)-1-(3-(Ethylamino)-7-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**



- 145 -

**Step 1: (R)-1-(7-Bromo-3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

(R)-1-(3-(Ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (Example 2; 316 mg, 0.974 mmol) was dissolved in acetonitrile (10 mL) and DMF (2 mL) then NBS (225 mg, 1.266 mmol) was added. The reaction was stirred at room temperature overnight. The solvents were concentrated *in vacuo* and the residue was purified by flash chromatography (2-10% MeOH/DCM) to give (R)-1-(7-bromo-3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for C<sub>17</sub>H<sub>19</sub>BrN<sub>6</sub>O [M+1]<sup>+</sup> 403, found 403.



10

**Step 2: (R)-1-(3-(Ethylamino)-7-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

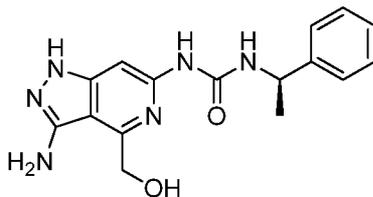
An oven-dried 5 mL microwave vial was charged with (R)-1-(7-bromo-3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (100 mg, 0.198 mmol), PdOAc<sub>2</sub> (8.5 mg, 0.038 mmol), and PCy<sub>3</sub>-BF<sub>4</sub>H (30 mg, 0.08 mmol). The reaction mixture was sealed under N<sub>2</sub>, then charged with dioxane (1.0 mL) and NMP (0.25 mL), followed by drop-wise addition of dimethylzinc (1.653 mL, 1.984 mmol, 1.2 M in toluene). The reaction was heated to 100 °C and stirred for 17 h. The reaction was quenched with TFA until gas evolution ceased and then poured into sat. aq. NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (0-20% MeOH/DCM) followed by purification via mass-triggered reverse-phase HPLC. Fractions containing pure compound were filtered through a PS-HCO<sub>3</sub> cartridge and the filtrate was concentrated *in vacuo* to give (R)-1-(3-(ethylamino)-7-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for C<sub>18</sub>H<sub>22</sub>N<sub>6</sub>O [M+1]<sup>+</sup> 339, found 339. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.55 (s, 1H), 7.42 – 7.19 (m, 5H), 5.01 (q, *J* = 6.9 Hz, 1H), 3.36 (m, 2H), 2.29 (s, 3H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).

15

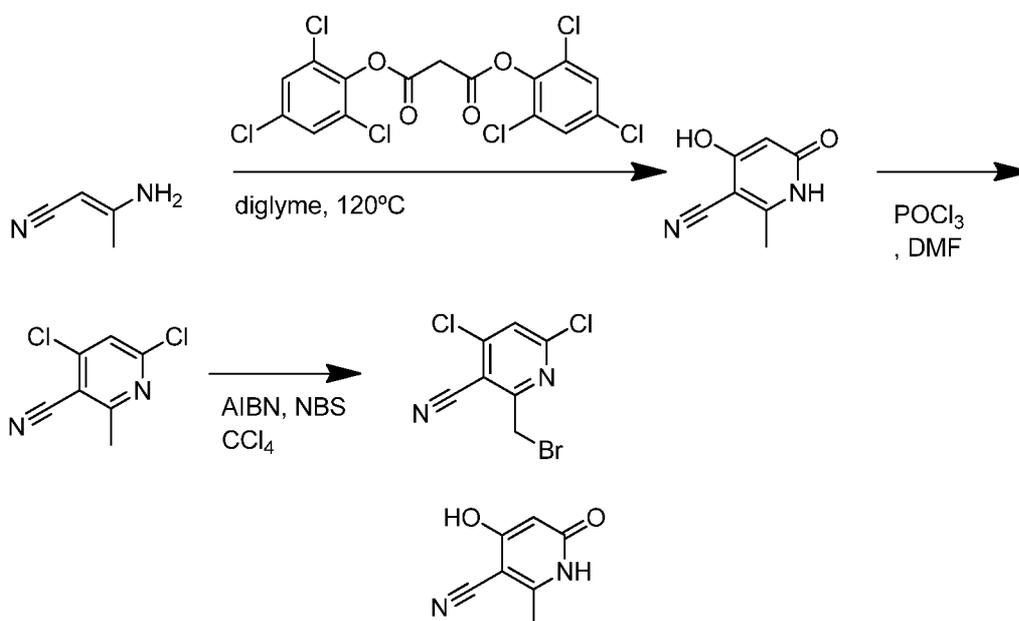
20

25

- 146 -

**Example 68**

**(R)-1-(3-amino-4-(hydroxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

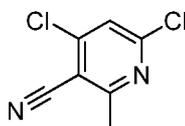


5

**4-hydroxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile**

A mixture of (E)-3-aminobut-2-enitrile (9.7 g, 118 mmol) and bis(2,4,6-trichlorophenyl) malonate (58.4 g, 126 mmol) in diglyme (120 ml) was heated to 120 °C for 2.5 hr. The mixture was cooled to RT and poured into Et<sub>2</sub>O and filtered to collect the precipitate. The precipitate was washed with Et<sub>2</sub>O to obtain 4-hydroxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile. MS ESI calc'd. for C<sub>7</sub>H<sub>7</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 151, found 151.

10



15

**4,6-dichloro-2-methylnicotinonitrile**

A mixture of 4-hydroxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (10.36 g, 69.0 mmol) in DMF (21.4 ml, 276 mmol) was charged slowly with POCl<sub>3</sub> (25.7 ml, 276 mmol) and

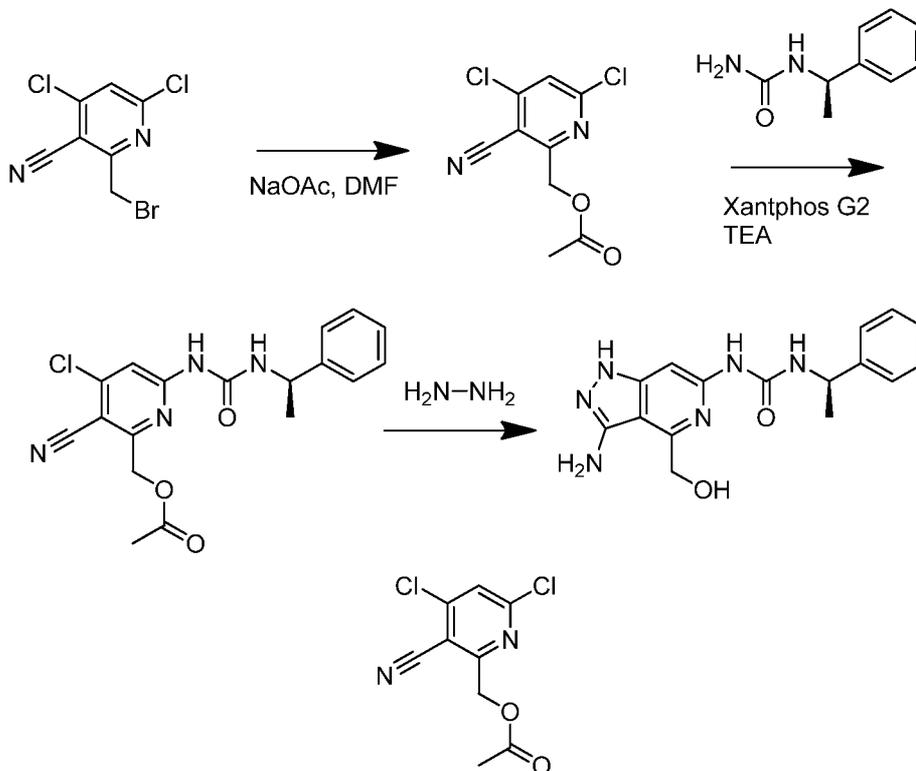
- 147 -

heated to 90 °C for 17 hr. The mixture was carefully poured into 200 ml of a 1:1 mixture of 6N KOH and MeCN, rinsing flask with MeCN and carefully basified further with 6N KOH and sat aq NaHCO<sub>3</sub>, then extracted into Et<sub>2</sub>O (2x). Organics were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified via flash chromatography (0-30% EtOAc/Hex) to provide 4,6-dichloro-2-methylnicotinonitrile.



### 2-(bromomethyl)-4,6-dichloronicotinonitrile

A solution of 4,6-dichloro-2-methylnicotinonitrile (2.15 g, 11.50 mmol) in CCl<sub>4</sub> (45 ml) was charged with AIBN (1.93 g, 11.75 mmol) and NBS (4.37 g, 24.55 mmol), sealed and heated to 75°C for 16 hr. The mixture was poured directly onto SiO<sub>2</sub> and purified via flash chromatography (5-15% Et<sub>2</sub>O/hexane) to provide 2-(bromomethyl)-4,6-dichloronicotinonitrile. MS ESI calc'd. for C<sub>7</sub>H<sub>4</sub>BrCl<sub>2</sub>N<sub>2</sub> [M+H]<sup>+</sup> 265, found 265.



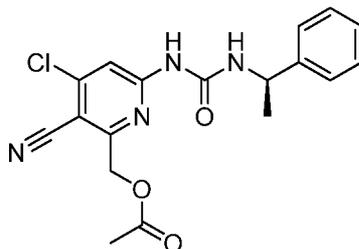
15

### 4,6-dichloro-3-(2-((S)-1-phenylethylamino)acetamido)-2-hydroxy-5-nitro-1H-imidazo[4,5-b]pyridin-4-yl)methyl acetate

A solution of 2-(bromomethyl)-4,6-dichloronicotinonitrile (354.8 mg, 1.334 mmol) in DMF (7 ml) was charged with sodium acetate (198 mg, 2.414 mmol) and stirred at RT for 2 hr. The

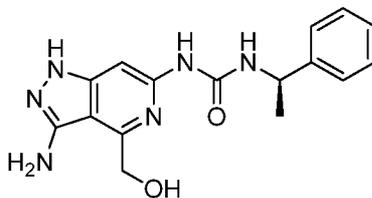
- 148 -

reaction was quenched with water, extracted twice with Et<sub>2</sub>O. The organics was washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to give (4,6-dichloro-3-cyanopyridin-2-yl)methyl acetate. MS ESI calc'd. For C<sub>9</sub>H<sub>7</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 245, found 245.



5 **(R)-(4-chloro-3-cyano-6-(3-(1-phenylethyl)ureido)pyridin-2-yl)methyl acetate**

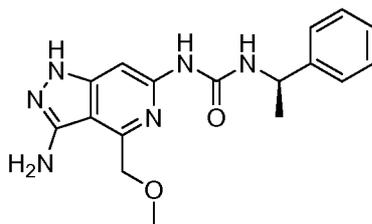
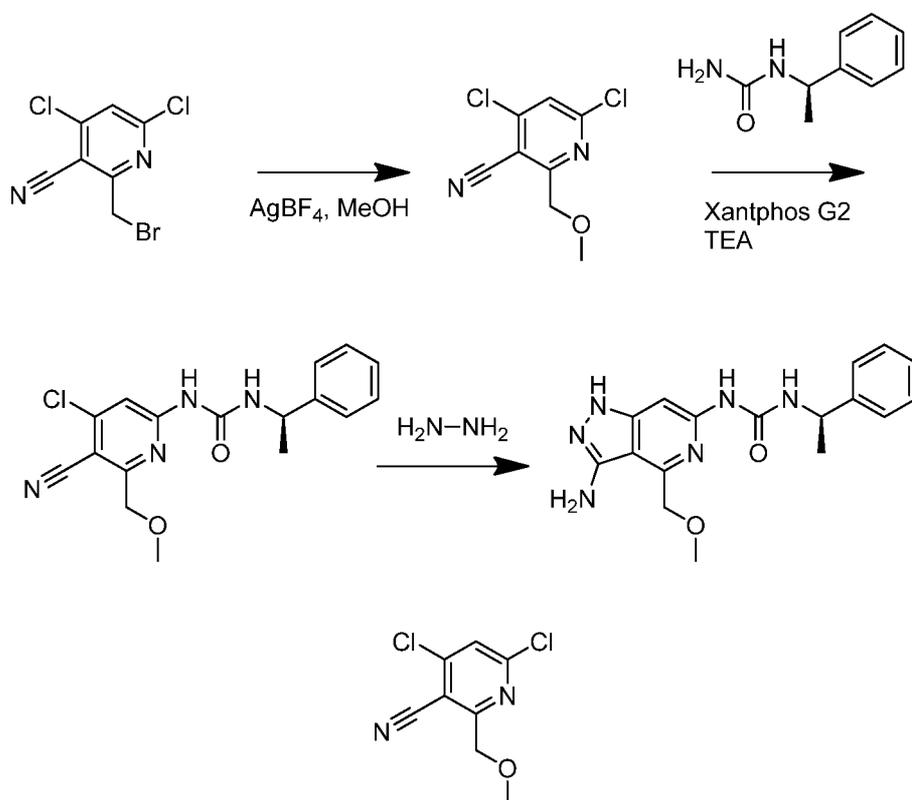
A mixture of (4,6-dichloro-3-cyanopyridin-2-yl)methyl acetate (366.3 mg, 1.495 mmol), (R)-1-(1-phenylethyl)urea (443 mg, 2.70 mmol) and Xantphos G2 precatalyst (130 mg, 0.146 mmol) in THF (2 ml) was sealed, sparged with argon, charged with triethylamine (0.73 ml, 5.24 mmol) and heated to 50 °C for 17 hr. The mixture was filtered through celite, eluted with  
10 EtOAc, concentrated in vacuo and purified via flash chromatography (25-100% Et<sub>2</sub>O/Hex) to provide (R)-(4-chloro-3-cyano-6-(3-(1-phenylethyl)ureido)pyridin-2-yl)methyl acetate. MS ESI calc'd. For C<sub>18</sub>H<sub>18</sub>ClN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup> 373, found 373.



15 **(R)-1-(3-amino-4-(hydroxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

A solution of (R)-(4-chloro-3-cyano-6-(3-(1-phenylethyl)ureido)pyridin-2-yl)methyl acetate (59.1 mg, 0.159 mmol) in ethanol (2 ml) was charged with hydrazine, H<sub>2</sub>O (46 μl, 0.948 mmol), sealed and heated to 100 °C for 14.5 hr. The mixture was concentrated in vacuo and the residue was purified via flash chromatography (0-20% MeOH/DCM, then 0-20%  
20 MeOH/EtOAc) to provide (R)-1-(3-amino-4-(hydroxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. For C<sub>16</sub>H<sub>19</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 327, found 327. <sup>1</sup>H NMR (ppm, 500 MHz, DMSO-d<sub>6</sub>) δ 11.51 (s, 1H), 8.91 (s, 1H), 7.33 (m, 5H), 7.22 (m, 1H), 6.00 (t, J = 5.6 Hz, 1H), 5.60 (s, 2H), 4.84 (m, 1H), 4.67 (d, J = 5.6, 2H), 1.39 (d, J = 7.1 Hz, 3H).

- 149 -

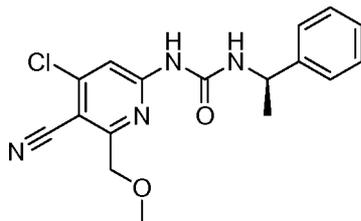
**Example 69****(R)-1-(3-amino-4-(methoxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

5

**4,6-dichloro-2-(methoxymethyl)nicotinonitrile**

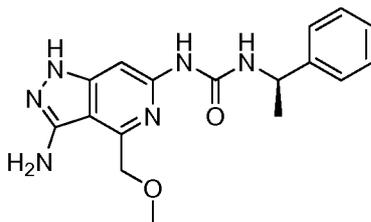
10 A solution of 2-(bromomethyl)-4,6-dichloronicotinonitrile (378.9 mg, 1.425 mmol) in MeOH (5.0 ml) was charged with silver(I) tetrafluoroborate (360 mg, 1.849 mmol) and stirred at 50 °C for 17 hr. LCMS showed conversion to the desired mass. The mixture was concentrated in vacuo and purified via flash chromatography (15-60% Et<sub>2</sub>O/Hexane) to provide 4,6-dichloro-2-(methoxymethyl)nicotinonitrile. MS ESI calc'd for C<sub>8</sub>H<sub>7</sub>Cl<sub>2</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 217, found 217.

- 150 -



**(R)-1-(4-chloro-5-cyano-6-(methoxymethyl)pyridin-2-yl)-3-(1-phenylethyl)urea**

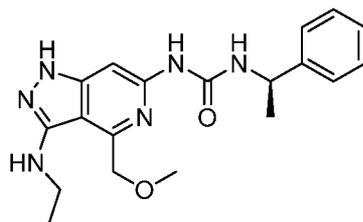
A mixture of 4,6-dichloro-2-(methoxymethyl)nicotinonitrile (75.7 mg, 0.349 mmol), (R)-1-(1-phenylethyl)urea (77 mg, 0.469 mmol) and Xantphos G2 (39 mg, 0.044 mmol) in THF (2 ml) was sealed, sparged with argon, charged with triethylamine (0.17 ml, 1.220 mmol) and heated to 50 °C for 17 hr. The mixture was cooled and filtered through celite, eluted with EtOAc before it was concentrated in vacuo and purified via flash chromatography (25-100% Et<sub>2</sub>O/hexane) to provide (R)-1-(4-chloro-5-cyano-6-(methoxymethyl)pyridin-2-yl)-3-(1-phenylethyl)urea. MS ESI calc'd for C<sub>17</sub>H<sub>18</sub>ClN<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup> 345, found 345.



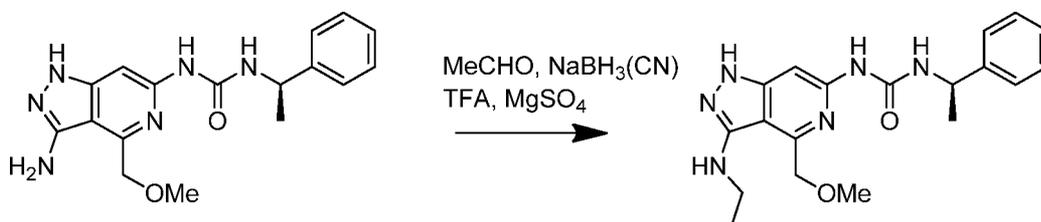
**(R)-1-(3-amino-4-(methoxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

A solution of (R)-1-(4-chloro-5-cyano-6-(methoxymethyl)pyridin-2-yl)-3-(1-phenylethyl)urea (151.4 mg, 0.439 mmol) and hydrazine hydrate (75 μl, 1.546 mmol) in EtOH (4 ml) was heated to 100 °C in a sealed vial for 18 hr. The mixture was concentrated in vacuo and purified via flash chromatography (0-20% MeOH/EtOAc) to provide (R)-1-(3-amino-4-(methoxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd for C<sub>17</sub>H<sub>21</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 341, found 341. <sup>1</sup>H NMR (ppm, 500 MHz, DMSO-d<sub>6</sub>) δ 11.60 (s, 1H), 8.97 (s, 1H), 7.33 (m, 4H), 7.22 (m, 1H), 7.14 (s, 1H), 5.35 (s, 2H), 4.85 (t, *J* = 7.1, 1H), 4.65 (m, 2H), 3.31 (s, 3H, overlaps with H<sub>2</sub>O peak), 3.15 (d, *J* = 5.1 Hz, 1H), 1.39 (d, *J* = 7.1 Hz, 1H).

- 151 -

**Example 71**

**(R)-1-(3-(ethylamino)-4-(methoxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

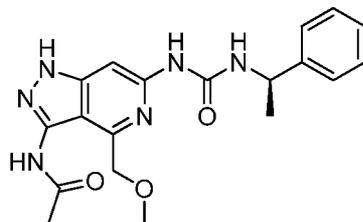


5

A solution of (R)-1-(3-amino-4-(methoxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (34.8 mg, 0.102 mmol) in chloroform (0.6 ml) and MeOH (0.3 ml) was charged with MgSO<sub>4</sub> (45 mg, 0.374 mmol), TFA (24  $\mu$ l, 0.312 mmol) and acetaldehyde (0.02 ml, 0.354 mmol). The mixture was stirred at RT for 1 hr, then charged with sodium

10 cyanoborohydride (22 mg, 0.350 mmol) before it was stirred at RT for 1.5 hr. The mixture was filtered to remove insoluble matter, rinsing with MeOH and DCM and concentrated in vacuo. The residue was purified by mass-triggered reverse-phase HPLC to provide (R)-1-(3-(ethylamino)-4-(methoxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI calc'd for C<sub>19</sub>H<sub>25</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 369, found 369. <sup>1</sup>H NMR (ppm, 500 MHz, DMSO-d<sub>6</sub>)  $\delta$  11.64 (s, 1H), 8.96 (s, 1H), 7.33 (m, 4H), 7.23 (m, 1H), 7.15 (s, 1H), 5.56 (t, *J* = 6.5 Hz, 1H), 4.85 (t, *J* = 7.3 Hz), 4.63 (m, 2H), 3.32 (s, 3H, overlaps with H<sub>2</sub>O peak), 3.22 (m, 2H), 1.39 (d, 6.8 Hz, 3H), 1.20 (t, *J* = 4.9 Hz, 3H).

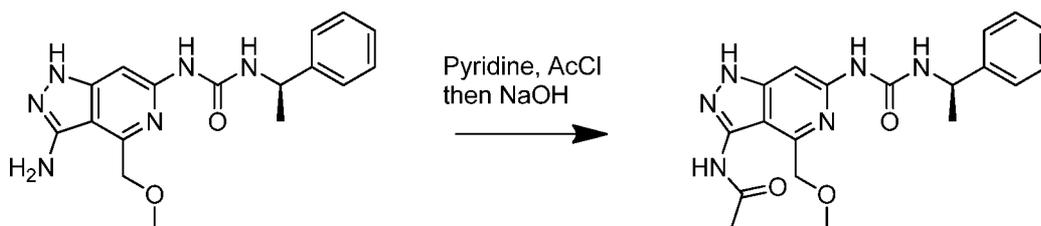
15

**Example 72**

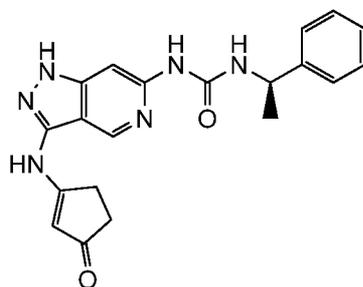
20

**(R)-N-(4-(methoxymethyl)-6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide**

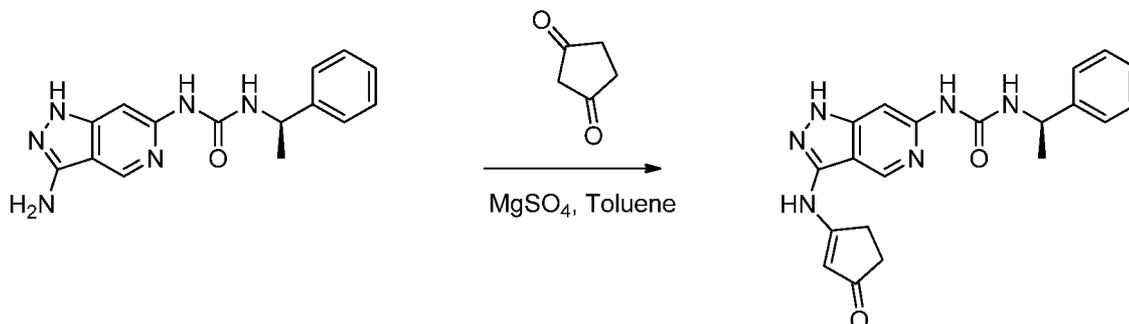
- 152 -



A solution of (R)-1-(3-amino-4-(methoxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (30 mg, 0.088 mmol) in THF (1 ml) was charged with pyridine (72  $\mu$ l, 0.890 mmol) and AcCl (62  $\mu$ l, 0.872 mmol). The mixture was stirred at RT for 17 hr before 1N NaOH (1.2 ml, 1.200 mmol) was added and stirred at RT for 2 hr and then heated to 50  $^{\circ}$ C for 1 hr. The reaction was quenched with sat aq  $\text{NH}_4\text{Cl}$  and extracted into EtOAc. The mixture was washed with sat aq  $\text{NH}_4\text{Cl}$  followed by brine, dried over  $\text{MgSO}_4$ , filtered, concentrated in vacuo and purified via flash chromatography (0-20% MeOH/DCM) to give (R)-N-(4-(methoxymethyl)-6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide. MS ESI calc'd for  $\text{C}_{19}\text{H}_{23}\text{N}_6\text{O}_3$   $[\text{M}+\text{H}]^+$  383, found 383.  $^1\text{H}$  NMR (ppm, 500 MHz, DMSO- $d_6$ )  $\delta$  12.81 (s, 1H), 10.01 (s, 1H), 9.13 (s, 1H), 7.33 (m, 5H), 7.22 (m, 1H), 4.89 (t,  $J$  = 6.8 Hz), 4.59 (s, 2H), 3.28 (s, 3H), 2.06 (s, 3H), 1.39 (d, 5.1 Hz).

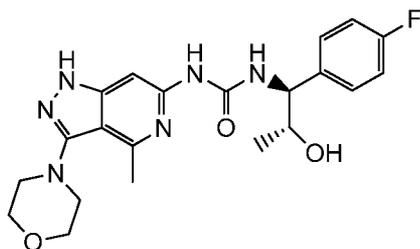
**Example 73**

15 (R)-1-(3-((3-oxocyclopent-1-en-1-yl)amino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea

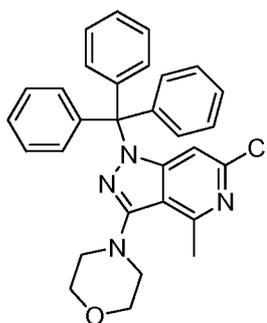


- 153 -

A mixture of (R)-1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (52.9 mg, 0.179 mmol), cyclopentane-1,3-dione (34.1 mg, 0.348 mmol) and MgSO<sub>4</sub> (167.7 mg, 1.393 mmol) in toluene (2 ml) was heated in a sealed 5 ml microwave vial to 150 °C for 1 hr. LCMS shows formation of product. The mixture was poured directly onto silica gel and purified via flash chromatography (Biotage SNAP 10g, 0-20% MeOH/DCM) to provide (R)-1-(3-((3-oxocyclopent-1-en-1-yl)amino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (3.11 mg, 8.26 μmol, 4.63 % yield) as a yellow solid. MS ESI calc'd. For C<sub>20</sub>H<sub>21</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 377, found 377. <sup>1</sup>H NMR (ppm, 500 MHz, DMSO-d<sub>6</sub>) δ 12.49 (s, 1H), 10.39 (s, 1H), 8.99 (s, 1H), 8.87 (s, 1H), 7.77 (br s, 1H), 1.53 (s, 1H), 7.34 (m, 5H), 7.23 (s, 1H), 6.11 (br s, 1H), 4.86 (t, *J* = 6.5 Hz, 1H), 3.32 (s, 3H, overlaps with H<sub>2</sub>O peak), 2.81 (s, 2H), 2.26 (s, 2H), 1.40 (d, *J* = 6.8 Hz, 3H).

**Example 106**

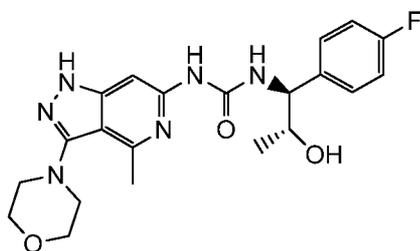
**1-((1S,2R)-1-(4-Fluorophenyl)-2-hydroxypropyl)-3-(4-methyl-3-morpholino-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

**Step 1: 4-(6-Chloro-4-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)morpholine**

6-Chloro-3-iodo-4-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridine (**Intermediate 1C**; 2 g, 3.73 mmol), morpholine (0.488 mL, 5.60 mmol), sodium tert-butoxide (0.538 g, 5.60 mmol), and chloro(2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(II), methyl-*t*-butylether adduct (0.152 g, 0.187 mmol) was dissolved in dioxane (10 mL) and degassed under argon for five minutes. The reaction

- 154 -

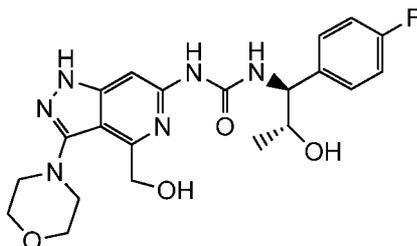
mixture was heated to 60 °C for 30 min under microwave irradiation. The reaction mixture was diluted with ethyl acetate and washed with saturated ammonium chloride and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* while loading onto silica gel. Purification by flash chromatography (5-30% EtOAc/Hexanes) gave 4-(6-chloro-4-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)morpholine. MS ESI calc'd. For  $C_{30}H_{28}ClN_4O$   $[M+H]^+$  495, found 495.



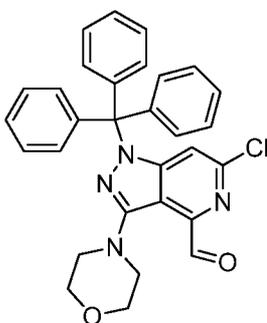
**Step 2: 1-((1S,2R)-1-(4-Fluorophenyl)-2-hydroxypropyl)-3-(4-methyl-3-morpholino-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

4-(6-Chloro-4-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)morpholine (75 mg, 0.152 mmol), 1-((1S,2R)-1-(4-fluorophenyl)-2-hydroxypropyl)urea, (48.2 mg, 0.227 mmol), BrettPhos palladacycle (12.10 mg, 0.015 mmol), cesium carbonate (128 mg, 0.394 mmol) 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl (8.13 mg, 0.015 mmol) were dissolved in dioxane (1 mL) and purged under argon for five minutes. The reaction mixture was heated to 90 °C and stirred for six hrs. The reaction mixture was filtered through celite, rinsed with methanol, and concentrated *in vacuo*. The crude residue was dissolved in TFA (1 mL) and triethylsilane (0.036 mL, 0.227 mmol) was added. The reaction mixture was stirred at rt for 30 min then diluted with DCM and concentrated *in vacuo*. The reaction mixture was diluted with DMF (1 mL), filtered, and purified by mass-triggered reverse-phase HPLC. Fractions containing pure compound were filtered through a PS-HCO<sub>3</sub> cartridge and the filtrate was concentrated *in vacuo* to give 1-((1S,2R)-1-(4-fluorophenyl)-2-hydroxypropyl)-3-(4-methyl-3-morpholino-1H-pyrazolo[4,3-c]pyridin-6-yl)urea. MS ESI calc'd. For  $C_{21}H_{26}FN_6O_3$   $[M+H]^+$  429, found 429. <sup>1</sup>H NMR (ppm, 500 MHz, DMSO-d<sub>6</sub>) δ 12.17 (s, 1H), 9.11 (s, 1H), 7.31 (dd, *J* = 5.6 Hz, 8.7 Hz, 2H), 7.12 (t, *J* = 8.9 Hz, 2H), 7.06 (s, 1H), 4.91 (s, 1H), 4.69 (dd, *J* = 4.2 Hz, 8.5 Hz, 1H), 3.90 (s, 1H), 3.77 – 3.73 (m, 5H), 3.08 (d, *J* = 4.2 Hz, 4H), 2.68 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H).

- 155 -

**Example 108**

**1-[(1S,2R)-1-(4-Fluorophenyl)-2-hydroxypropyl]-3-[4-(hydroxymethyl)-3-morpholin-4-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl urea**

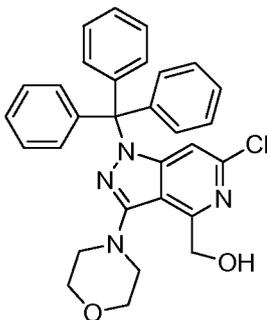


5

**Step 1: 6-Chloro-3-morpholino-1-trityl-1H-pyrazolo[4,3-c]pyridine-4-carbaldehyde**

4-(6-Chloro-4-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)morpholine (**Example 106, Step 1**; 450.9 mg, 0.911 mmol) was dissolved in dioxane (10 mL) and selenium dioxide (303 mg, 2.73 mmol) was added. The reaction mixture was stirred at reflux over the weekend. The reaction was filtered over celite, rinsed with ethyl acetate, and concentrated *in vacuo*. The residue was diluted with DCM and filtered over celite. The filtrate was concentrated *in vacuo* while loading onto silica gel. Purification by flash chromatography (5-40% EtOAc/Hexanes) gave 6-chloro-3-morpholino-1-trityl-1H-pyrazolo[4,3-c]pyridine-4-carbaldehyde. MS ESI calc'd. For  $C_{30}H_{26}ClN_4O_2$   $[M+H]^+$  509, found 509.

10



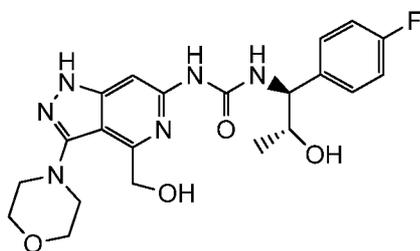
15

**Step 2: (6-Chloro-3-morpholino-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)methanol**

6-Chloro-3-morpholino-1-trityl-1H-pyrazolo[4,3-c]pyridine-4-carbaldehyde (292.2 mg, 0.574 mmol) was dissolved in DCM (3 mL) and methanol (3 mL). Sodium borohydride

- 156 -

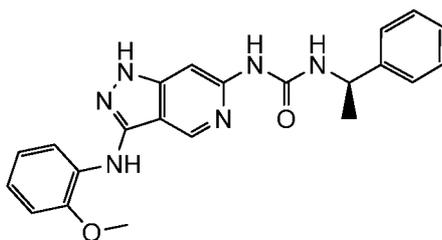
(21.72 mg, 0.574 mmol) was then added and the reaction mixture was stirred at rt for 15 min. The reaction was quenched with water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* while loading onto silica gel. Purification by flash chromatography (5-40%EtOAc/Hexanes) gave  
 5 (6-chloro-3-morpholino-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)methanol. MS ESI calc'd. For  $C_{30}H_{28}ClN_4O_2$   $[M+H]^+$  511, found 511.



**Step 3: 1-[(1S,2R)-1-(4-Fluorophenyl)-2-hydroxypropyl]-3-[4-(hydroxymethyl)-3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl]urea**

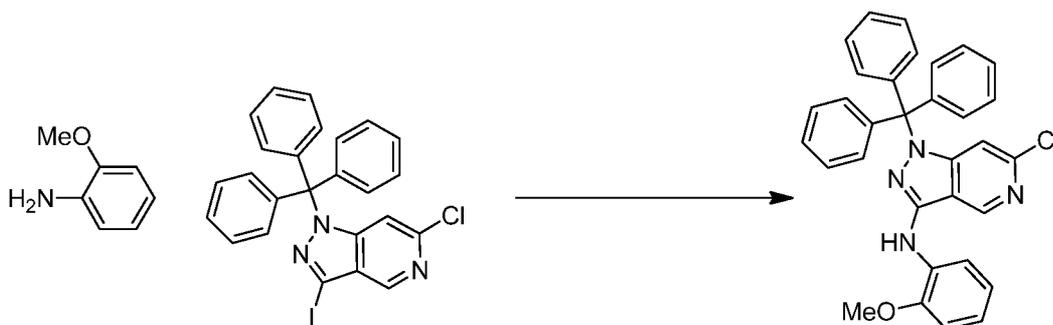
10 1-[(1S,2R)-1-(4-Fluorophenyl)-2-hydroxypropyl]-3-[4-(hydroxymethyl)-3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl]urea was prepared using the same procedure described for 1-((1S,2R)-1-(4-fluorophenyl)-2-hydroxypropyl)-3-(4-methyl-3-morpholino-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (**Example 106, Step 2**). MS ESI calc'd. For  $C_{21}H_{25}FN_6O_4$   $[M+H]^+$  445, found 445.  $^1H$  NMR (ppm, 500 MHz, DMSO- $d_6$ )  $\delta$  12.30 (s, 1H), 9.20 (s, 1H),  
 15 7.34 (dd,  $J = 5.6$  Hz, 8.7 Hz, 2H), 7.18 (s, 1H), 7.11 (t,  $J = 8.9$  Hz, 2H), 5.27 (s, 1H), 4.91 (s, 1H), 4.80 (s, 2H), 4.68 (dd,  $J = 4.7$  Hz, 8.5 Hz, 1H), 3.89 (s, 1H), 3.79 – 3.73 (m, 5H), 3.12 (d,  $J = 4.4$  Hz, 4H), 0.95 (d,  $J = 6.4$  Hz, 3H).

**Example 121**



20 **1-{3-[(2-methoxyphenyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea**

- 157 -

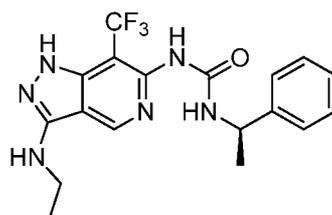


**Step 1: 6-chloro-N-(2-methoxyphenyl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine**

A mixture of 2-methoxyaniline (0.18 g), 6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridine (0.50 g),  $\text{Cs}_2\text{CO}_3$  (0.94 g), and (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) chloride (0.071 g) in toluene (6 mL) was degassed and back filled with nitrogen (3 times) before it was heated at 80 °C for overnight. The reaction was cooled and diluted with ethyl acetate (15 mL) and water (10 mL). The mixture was filtered through celite and the filtrate was separated, the organic layer was wash with with brine (10 mL), dried ( $\text{MgSO}_4$ ), filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/isohexane = 25% to give 6-chloro-N-(2-methoxyphenyl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (380 mg, 77 % yield) as a brown solid.

**Step 2 and 3: 1-{3-[(2-methoxyphenyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea** was prepared from 6-chloro-N-(2-methoxyphenyl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine following a similar procedure in Example 1, steps 2 and 3. MS ESI Calc'd For  $\text{C}_{22}\text{H}_{22}\text{N}_6\text{O}_2$   $[\text{M}+\text{H}]^+$  403, found 403.

**Example 135**



**(R)-1-(3-(ethylamino)-7-(trifluoromethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

20

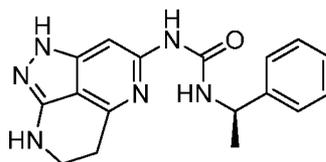
(R)-1-(3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (50 mg, 0.154 mmol) and sodium trifluoromethanesulfonate (72.2 mg, 0.462 mmol) were taken in a solvent mixture containing DCE: water: DMSO in a ratio of 2.5:1:0.5, cooled to 0 °C and added tert-

- 158 -

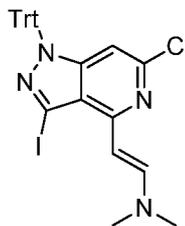
butyl hydroperoxide (0.107 mL, 0.771 mmol) and reaction gradually warmed to room temperature. After two more additions of tert-butyl hydroperoxide in equal concentrations in a span of 36 hours, the reaction was partitioned between DCM and aqueous sodium bicarbonate. The organics were washed with brine, dried with sodium sulfate and concentrated.

- 5 Purification of residue by flash column (0-15% MeOH-DCM) gave (R)-1-(3-(ethylamino)-7-(trifluoromethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. MS ESI  $[M+H]^+$  calc'd. 393, found 393.  $^1H$  NMR (ppm, 500 MHz, DMSO- $d_6$ )  $\delta$  8.60 (s, 1H), 7.40 – 7.30 (m, 4H), 7.20 (m, 1H), 7.10 (s, 1H), 4.97 (m, 1H), 3.29, (m, 2H), 1.38 (d, J = 6.5 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H).

10

**Example 136**

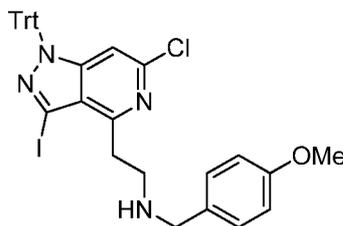
**(R)-1-(1-phenylethyl)-3-(1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)urea**



- 15 **Step 1: (E)-2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N,N-dimethylethanamine**

6-chloro-3-iodo-trityl-1H-pyrazolo[4,3-c]pyridine (Intermediate 1C, 2 g, 3.73 mmol), N, N-dimethylformamide-dimethyl acetal (DMF-DMA) (4.45 g, 37.3 mmol) were stirred at 125 °C for 12 hrs. Reaction was concentrated and excess DMF-DMA azeotroped with toluene. Trituration with cyclopentylmethylether gave (E)-2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N,N-dimethylethanamine. MS ESI calc'd. for  $C_{29}H_{24}ClIN_4$   $[M+H]^+$  591, found 591.

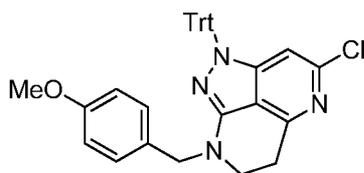
20



- 159 -

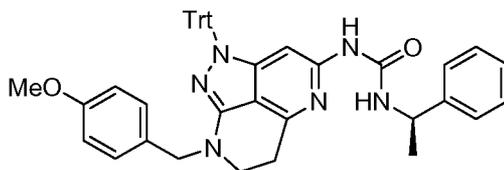
**Step 2: 2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N-(4-methoxybenzyl)ethanamine**

(E)-2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N,N-dimethylethanamine (2.2 g, 3.73 mmol) and benzylamine (1.02 g, 7.46 mmol) were stirred in a 3:1:1 solution of DCE:AcOH:EtOH (10 ml) at 85 °C for 3 hrs. Solvent removed by vacuum and residue taken in DCE (15 ml), added sodium triacetoxyborohydride (3.16 g, 14.9 mmol), acetic acid (0.9 g, 14.9 mmol) and stirred at room temperature for 6 hours. Reaction was partitioned between DCM and aqueous sodium bicarbonate and the organics was separated, washed with brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-10% MeOH-EtOAc) gave 2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N-(4-methoxybenzyl)ethanamine. MS ESI calc'd. for C<sub>34</sub>H<sub>28</sub>ClIN<sub>4</sub> [M+H]<sup>+</sup> 685, found 685.



**Step 3: 7-chloro-3-(4-methoxybenzyl)-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine**

2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N-(4-methoxybenzyl)ethanamine (268 mg, 0.391 mmol) and RuPhos pre-catalyst (16 mg, 0.02 mmol) were charged in a 1 dram vial, evacuated and backfilled with nitrogen and taken in 1,4-dioxane (2 mL). Added a solution of 2M NaOtBu in THF (0.5 ml, 0.978 mmol) and reaction heated to 55 °C for 1 hour. The reaction mixture was diluted with EtOAc and washed with water, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-25% EtOAc-hexanes) gave 7-chloro-3-(4-methoxybenzyl)-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine. MS ESI calc'd. for C<sub>35</sub>H<sub>29</sub>ClN<sub>4</sub>O [M+H]<sup>+</sup> 558, found 558.

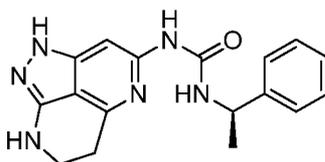


25

**Step 4: (R)-1-(3-(4-methoxybenzyl)-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea**

- 160 -

7-chloro-3-(4-methoxybenzyl)-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine (30 mg, 0.054 mmol), (R)-1-(1-phenylethyl)urea (13.26 mg, 0.081 mmol), cesium carbonate (61.4 mg, 0.188 mmol) and BrettPhos pre-catalyst (4.8 mg) were charged in a 1 dram vial, evacuated and backfilled with nitrogen and taken in 1,4-dioxane (0.4 mL) and heated reaction to 100 °C for 1 hour. The reaction mixture was diluted with DCM, washed with water, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-75% EtOAc-hexanes) gave (R)-1-(3-(4-methoxybenzyl)-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for C<sub>44</sub>H<sub>40</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 685, found 685.



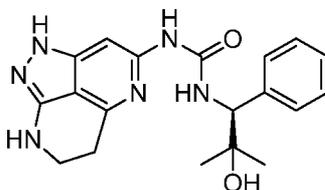
10

**Step 5: (R)-1-(1-phenylethyl)-3-(1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)urea**

(R)-1-(3-(4-methoxybenzyl)-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea (22 mg, 0.032 mmol) was taken in TFA (0.1 mL) and stirred at room temperature for 30 minutes. To the reaction was added triethylsilane (21 uL, 0.128 mmol) stirred for 15 minutes at room temperature then heated to 80 °C for 30 minutes. The reaction mixture was concentrated, taken in DCM and washed with aqueous sodium bicarbonate, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-15% MeOH-DCM) gave (R)-1-(1-phenylethyl)-3-(1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)urea. MS ESI calc'd. for C<sub>17</sub>H<sub>18</sub>N<sub>6</sub>O [M+H]<sup>+</sup> 323, found 323. <sup>1</sup>H NMR (ppm, 500 MHz, DMSO-d<sub>6</sub>) δ 8.98 (s, 1H), 8.45 (br, s, 1H), 7.38 (m, 4H), 7.20 (m, 1H), 7.00 (s, 1H), 6.23 (s, 1H), 4.83 (m, 1H), 3.42 (dd, J = 8.0, 5.0 Hz, 2H), 2.80 (dd, J = 8.0, 5.0 Hz, 2H), 1.40 (d, J = 11 Hz, 3H).

20

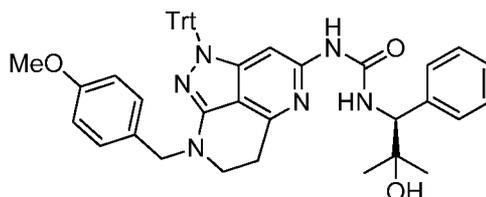
**Example 137**



25

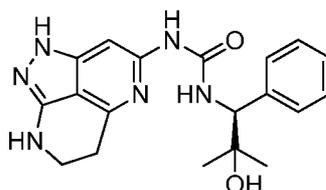
**(S)-1-(2-hydroxy-2-methyl-1-phenylpropyl)-3-(1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)urea**

- 161 -



**Step 1: (S)-1-(2-hydroxy-2-methyl-1-phenylpropyl)-3-(3-(4-methoxybenzyl)-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)urea**

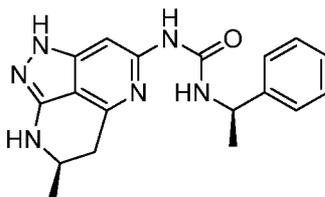
7-chloro-3-(4-methoxybenzyl)-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine (40 mg, 0.072 mmol), (S)-1-(2-hydroxy-2-methyl-1-phenylpropyl)urea (22.4 mg, 0.108 mmol), cesium carbonate (82 mg, 0.25 mmol) and BrettPhos pre-catalyst (6.5 mg, 7.18  $\mu$ M) were charged in a 1 dram vial, evacuated and backfilled with nitrogen and taken in 1,4-dioxane (0.4 mL) and heated reaction to 100 °C for 30 minutes. The reaction mixture was diluted with DCM, washed with water, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-75% EtOAc-hexanes) gave (S)-1-(2-hydroxy-2-methyl-1-phenylpropyl)-3-(3-(4-methoxybenzyl)-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)urea. MS ESI calc'd. for  $C_{46}H_{44}N_6O_3$   $[M+H]^+$  729, found 729.



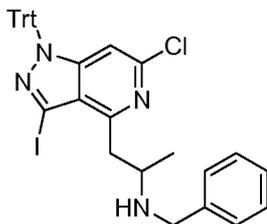
**Step 2: (S)-1-(2-hydroxy-2-methyl-1-phenylpropyl)-3-(1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)urea**

(S)-1-(2-hydroxy-2-methyl-1-phenylpropyl)-3-(3-(4-methoxybenzyl)-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)urea (38 mg, 0.052 mmol) was taken in TFA (0.17 mL) and stirred at room temperature for 30 minutes. To the reaction was added triethylsilane (34  $\mu$ L, 0.209 mmol) stirred for 15 minutes at room temperature then heated to 80 °C for 30 minutes. The reaction mixture was concentrated, taken in DCM and washed with aqueous sodium bicarbonate, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-15% MeOH-DCM) gave (S)-1-(2-hydroxy-2-methyl-1-phenylpropyl)-3-(1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)urea. MS ESI calc'd. for  $C_{19}H_{22}N_6O_2$   $[M+H]^+$  367, found 367.  $^1H$  NMR (ppm, 500 MHz, DMSO- $d_6$ )  $\delta$  9.25 (br, 2H), 7.28 (m, 4H), 7.20 (m, 1H), 6.90 (s, 1H), 4.59 (d, J = 14 Hz, 1H), 3.42 (dd, J = 8.0, 5.0 Hz, 2H), 2.92 (dd, J = 8.0, 5.0 Hz, 2H), 1.95 (s, 3H), 1.0 (s, 3H).

- 162 -

**Example 138**

**1-((R)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-((R)-1-phenylethyl)urea**

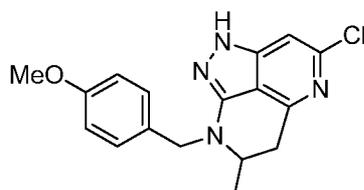


5

**Step 1: N-benzyl-1-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)propan-2-amine**

6-chloro-3-iodo-trityl-1H-pyrazolo[4,3-c]pyridine (Intermediate 1C, 2 g, 3.73 mmol), N, N dimethylacetamide-dimethyl acetal (DMA-DMA) (4.97 g, 37.3 mmol) were stirred at 125 °C for 12 hrs. Reaction was concentrated and excess DMF-DMA azeotroped with Toluene. The resulting intermediate and p-methoxybenzylamine (2.05 g, 14.9 mmol) were stirred in a 3:1:1 solution of DCE:AcOH:EtOH (20 ml) at 85 °C for 3 hrs. Solvent was removed by vacuum and the residue was taken in DCE (15 ml) followed with addition of sodium triacetoxyborohydride (3.16 g, 14.9 mmol) and acetic acid (0.9 g, 14.9 mmol) before the mixture was stirred at room temperature for 6 hours. The reaction mixture was partitioned between DCM and aqueous sodium bicarbonate and the organics was separated, washed with brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-90% -EtOAc-hexanes) gave N-benzyl-1-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)propan-2-amine. MS ESI calc'd. for  $C_{35}H_{30}ClIN_4$   $[M+H]^+$  700, found 700.

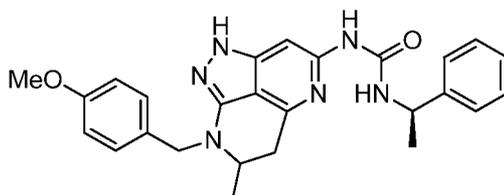
20



**Step 2: 7-chloro-3-(4-methoxybenzyl)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine**

- 163 -

N-benzyl-1-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)propan-2-amine (670 mg, 0.958 mmol) and RuPhos pre-catalyst (70 mg, 0.096 mmol) were charged in a 2 dram vial, evacuated and backfilled with nitrogen and taken in toluene (4.8 mL). A solution of 2M NaOtBu in THF (1.2 ml, 2.4 mmol) was added and the reaction mixture was heated to 55 °C for 12 hours. The reaction mixture was cooled and diluted with EtOAc and washed with water, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-50% EtOAc-hexanes) gave 7-chloro-3-(4-methoxybenzyl)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine. MS ESI calc'd. for C<sub>35</sub>H<sub>30</sub>ClIN<sub>4</sub> [M+H]<sup>+</sup> 572, found 572.

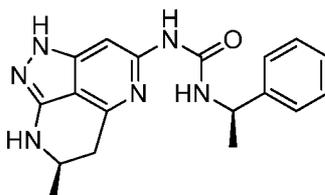


10

**Step 3: 1-(3-(4-methoxybenzyl)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-((R)-1-phenylethyl)urea**

7-chloro-3-(4-methoxybenzyl)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine (150 mg, 0.263 mmol), (R)-1-(1-phenylethyl)urea (64.7 mg, 0.394 mmol), cesium carbonate (257 mg, 0.788 mmol) and BrettPhos pre-catalyst (23.8 mg, 0.026 mmol) were charged in a 1 dram vial, evacuated and backfilled with nitrogen and taken in 1,4-dioxane (1.4 mL). The mixture was heated at 100 °C for 1 hour before it was diluted with DCM, washed with water, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-80% EtOAc-hexanes) gave 1-(3-(4-methoxybenzyl)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-((R)-1-phenylethyl)urea. MS ESI calc'd. for C<sub>26</sub>H<sub>28</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 699, found 699.

20



**Step 4: 1-((R)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-((R)-1-phenylethyl)urea**

1-(3-(4-methoxybenzyl)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-((R)-1-phenylethyl)urea (100 mg, 0.143 mmol) was taken in TFA (0.7 mL) and stirred at room temperature for 30 minutes. Triethylsilane (91 uL, 0.572 mmol)

25

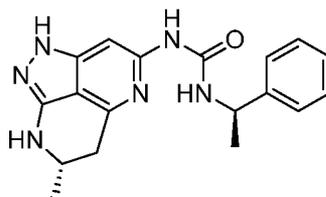
- 164 -

was added to the reaction mixture and stirred for 15 minutes at room temperature then heated at 80 °C for 30 minutes. The reaction mixture was concentrated, taken in DCM and washed with aqueous sodium bicarbonate, brine, dried with sodium sulfate and concentrated.

Purification of the residue by flash column (0-15% MeOH-DCM) followed by SFC separation

5 with a Chiralpak AS-H column gave 1-((R)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-((R)-1-phenylethyl)urea as peak 1. MS ESI calc'd. for  $C_{18}H_{20}N_6O$   $[M+H]^+$  337, found 337.  $^1H$  NMR (ppm, 500 MHz, DMSO- $d_6$ )  $\delta$  11.29 (s, 1H), 8.90 (s, 1H), 8.40 (br, s, 1H), 7.32 (dd,  $J = 3.4, 7.9$ , 4H), 7.24 - 7.14 (m, 1H), 7.00 (s, 1H), 6.30 (s, 1H), 4.83 (m, 1H), 3.65 (m, 1H), 2.88 - 2.77 (m, 1H), 2.67 - 2.53 (m, 1H), 1.39 (d,  $J = 6.9$ , 3H), 1.29 (d,  $J = 6.3$ , 3H).

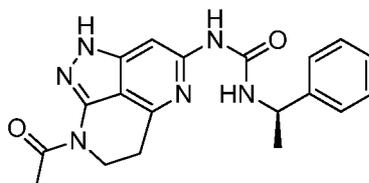
#### Example 139



#### 1-((S)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-((R)-1-phenylethyl)urea

15 SFC separation with a Chiralpak AS-H column of Step 4 in Example 138 gave 1-((S)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-((R)-1-phenylethyl)urea as peak 2. MS ESI calc'd. for  $C_{18}H_{20}N_6O$   $[M+H]^+$  337, found 337.  $^1H$  NMR (ppm, 500 MHz, DMSO- $d_6$ )  $\delta$  11.29 (s, 1H), 8.90 (s, 1H), 8.40 (br, s, 1H), 7.32 (dd,  $J = 3.4, 7.9$ , 4H), 7.24 - 7.14 (m, 1H), 7.00 (s, 1H), 6.30 (s, 1H), 4.83 (m, 1H), 3.65 (m, 1H), 2.88 - 2.77 (m, 1H), 2.67 - 2.53 (m, 1H), 1.39 (d,  $J = 6.9$ , 3H), 1.29 (d,  $J = 6.3$ , 3H).

#### Example 140

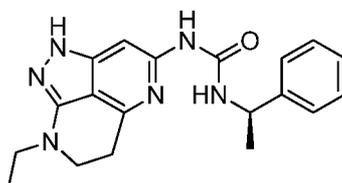


#### (R)-1-(3-acetyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea

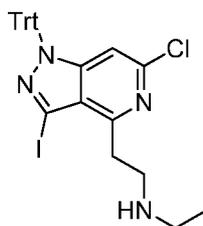
25 (R)-1-(1-phenylethyl)-3-(1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)urea (**Example 136**; 13 mg, 0.040 mmol) and triethylamine (50 mg, 0.494 mmol) were taken in DCM (0.15 mL) and added acetyl chloride (20 mg, 0.255 mmol) and stirred for 1 hour. The

- 165 -

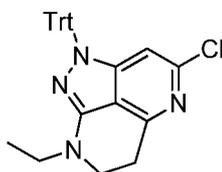
reaction mixture was diluted with DCM, washed with aqueous sodium bicarbonate, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-15% MeOH-DCM) gave (R)-1-(3 acetyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for  $C_{19}H_{20}N_6O_2$   $[M+H]^+$  365, found 365.  $^1H$  NMR (ppm, 500 MHz, DMSO- $d_6$ )  $\delta$  12.35 (s, 1H), 9.13 – 9.05 (m, 1H), 8.05 – 7.86 (m, 1H), 7.39 – 7.28 (m, 6H), 7.27 – 7.18 (m, 1H), 3.06 – 2.96 (m, 2H), 1.38 (t,  $J$  = 9.1, 3H), 1.25 – 1.18 (m, 2H).

**Example 141**

10 **(R)-1-(3-ethyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea**

**Step 1: 2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N-ethylethanamine**

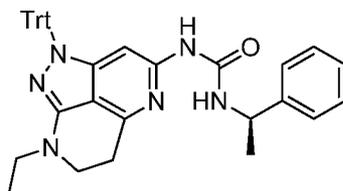
15 (E)-2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N,N-dimethylethanamine (1.0 g, 1.692 mmol) and ethanamine.HCl (0.552 g, 6.77 mmol) were stirred in a 3:1:1 solution of DCE:AcOH:EtOH (5 ml) at 100 °C for 2 hrs. Solvent was removed by vacuum and the residue was taken in DCE (15 ml) and treated with sodium triacetoxyborohydride (0.9 g, 4.23 mmol), acetic acid (0.4 g, 6.7 mmol) and stirred at room temperature for 6 hours. The reaction mixture was partitioned between DCM and aqueous sodium bicarbonate and the organics was separated, washed with brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-15% MeOH-DCM) gave 2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N-ethylethanamine. MS ESI calc'd. for  $C_{29}H_{26}ClIN_4$   $[M+H]^+$  593, found 593.



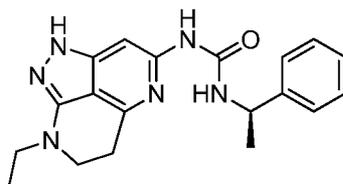
- 166 -

**Step 2: 7-chloro-3-ethyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine**

2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N-ethylethanamine (160 mg, 0.270 mmol) and RuPhos pre-catalyst (19.6 mg, 0.027 mmol) were charged in a 1 dram vial, evacuated and backfilled with nitrogen and taken in toluene (1.8 mL) before a solution of 2M NaOtBu in THF (0.34 ml, 0.675 mmol) was added. The reaction mixture was heated at 55 °C for 1 hour before it was diluted with EtOAc and washed with water, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-50% EtOAc-hexanes) gave 7-chloro-3-ethyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine. MS ESI calc'd. for C<sub>29</sub>H<sub>25</sub>ClN<sub>4</sub> [M+H]<sup>+</sup> 465, found 465.

**Step 3: (R)-1-(3-ethyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea**

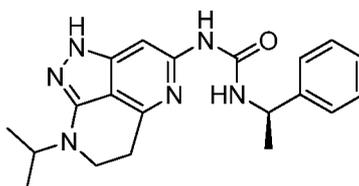
7-chloro-3-ethyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine (35 mg, 0.075 mmol), (R)-1-(1-phenylethyl)urea (18.5 mg, 0.113 mmol), cesium carbonate (73.6 mg, 0.226 mmol) and BrettPhos pre-catalyst (6.8 mg) were charged in a 1 dram vial, evacuated and backfilled with nitrogen and taken in 1,4-dioxane (0.4 mL) and heated reaction at 100 °C for 1 hour. The reaction mixture was diluted with DCM, washed with water, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-75% EtOAc-hexanes) gave (R)-1-(3-ethyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for C<sub>38</sub>H<sub>36</sub>N<sub>6</sub>O [M+H]<sup>+</sup> 593, found 593.

**Step 4: (R)-1-(3-ethyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea**

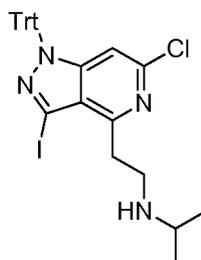
(R)-1-(3-ethyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea (27 mg, 0.045 mmol) was taken in TFA (0.1 mL) and stirred at room temperature for 30 minutes. To the reaction was added triethylsilane (21 uL, 0.128 mmol) and the mixture was stirred for 15 minutes at room temperature before it was heated at 80 °C for 30

- 167 -

minutes. The reaction mixture was concentrated, taken in DCM and washed with aqueous sodium bicarbonate, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-15% MeOH-DCM) gave (R)-1-(3-ethyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for  $C_{19}H_{22}N_6O$   $[M+H]^+$  351, found 351.  $^1H$  NMR (ppm, 500 MHz, DMSO- $d_6$ )  $\delta$  7.32 (dd,  $J = 3.4, 7.9$ , 4H), 7.24 - 7.14 (m, 1H), 6.40 (s, 1H), 4.90 - 4.79 (m, 1H), 4.02 - 3.89 (m, 2H), 3.40 (m, 2H), 3.01 (m, 2H), 1.40 (d,  $J = 6.9$ , 3H), 1.24 (t,  $J = 9.4$ , 3H).

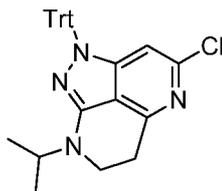
**Example 142**

10 **(R)-1-(3-isopropyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea**

**Step 1: N-(2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)ethyl)propan-2-amine**

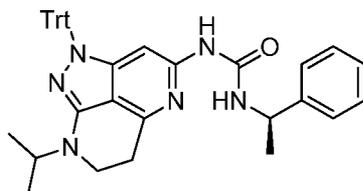
15 (E)-2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)-N,N-dimethylethanamine (1.0 g, 1.692 mmol) and propan-2-amine.HCl (0.647 g, 6.77 mmol) were stirred in a 3:1:1 solution of DCE:AcOH:EtOH (5 ml) at 100 °C for 2 hrs. Solvent was removed by vacuum and the residue was taken in DCE (15 ml) and treated with sodium triacetoxyborohydride (0.9 g, 4.23 mmol), acetic acid (0.4 g, 6.7 mmol) and stirred at room  
20 temperature for 6 hours. The reaction mixture was partitioned between DCM and aqueous sodium bicarbonate and the organics separated, washed with brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-15% MeOH-DCM) gave N-(2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)ethyl)propan-2-amine. MS ESI calc'd. for  $C_{30}H_{28}ClIN_4$   $[M+H]^+$  607, found 607.

- 168 -



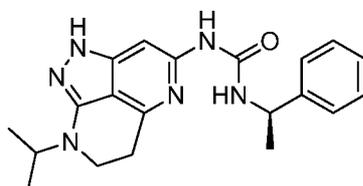
**Step 2: 7-chloro-3-isopropyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine**

N-(2-(6-chloro-3-iodo-1-trityl-1H-pyrazolo[4,3-c]pyridin-4-yl)ethyl)propan-2-amine (554 mg, 0.913 mmol) and RuPhos pre-catalyst (66.5 mg, 0.091 mmol) were charged in a 2 dram vial, evacuated and backfilled with nitrogen and taken in toluene (4 mL) before the addition of a solution of 2M NaOtBu in THF (1.15 mL, 2.3 mmol). The reaction mixture was heated at 55 °C for 1 hour before it was diluted with EtOAc and washed with water, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-50% EtOAc-hexanes) gave 7-chloro-3-isopropyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine. MS ESI calc'd. for C<sub>30</sub>H<sub>27</sub>ClN<sub>4</sub> [M+H]<sup>+</sup> 480, found 480.



**Step 3: (R)-1-(3-isopropyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea**

7-chloro-3-isopropyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridine (116 mg, 0.242 mmol), (R)-1-(1-phenylethyl)urea (60 mg, 0.363 mmol), cesium carbonate (237 mg, 0.726 mmol) and BrettPhos pre-catalyst (22 mg, 0.024 mmol) were charged in a 1 dram vial, evacuated and backfilled with nitrogen and taken in 1,4-dioxane (1.2 mL) before the mixture was heated reaction at 100 °C for 1 hour. The reaction mixture was diluted with DCM, washed with water, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-75% EtOAc-hexanes) gave (R)-1-(3-isopropyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for C<sub>39</sub>H<sub>38</sub>N<sub>6</sub>O [M+H]<sup>+</sup> 607, found 607.

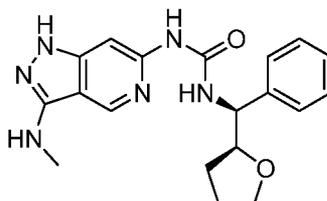


- 169 -

**Step 4: (R)-1-(3-isopropyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea**

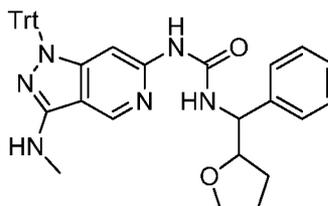
(R)-1-(3-isopropyl-1-trityl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea (75 mg, 0.123 mmol) was taken in TFA (0.5 mL) and stirred at room temperature for 30 minutes before triethylsilane (155  $\mu$ L, 0.97 mmol) was added. The reaction mixture was stirred for 15 minutes at room temperature then heated at 80 °C for 30 minutes before it was concentrated, taken in DCM and washed with aqueous sodium bicarbonate, brine, dried with sodium sulfate and concentrated. Purification of the residue by flash column (0-15% MeOH-DCM) gave (R)-1-(3-isopropyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]naphthyridin-7-yl)-3-(1-phenylethyl)urea. MS ESI calc'd. for  $C_{20}H_{24}N_6O$   $[M+H]^+$  365, found 365.  $^1H$  NMR (ppm, 500 MHz, DMSO- $d_6$ )  $\delta$  7.34 – 7.23 (m, 4H), 7.18 (m, 1H), 6.40 (s, 1H), 4.90 (m, 1H), 3.40 (m, 2H), 3.22 (m, 2H), 2.90 (m, 1H), 1.38 (d,  $J = 7.0$ , 3H), 1.07 (d,  $J = 9.4$ , 6H).

**Example 144**



15

**1-(3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-((S)-phenyl((S)-tetrahydrofuran-2-yl)methyl)urea**



**Step 1: 1-(3-(methylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(phenyl(tetrahydrofuran-2-yl)methyl)urea**

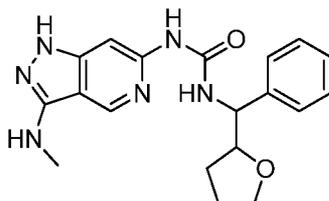
20

6-chloro-N-methyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (400 mg, 0.941 mmol), 1-(phenyl(tetrahydrofuran-2-yl)methyl)urea (228 mg, 1.035 mmol), cesium carbonate (920 mg, 2.82 mmol) and BrettPhos precatalyst (52.6 mg, 0.066 mmol) were taken up in dioxane (9.5 ml) in a 20 mL microwave vial. The vial was evacuated and back-filled with  $N_2$  (x3). The reaction mixture was stirred at 100 °C for two hours. Room temperature was attained. The crude reaction mixture was diluted with EtOAc and filtered through celite. The filtrate was concentrated *in vacuo*, taken up in 5 ml of DCM, and purified on silica gel 5-50%

25

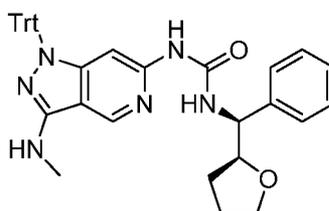
- 170 -

DCM/EtOAc to give 1-(3-(methylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(phenyl(tetrahydrofuran-2-yl)methyl)urea. MS ESI calc'd. for  $C_{38}H_{37}N_6O_2$   $[M+H]^+$  609, found 609.



5 **Step 2: 1-(3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(phenyl(tetrahydrofuran-2-yl)methyl)urea**

1-(3-(methylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(phenyl(tetrahydrofuran-2-yl)methyl)urea (320 mg, 0.526 mmol) was taken up in TFA (3.0 ml). Triethylsilane (0.126 ml, 0.789 mmol) was added and the reaction was allowed to stir at  
10 rt for 30 mins. The reaction mixture was concentrated *in vacuo*. Saturated  $NaHCO_3$  was slowly added. The products were then washed with EtOAc (3X). The combined organic layers were then washed with brine, dried over  $MgSO_4$ , filtered through celite, then concentrated *in vacuo*. The oil was taken up in 2 ml of DCM and loaded directly onto silica gel. Purification by MPLC 0-15% EtOAc/MeOH gave 1-(3-(methylamino)-1H-pyrazolo[4,3-  
15 c]pyridin-6-yl)-3-(phenyl(tetrahydrofuran-2-yl)methyl)urea. MS ESI calc'd. for  $C_{19}H_{23}N_6O_2$   $[M+H]^+$  367, found 367.



**Step 3: 1-(3-(methylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-((S)-phenyl((S)-tetrahydrofuran-2-yl)methyl)urea**

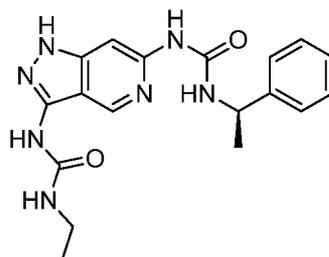
20 The enantiomers of 1-(3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(phenyl(tetrahydrofuran-2-yl)methyl)urea (213mg, 0.518 mmol) were separated by SFC (Berger Multigram II, Column: Phenomenex Lux-4 2.1 X 25cm, 5uM, UV wavelength: 220 nM, mobile phase: 45% / 55% Methanol + 0.25% dimethyl ethylamine/ $CO_{2(l)}$ , flow rate: 70 mL/Min, 9 min run time). Elution was observed at 3.46 min. The fractions were collected  
25 and the solvent evaporated *in vacuo* to afford 1-(3-(methylamino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-((S)-phenyl((S)-tetrahydrofuran-2-yl)methyl)urea and Examples 145-147. MS ESI calc'd. for  $C_{19}H_{23}N_6O_2$   $[M+H]^+$  367, found 367.  $^1H$  NMR (ppm, 500 MHz,  $DMSO-d_6$ )

- 171 -

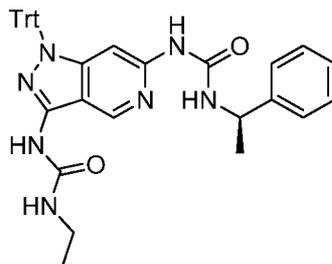
$\delta$  11.46 (s, 1H), 8.99 (s, 1H), 8.61 (br s, 1H), 7.31 (m, 4H), 7.22 (m, 1H), 7.14 (s, 1H), 6.23 (t, J= 5.0, 1H), 4.80 (dd, J= 5.5, J= 3.0, 1H), 4.10 (q, J= 5.5, 1H), 3.67-3.60 (m, 2H), 3.21 (p, J= 7.0, 2H), 1.83 (m, 1H), 1.71 (m, 1H), 1.56 (m, 2H), 1.20 (t, J = 7.0, 3H).

<u>No.</u>	<u>Structure</u>	<u>IUPAC Name</u>	<u>Exact Mass</u> <u>[M+H]<sup>+</sup></u>
145		1-(3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-((S)-phenyl((R)-tetrahydrofuran-2-yl)methyl)urea	Calc'd 367, found 367
146		1-(3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-((R)-phenyl((S)-tetrahydrofuran-2-yl)methyl)urea	Calc'd 367, found 367
147		1-(3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-((R)-phenyl((R)-tetrahydrofuran-2-yl)methyl)urea	Calc'd 367, found 367

5

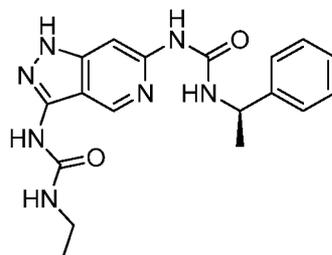
**Example 313****(R)-1-(3-(3-ethylureido)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

- 172 -



**Step 1: (R)-1-(3-(3-ethylureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

To an 8 mL vial charged with (R)-1-(3-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-  
 5 3-(1-phenylethyl)urea (25 mg, 0.046 mmol) in DCM (1 ml) was added ethyl isocyanate (5.51  
 μl, 0.070 mmol) and DIEA (0.024 ml, 0.139 mmol). The vial was capped and the contents  
 stirred at room temperature for 16 h. The course of reaction was followed by LCMS analysis.  
 Only minor product formation was observed. Excess isocyanate (1.5 eq) was added and the  
 reaction mixture heated to 40 °C for a further 16 h. Unreacted isocyanate was quenched by  
 10 adding MP-Trisamine (229 mg, 0.464 mmol) and tumbling the vial for 3 h. The resin was  
 filtered and the volatiles removed *in vacuo* to afford crude (R)-1-(3-(3-ethylureido)-1-trityl-  
 1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea which was taken forward without  
 purification. MS ESI calc'd. For C<sub>37</sub>H<sub>36</sub>N<sub>7</sub>O<sub>2</sub> [M+H]<sup>+</sup> 610, found 610.

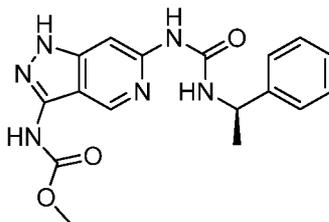


**15 Step 2: (R)-1-(3-(3-ethylureido)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

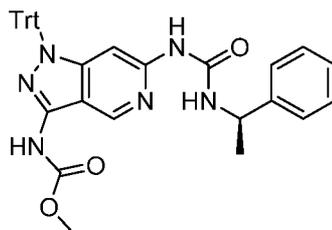
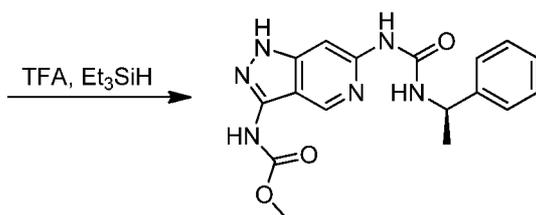
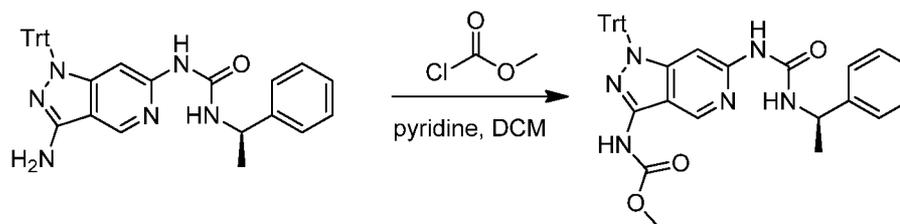
(R)-1-(3-(3-ethylureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-  
 phenylethyl)urea (0.046 mmol) was taken up in TFA (1 ml) and the reaction mixture stirred at  
 room temperature for 1 h. Triethylsilane (0.008ml, 0.046 mmol) was added drop wise, and the  
 reaction mixture stirred for an additional 5 minutes. The mixture was concentrated, re-  
 20 dissolved in DMSO (1.5 mL) and submitted for purification by mass-triggered preparative  
 HPLC to afford (R)-1-(3-(3-ethylureido)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-  
 phenylethyl)urea.TFA (9.2 mg, 0.019 mmol, 41.2 % yield) as a white solid. MS ESI calc'd.  
 For C<sub>18</sub>H<sub>27</sub>N<sub>7</sub>O<sub>2</sub> [M+H]<sup>+</sup> 368, found 368. <sup>1</sup>H NMR (ppm, 600 MHz, DMSO): δ 9.67 (s, 1 H);

- 173 -

9.08 (s, 1 H); 7.81 (s, 1 H); 7.36 (s, 1 H); 7.31-7.32 (m, 4 H); 7.19-7.22 (m, 1 H); 4.81-4.86 (m, 1 H); 3.16-3.20 (m, 2 H); 1.39 (d,  $J = 7.0$  Hz, 3 H); 1.07 (t,  $J = 7.2$  Hz, 3 H).

**Example 220**

5 **(R)-methyl (6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**



10

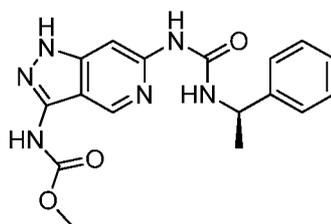
**Step 1: (R)-methyl (6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**

To a 50 mL round bottom flask charged with (R)-1-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-ylamine (380 mg, 0.705 mmol) in DCM (10 ml) was added pyridine (1 ml) followed by methyl chloroformate (65  $\mu$ l, 0.847 mmol). The flask was capped and the contents stirred at room temperature for 16 h. An additional aliquot of methyl

15

- 174 -

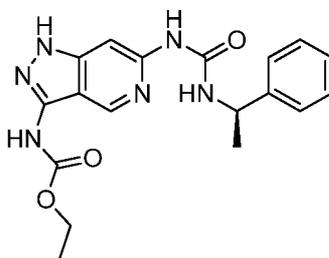
chloroformate (65  $\mu$ l, 0.847 mmol) was added to push the reaction to completion. The volatiles were removed *in vacuo*, the resulting residue redissolved in DCM and washed with saturated copper sulfate solution (2 x 10 mL). The organics were separated using a phase separator cartridge and concentrated. The resulting residue was purified by flash column chromatography on silica gel (ISCO; 80 g prepacked) eluting with ethyl acetate/hexanes to give (R)-methyl (6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate (371 mg, 0.622 mmol, 88 %) as a white solid. MS ESI calc'd. For  $C_{36}H_{33}N_6O_3$   $[M+H]^+$  597, found 597.



10 **Step 2: (R)-methyl (6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**

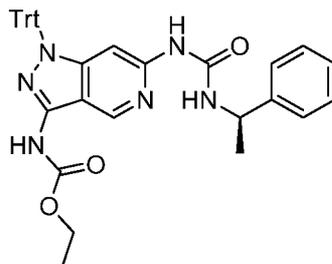
(R)-methyl (6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate (0.622 mmol) was taken up in TFA (5 ml) and the reaction mixture stirred at room temperature for 1 h. Triethylsilane (0.113 ml, 0.705 mmol) was added drop wise, and the reaction mixture stirred for an additional 5 minutes. The mixture was concentrated, re-dissolved in DMSO (1.5 mL) and submitted for purification by mass-triggered preparative HPLC to afford (R)-methyl (6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate, TFA (190 mg, 0.406 mmol, 57.5 % yield) as a white solid. MS ESI calc'd. For  $C_{17}H_{19}N_6O_3$   $[M+H]^+$  355, found 355.  $^1H$  NMR (600 MHz, DMSO): 12.69 (br s, 1 H); 10.39 (br s, 1 H); 9.27 (br s, 1 H); 8.95 (s, 1 H); 7.76 (br s, 1 H); 7.43 (s, 1 H); 7.31 (d, J = 4.5 Hz, 4 H); 7.21 (m, 1 H); 4.85 (t, J = 7.3 Hz, 1 H); 3.68 (s, 3 H); 1.39 (d, J = 6.9 Hz, 3 H).

**Example 315**



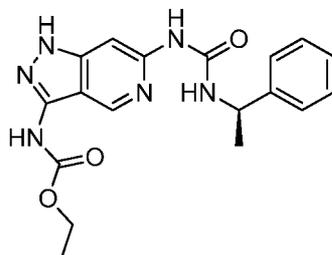
**(R)-ethyl (6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**

- 175 -



**Step 1: (R)-ethyl (6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**

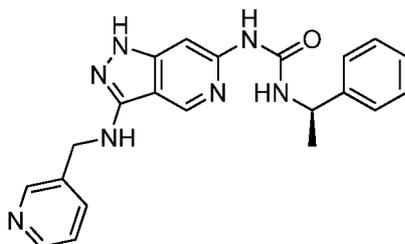
To an 8 mL vial charged with (R)-1-(3-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-  
 5 3-(1-phenylethyl)urea (20 mg, 0.037 mmol) in DCM (1 ml) was added pyridine (0.1 ml)  
 followed by ethyl chloroformate (10.70  $\mu$ l, 0.111 mmol). The vial was capped and the contents  
 stirred at room temperature for 16 h. Un-reacted chloroformate was quenched by adding MP-  
 Trisamine (91 mg, 0.186 mmol) and tumbling the vial for an additional 3 h. The resin was  
 filtered and the volatiles removed *in vacuo* to afford crude (R)-ethyl (6-(3-(1-  
 10 phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate which was taken  
 forward without purification. MS ESI calc'd. For  $C_{37}H_{35}N_6O_3$   $[M+H]^+$  611, found 611.



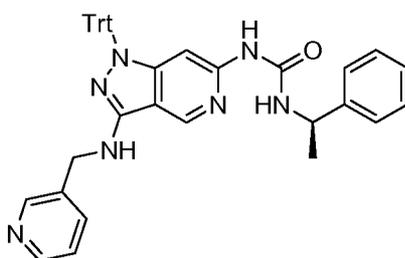
**Step 2: (R)-ethyl (6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**

(R)-ethyl (6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-  
 15 yl)carbamate (0.037 mmol) was taken up in TFA (1 ml) and the reaction mixture stirred at  
 room temperature for 1 h. Triethylsilane (0.006 ml, 0.037 mmol) was added drop wise, and  
 the reaction mixture stirred for an additional 5 minutes. The mixture was concentrated, re-  
 dissolved in DMSO (1.5 mL) and submitted for purification by mass-triggered preparative  
 HPLC to afford (R)-ethyl (6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-  
 20 yl)carbamate (5.7 mg, 0.015 mmol, 41.7 % yield) as a white solid. MS ESI calc'd. For  
 $C_{18}H_{21}N_6O_3$   $[M+H]^+$  369, found 369.  $^1H$  NMR (ppm, 600 MHz, DMSO):  $\delta$  8.95 (s, 1 H); 7.78  
 (s, 1 H); 7.42 (s, 1 H); 7.30-7.31 (m, 4 H); 7.19-7.22 (m, 1 H); 4.85 (t,  $J = 7.2$  Hz, 1 H); 4.14  
 (q,  $J = 7.1$  Hz, 2 H); 1.39 (d,  $J = 7.0$  Hz, 3 H); 1.22 (t,  $J = 7.1$  Hz, 3 H).

- 176 -

**Example 316**

**(R)-1-(1-phenylethyl)-3-(3-((pyridin-3-ylmethyl)amino)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**



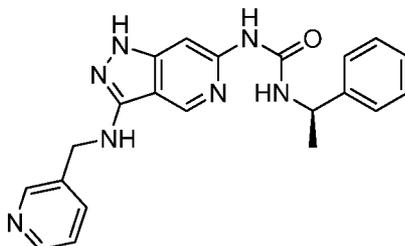
5

**Step 1: (R)-1-(1-phenylethyl)-3-(3-((pyridin-3-ylmethyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

To an 8 mL vial charged with nicotinaldehyde (30 mg, 0.278 mmol) was added (R)-1-(3-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (30 mg, 0.056 mmol) in methanol (1 ml) and acetic acid (0.1 ml). The vial was capped and the contents stirred at room temperature for 2 h. Sodium cyanoborohydride (10.5 mg, 0.167 mmol) was added and the reaction mixture stirred for an additional 16 h. The reaction mixture was diluted with DCM (1 mL), trisamine MP-resin (274 mg, 0.557 mmol) added, and the contents of the vial shaken at room temperature for 3 h. The resin was filtered, and washed through with DCM (1 mL). The volatiles were removed *in vacuo* to afford crude (R)-1-(1-phenylethyl)-3-(3-((pyridin-3-ylmethyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea, which was taken forward without purification. MS ESI calc'd. For C<sub>40</sub>H<sub>36</sub>N<sub>7</sub>O [M+H]<sup>+</sup> 630, found 630.

10

15



20

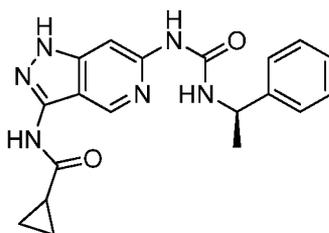
**Step 2: (R)-1-(1-phenylethyl)-3-(3-((pyridin-3-ylmethyl)amino)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea**

- 177 -

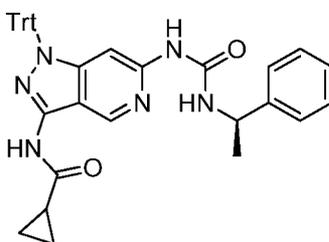
(R)-1-(1-phenylethyl)-3-(3-((pyridin-3-ylmethyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea (0.056 mmol) was taken up in TFA (1 ml) and the reaction mixture was stirred at room temperature for 1 h. Triethylsilane (0.009 ml, 0.056 mmol) was added drop wise, and the reaction mixture stirred for an additional 5 minutes. The mixture was

5 concentrated, re-dissolved in DMSO (1.5 mL) and submitted for purification by mass-triggered preparative HPLC to afford (R)-1-(1-phenylethyl)-3-(3-((pyridin-3-ylmethyl)amino)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea.TFA (16.7 mg, 0.033 mmol, 59.5 % yield) as a white solid. MS ESI calc'd. For  $C_{21}H_{22}N_7O$   $[M+H]^+$  388, found 388.  $^1H$  NMR (ppm, 600 MHz, DMSO):  $\delta$  8.81 (s, 1 H); 8.70 (s, 1 H); 8.58 (d,  $J = 5.0$  Hz, 1 H); 8.09 (s, 1 H); 7.96 (s, 1 H);

10 7.62 (s, 1 H); 7.31-7.32 (m, 4 H); 7.21 (t,  $J = 6.6$  Hz, 1 H); 7.05 (s, 1 H); 4.84 (t,  $J = 7.2$  Hz, 1 H); 4.52 (s, 2 H); 1.40 (d,  $J = 7.0$  Hz, 3 H).

**Example 317**

15 **(R)-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)cyclopropanecarboxamide**



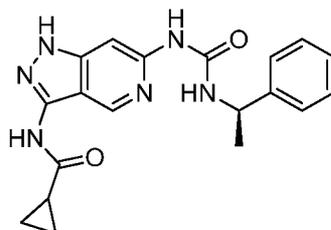
**Step 1: (R)-N-(6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)cyclopropanecarboxamide**

To an 8 mL vial charged with (R)-1-(3-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-

20 3-(1-phenylethyl)urea (20 mg, 0.037 mmol), cyclopropanecarboxylic acid (4.79 mg, 0.056 mmol), and HATU (21.18 mg, 0.056 mmol) was added DIEA (0.013 ml, 0.074 mmol) and DMA (1 ml). The vial was capped and the contents heated to 60 °C and stirred for 16 h. The reaction mixture was concentrated to afford crude (R)-N-(6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)cyclopropanecarboxamide which was taken forward without

25 purification. MS ESI calc'd. For  $C_{38}H_{35}N_6O_2$   $[M+H]^+$  607, found 607.

- 178 -

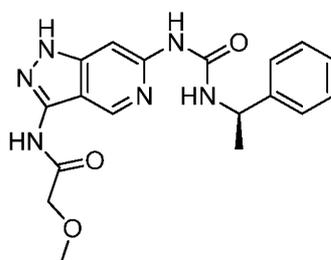


**Step 2: (R)-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)cyclopropanecarboxamide**

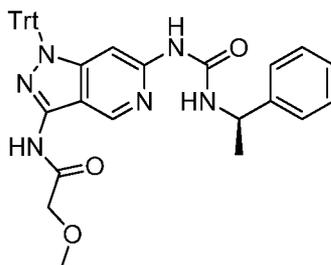
(R)-N-(6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)cyclopropanecarboxamide (0.037 mmol) was taken up in TFA (1 ml) and the reaction mixture was stirred at room temperature for 1 h. Triethylsilane (0.006 ml, 0.037 mmol) was added drop wise, and the reaction mixture stirred for an additional 5 minutes. The mixture was concentrated, re-dissolved in DMSO (1.5 mL) and submitted for purification by mass-triggered preparative HPLC to afford (R)-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)cyclopropanecarboxamide (4.3 mg, 0.012 mmol, 31.8 % yield) as a white solid. MS ESI calc'd. For  $C_{19}H_{21}N_6O_2$   $[M+H]^+$  365, found 365.  $^1H$  NMR (ppm, 600 MHz, DMSO):  $\delta$  11.15 (s, 1 H); 9.33 (br s, 1 H); 9.05 (s, 1 H); 7.79 (br s, 1 H); 7.41 (s, 1 H); 7.31 (d, J = 4.4 Hz, 4 H); 7.21 (d, J = 5.7 Hz, 1 H); 4.84 (t, J = 7.2 Hz, 1 H); 1.93 (m, 1 H); 1.38 (d, J = 7.0 Hz, 3 H); 0.83 (t, J = 6.9 Hz, 4 H).

15

**Example 318**



**(R)-2-methoxy-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide**

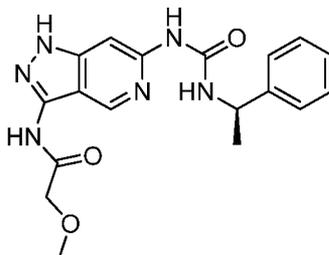


**Step 1: (R)-2-methoxy-N-(6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide**

20

- 179 -

To an 8 mL vial charged with 2-methoxyacetyl chloride (6.6 mg, 0.061 mmol) was added (R)-1-(3-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (30 mg, 0.056 mmol) in DCM (1 ml) and pyridine (0.045 ml, 0.557 mmol). The vial was capped and the contents stirred at room temperature for 16 h. The reaction mixture was diluted with DCM (1 mL), MP-Trisamine (137 mg, 0.278 mmol) added, and the contents of the vial shaken at room temperature for 3 h. The resin was filtered, and washed through with DCM (1 mL). The volatiles were removed *in vacuo* to afford crude (R)-2-methoxy-N-(6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide, which was taken forward without purification. MS ESI calc'd. For  $C_{37}H_{35}N_6O_3$   $[M+H]^+$  611, found 611.



10

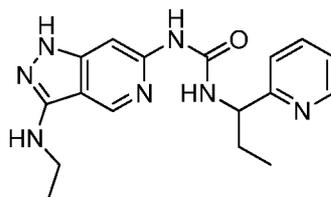
**Step 2: (R)-2-methoxy-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide**

(R)-2-methoxy-N-(6-(3-(1-phenylethyl)ureido)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide (0.056 mmol) was taken up in TFA (1 ml) and the reaction mixture was stirred at room temperature for 1 h. Triethylsilane (0.009 ml, 0.056 mmol) was added drop wise, and the reaction mixture stirred for an additional 5 minutes. The mixture was concentrated, re-dissolved in DMSO (1.5 mL) and submitted for purification by mass-triggered prep. HPLC to afford (R)-2-methoxy-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide.TFA (15.9 mg, 0.033 mmol, 58.9 % yield) as a white solid. MS ESI calc'd. For  $C_{18}H_{21}N_6O_3$   $[M+H]^+$  369, found 369.  $^1H$  NMR (ppm, 600 MHz, DMSO):  $\delta$  10.62 (s, 1 H); 9.28 (br s, 1 H); 9.00 (s, 1 H); 7.75 (s, 1 H); 7.46 (s, 1 H); 7.31-7.32 (m, 4 H); 7.19-7.22 (m, 1 H); 4.85 (t, J = 7.2 Hz, 1 H); 4.09 (s, 2 H); 3.35 (s, 3 H); 1.39 (d, J = 6.9 Hz, 3 H).

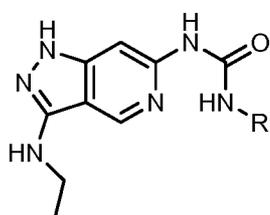
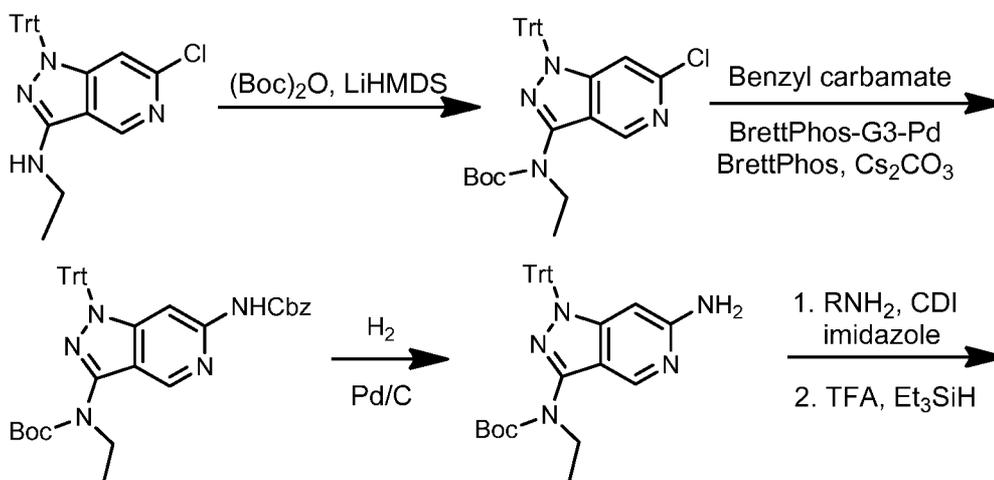
20

- 180 -

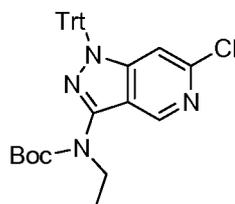
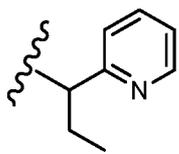
## Example 320



## 1-(3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-(pyridin-2-yl)propyl)urea



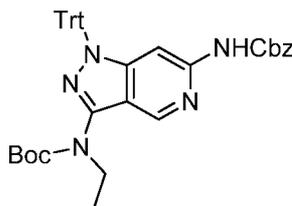
( R = 1-(pyridin-2-yl)propyl: )

10 Step 1: *tert*-butyl (6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)(ethyl)carbamate

A 200 mL round bottom flask containing 6-chloro-N-ethyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (2 g, 4.56 mmol) in THF (30 ml) was cooled to 0 °C under an argon

- 181 -

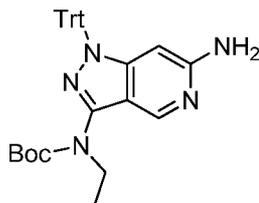
atmosphere and charged with LiHMDS (9.11 ml, 9.11 mmol). The reaction mixture was stirred at 0 °C for 15 minutes. A solution of di-*tert*-butyl dicarbonate (1.293 g, 5.92 mmol) in THF (10 ml) was added and the reaction mixture warmed to ambient temperature and stirred for 16 h. Water (20 ml) was added and the reaction mixture stirred for an additional 5  
5 minutes. The mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic fractions were washed with brine (20 mL), dried (MgSO<sub>4</sub>), filtered and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (ISCO; 40 g prepacked) eluting with ethyl acetate/hexanes to afford *tert*-butyl (6-chloro-1-trityl-1H-pyrazolo[4,3-*c*]pyridin-3-yl)(ethyl)carbamate (2.18 g,  
10 4.04 mmol, 89 % yield) as a white solid.. MS ESI calc'd. For C<sub>32</sub>H<sub>32</sub>ClN<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup> 539, found 539.



**Step 2: *tert*-butyl (6-(((benzyloxy)carbonyl)amino)-1-trityl-1H-pyrazolo[4,3-*c*]pyridin-3-yl)(ethyl)carbamate**

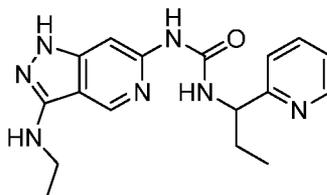
15 A 20 mL microwave vial was charged with cesium carbonate (907 mg, 2.78 mmol), *tert*-butyl (6-chloro-1-trityl-1H-pyrazolo[4,3-*c*]pyridin-3-yl)(ethyl)carbamate (500 mg, 0.928 mmol), benzyl carbamate (421 mg, 2.78 mmol), 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl (34.9 mg, 0.065 mmol) and BrettPhos-G3-Pd (58.9 mg, 0.065 mmol). Dioxane (10 ml) was added, the vial was flushed with argon, capped and the contents  
20 heated to 100 °C with stirring for 16 h. The reaction mixture was diluted with DCM / *i*-PrOH (4:1, 50 mL) and washed with brine (2 x 50 mL), dried (MgSO<sub>4</sub>), filtered and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (ISCO; 24 g prepacked) eluting with ethyl acetate/hexanes to afford *tert*-butyl (6-(((benzyloxy)carbonyl)amino)-1-trityl-1H-pyrazolo[4,3-*c*]pyridin-3-yl)(ethyl)carbamate (225 mg, 0.344 mmol, 37.1 % yield) as a white solid. MS ESI calc'd. For C<sub>40</sub>H<sub>40</sub>N<sub>5</sub>O<sub>4</sub> [M+H]<sup>+</sup> 654, found 654.  
25

- 182 -



**Step 3: tert-butyl (6-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)(ethyl)carbamate**

To a 50 mL round bottom flask charged with *tert*-butyl (6-  
 (((benzyloxy)carbonyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)(ethyl)carbamate (225  
 5 mg, 0.344 mmol) in ethyl acetate (5 ml) and methanol (5 ml) was added palladium on carbon  
 (73.3 mg, 0.069 mmol). The flask was evacuated and back-filled with hydrogen gas using an  
 attached balloon. This procedure was attempted a further two times. The reaction mixture was  
 stirred under a hydrogen atmosphere at room temperature for 16 h. The palladium was filtered  
 off by passing the reaction mixture through celite and washing through with ethyl acetate. The  
 10 volatiles were removed *in vacuo* to afford crude *tert*-butyl (6-amino-1-trityl-1H-pyrazolo[4,3-  
 c]pyridin-3-yl)(ethyl)carbamate (159 mg, 0.306 mmol, 89 % yield) which was taken forward  
 without purification. MS ESI calc'd. For C<sub>32</sub>H<sub>34</sub>N<sub>5</sub>O [M+H]<sup>+</sup> 520, found 520.



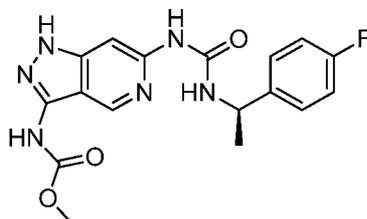
**Step 4: 1-(3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-(pyridin-2-yl)propyl)urea**

To a 8 mL vial charged with imidazole (17.3 mg, 0.26 mmol) and *tert*-butyl (6-amino-  
 1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)(ethyl)carbamate (26.5 mg, 0.051 mmol) in DCM (1  
 ml) was added 1,1'-carbonyldiimidazole (25 mg, 0.153 mmol). The reaction mixture was  
 stirred at room temperature for 5 h, leading to a clear yellow solution. A solution of 1-  
 (pyridin-2-yl)propan-1-amine, 2HCl (21.33 mg, 0.102 mmol) and DIEA (0.045 ml, 0.255  
 20 mmol) in DMF (1 ml) was added. The vial was capped and the contents stirred at room  
 temperature for 16 h. The reaction mixture was concentrated and the resulting residue re-  
 dissolved in TFA (1 ml) and stirred at room temperature for 20 minutes. Triethylsilane (0.008  
 ml, 0.051 mmol) was added drop wise, and the reaction mixture stirred for an additional 5  
 minutes. The mixture was concentrated, re-dissolved in DMSO (1.5 mL) and submitted for  
 25 purification by mass-triggered preparative HPLC to afford 1-(3-(ethylamino)-1H-  
 pyrazolo[4,3-c]pyridin-6-yl)-3-(1-(pyridin-2-yl)propyl)urea (4.1 mg, 0.012 mmol, 23.69 %  
 yield) as a white solid.. MS ESI calc'd. For C<sub>17</sub>H<sub>21</sub>N<sub>7</sub>O [M+H]<sup>+</sup> 340, found 340. <sup>1</sup>H NMR

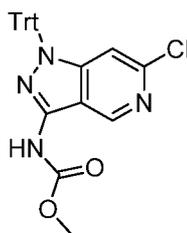
- 183 -

(ppm, 600 MHz, DMSO):  $\delta$  8.99 (s, 1 H); 8.57 (s, 1 H); 8.52 (d, J = 4.8 Hz, 1 H); 7.73 (td, J = 7.7, 1.8 Hz, 1 H); 7.31 (d, J = 7.8 Hz, 1 H); 7.21-7.24 (m, 2 H); 4.76 (q, J = 7.2 Hz, 1 H); 3.19-3.23 (m, 2 H); 1.77-1.82 (m, 1 H); 1.69-1.74 (m, 1 H); 1.17 (t, J = 7.2 Hz, 3 H); 0.80 (t, J = 7.4 Hz, 3 H).

5

**Example 321**

**(R)-methyl (6-(3-(1-(4-fluorophenyl)ethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**

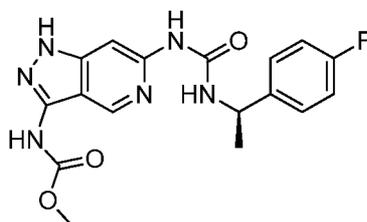


10 **Step 1: methyl (6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**

A 100 mL round bottom flask charged with 6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (1500 mg, 3.65 mmol) in DCM (30 ml) and pyridine (3 mL) was cooled to 0 °C using an ice bath. Methyl chloroformate (0.564 ml, 7.30 mmol) was added and the reaction mixture was stirred for 16 h warming to ambient temperature. The mixture was

15 washed with saturated copper sulfate solution (2 x 50 mL), dried (MgSO<sub>4</sub>), filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (ISCO; 40 g prepacked) eluting with ethyl acetate/hexanes to afford methyl (6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate (1492 mg, 3.18 mmol, 87 % yield) as a white solid. MS ESI calc'd. For C<sub>27</sub>H<sub>22</sub>ClN<sub>4</sub>O<sub>2</sub>

20 [M+H]<sup>+</sup> 469, found 469.

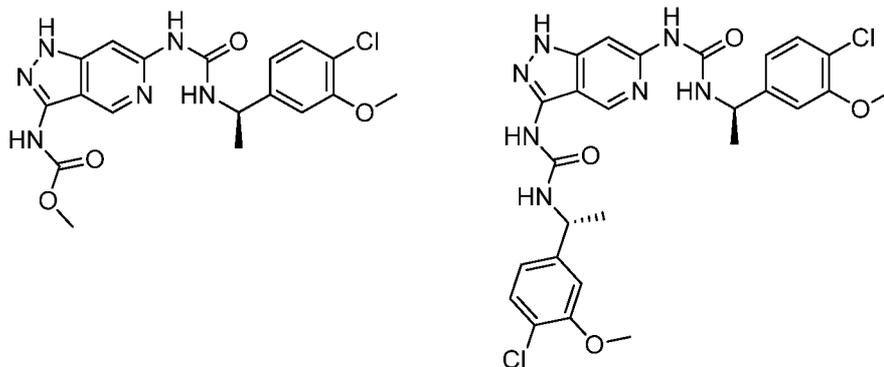


- 184 -

**Step 2: (R)-methyl (6-(3-(1-(4-fluorophenyl)ethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**

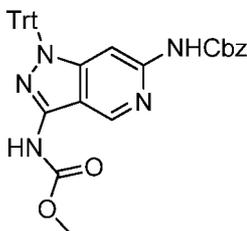
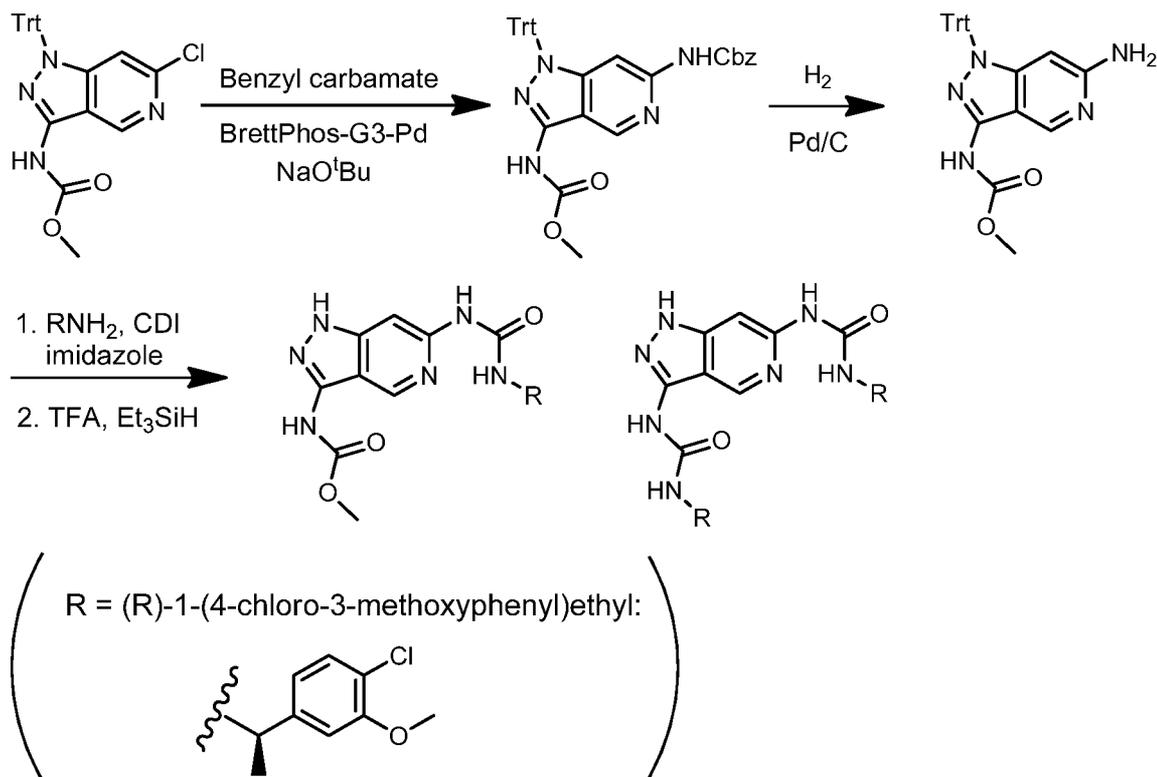
A 5 mL microwave vial was charged with cesium carbonate (71.7 mg, 0.220 mmol), (6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate (40 mg, 0.085 mmol), (R)-1-(1-(4-fluorophenyl)ethyl)urea (23.3 mg, 0.128 mmol), 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl (3.21 mg, 5.97  $\mu$ mol) and BrettPhos-G3-Pd (5.41 mg, 5.97  $\mu$ mol). Dioxane (1 ml) was added, the vial was flushed with argon, capped and the contents heated to 100 °C with stirring for 16 h. The reaction mixture was diluted with DCM (2 ml), MP-TMT (119 mg, 0.119 mmol) added and the contents heated to 65 °C for 4 h with shaking. The reaction mixture was filtered, washing through with DCM (2 mL) and concentrated. The resulting residue was re-dissolved in TFA (1 mL) and stirred at room temperature for 30 minutes. Triethylsilane (0.014 ml, 0.085 mmol) was added drop wise and the reaction mixture was stirred for an additional 5 minutes. The volatiles were removed *in vacuo*, the resulting residue was re-dissolved in DMSO (1.5 mL) and submitted for purification by mass-triggered HPLC to afford (R)-methyl (6-(3-(1-(4-fluorophenyl)ethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate. TFA (5.4 mg, 0.011 mmol, 13.1 % yield) as a white solid. MS ESI calc'd. For C<sub>17</sub>H<sub>18</sub>FN<sub>6</sub>O<sub>3</sub> [M+H]<sup>+</sup> 373, found 373. <sup>1</sup>H NMR (ppm, 600 MHz, DMSO-d<sub>6</sub>):  $\delta$  10.39 (s, 1 H); 9.26 (s, 1 H); 8.94 (s, 1 H); 7.76 (s, 1 H); 7.43 (s, 1 H); 7.35 (dd, J = 8.4, 5.5 Hz, 2 H); 7.13 (t, J = 8.8 Hz, 2 H); 4.84 (t, J = 7.2 Hz, 1 H); 3.68 (s, 3 H); 1.37 (d, J = 7.0 Hz, 3 H).

20

**Example 322 and 314**

**(R)-methyl (6-(3-(1-(4-chloro-3-methoxyphenyl)ethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate (Example 322) and 1,1'-(1H-pyrazolo[4,3-c]pyridine-3,6-diyl)bis(3-((R)-1-(4-chloro-3-methoxyphenyl)ethyl)urea) (Example 314)**

- 185 -



5

**Step 1: benzyl methyl (1-trityl-1H-pyrazolo[4,3-c]pyridine-3,6-diyl)dicarbamate**

A 20 mL microwave vial was charged with sodium *tert*-butoxide (103 mg, 1.075 mmol), methyl (6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate (252 mg, 0.537 mmol), benzyl carbamate (122 mg, 0.806 mmol) and BrettPhos-G3-Pd (24.36 mg, 0.027 mmol). THF (6 ml) was added, the vial was flushed with argon, capped and the contents heated to 50 °C with stirring for 10 h. LCMS analysis indicated incomplete conversion to the desired product. Excess benzyl carbamate (61 mg), sodium *tert*-butoxide (51 mg) and BrettPhos-G3-Pd (12 mg) was added. The vial was flushed with argon, capped and the contents heated to 50 °C for an additional 4 h. The mixture was cooled, diluted with ethyl acetate (10 mL), washed with saturated aqueous sodium hydrogen carbonate (2 x 20 mL), dried (MgSO<sub>4</sub>), filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (ISCO; 24 g prepacked)

15

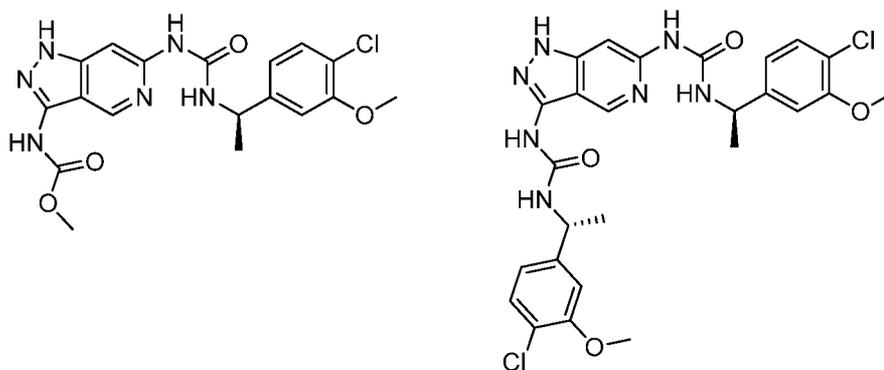
- 186 -

eluting with ethyl acetate/hexanes to afford benzyl methyl (1-trityl-1H-pyrazolo[4,3-c]pyridine-3,6-diyl)dicarbamate (126 mg, 0.216 mmol, 40.2 % yield) as a white solid.. MS ESI calc'd. For  $C_{35}H_{30}N_5O_4$   $[M+H]^+$  584, found 584.



5 **Step 2: methyl (6-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**

To a 50 mL round bottom flask charged with benzyl methyl (1-trityl-1H-pyrazolo[4,3-c]pyridine-3,6-diyl)dicarbamate (126 mg, 0.216 mmol) in ethyl acetate (4 ml) and methanol (4 ml) was added palladium on carbon (45.9 mg, 0.043 mmol). The flask was evacuated and back-filled with hydrogen gas using an attached balloon. This procedure was attempted a  
 10 further two times. The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 16 h. The palladium was filtered off by passing the reaction mixture through celite and washing through with ethyl acetate (20 mL). The volatiles were removed *in vacuo* to afford crude methyl (6-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate (95 mg, 0.211 mmol, 98 % yield) as a white solid. MS ESI calc'd. For  $C_{27}H_{24}N_5O_2$   $[M+H]^+$  450, found  
 15 450.

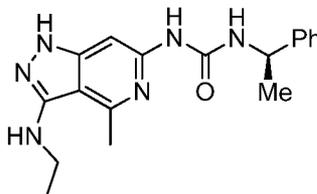


**Step 3: (R)-methyl (6-(3-(1-(4-chloro-3-methoxyphenyl)ethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate and 1,1'-(1H-pyrazolo[4,3-c]pyridine-3,6-diyl)bis(3-((R)-1-(4-chloro-3-methoxyphenyl)ethyl)urea)**

20 To a 8 mL vial charged with imidazole (18 mg, 0.26 mmol) and crude methyl (6-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate (23.8 mg, 0.053 mmol) in DCM (2 ml) was added 1,1'-carbonyldiimidazole (26 mg, 0.159 mmol). The reaction mixture was stirred at room temperature for 5 h, leading to a clear yellow solution. (R)-1-(4-chloro-3-

- 187 -

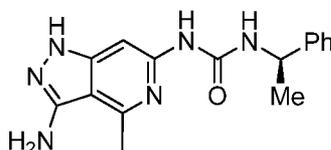
methoxyphenyl)ethanamine.HCl (23.41 mg, 0.105 mmol) and DIEA (0.046 ml, 0.264 mmol) was added. The vial was capped and the contents stirred at room temperature for 16 h. The reaction mixture was concentrated and the resulting residue was re-dissolved in TFA (1 ml) and stirred at room temperature for 20 minutes. Triethylsilane (0.013 ml, 0.079 mmol) was added drop wise, and the reaction mixture stirred for an additional 5 minutes. The mixture was concentrated, re-dissolved in DMSO (1.5 mL) and submitted for purification by mass-triggered preparative HPLC to afford (R)-methyl (6-(3-(1-(4-chloro-3-methoxyphenyl)ethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate. TFA (4.4 mg, 8.26  $\mu$ mol, 15.67 % yield) and 1,1'-(1H-pyrazolo[4,3-c]pyridine-3,6-diyl)bis(3-((R)-1-(4-chloro-3-methoxyphenyl)ethyl)urea), TFA (5 mg, 7.28  $\mu$ mol, 13.82 % yield) as white solids. (Example 322) MS ESI calc'd. For  $C_{18}H_{20}ClN_6O_4$   $[M+H]^+$  419, found 419.  $^1H$  NMR (ppm, 600 MHz, DMSO- $d_6$ ):  $\delta$  10.40 (s, 1 H); 8.95 (s, 1 H); 7.81 (br s, 1 H); 7.43 (s, 1 H); 7.35 (d, J = 8.1 Hz, 1 H); 7.09 (d, J = 1.9 Hz, 1 H); 6.90 (dd, J = 8.2, 1.9 Hz, 1 H); 4.84 (t, J = 7.2 Hz, 1 H); 3.83 (s, 3 H); 3.68 (s, 3 H); 1.39 (d, J = 6.9 Hz, 3 H). (Example 314) MS ESI calc'd. For  $C_{26}H_{28}Cl_2N_7O_4$   $[M+H]^+$  572, found 572.  $^1H$  NMR (600 MHz, DMSO-  $d_6$ ): 9.70 (s, 1 H); 9.06 (s, 1 H); 7.84 (br s, 2 H); 7.34-7.36 (m, 3 H); 7.09-7.10 (m, 2 H); 6.89-6.91 (m, 2 H); 4.89 (t, J = 7.2 Hz, 1 H); 4.82-4.86 (m, 1 H); 3.82 (s, 6 H); 1.40 (dd, J = 6.9 Hz, 6 H).

**Example 331**

**(R)-1-(3-(ethylamino)-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**  
 A conical vial was charged with (R)-1-(3-amino-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (32 mg, 0.103 mmol) and magnesium sulfate (37.2 mg, 0.309 mmol). chloroform (666  $\mu$ l), methanol (333  $\mu$ l), magnesium sulfate (37.2mg, 0.309 mmol) and trifluoroacetic acid (23.83  $\mu$ l, 0.309 mmol) were injected and the reaction was stirred at ambient temperature for 1 hour. Sodium cyanoborohydride (19.44 mg, 0.309 mmol) was then added and stirring was continued for one hour. The reaction was diluted with water and the aqueous layer was transferred to a separatory funnel and washed 3x chloroform/IPA. The combined organic washings were dried over magnesium sulfate and then filtered and concentrated. The residue was dissolved in DMSO (2mL) filtered and delivered to the purification group.  
 Reversed phase mass triggered HPLC was performed. The active fractions were dried down

- 188 -

on the Genevac which was free-based with  $\text{NH}_3$  in MeOH (7N) and concentrated to yield a white solid (14mg, 40.1%). MS ESI calc'd for  $\text{C}_{18}\text{H}_{22}\text{N}_6\text{O}$   $[\text{M}+\text{H}]^+$  339, found 339.  $^1\text{H}$  NMR (ppm, 500Mhz,  $\text{DMSO-d}_6$ ):  $\delta$  11.52 (s, 1H), 8.88 (s, 1H), 8.39 (s, 1H), 7.45-7.09 (m, 5H), 7.00-6.95 (m, 1H), 5.41 (q,  $J=5.6\text{Hz}$ , 1H), 4.98-4.69 (m, 1H), 3.26-3.15 (m, 2H), 2.61 (s, 3H),  
 5 1.44-1.35 (m, 3H), 1.19 (dd,  $J=3.6\text{Hz}$ , 3H).

**Example 333****(R)-1-(3-amino-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea****Step 1: (R)-1-(4-chloro-5-cyano-6-methylpyridin-2-yl)-3-(1-phenylethyl)urea**

10 A flask was charged with 4,6-dichloro-2-methylnicotinonitrile (1500mg), (R)-1-(1-phenylethyl)urea (1449mg), xantphos (371mg), palladium(II)acetate (90mg) and cesium carbonate (5.23g). Tetrahydrofuran (53mL) was injected and the reaction was heated to 50 °C for 3 hours. LC/MS showed that the reaction cleanly proceeded to completion. The reaction mixture was filtered through celite and the filtrate was concentrated and purified by silica gel  
 15 chromatography (0-30% DCM/EtOAc). (R)-1-(4-chloro-5-cyano-6-methylpyridin-2-yl)-3-(1-phenylethyl)urea (2.19g, 87 %) was isolated as an off-white solid. MS ESI calc'd for  $\text{C}_{16}\text{H}_{15}\text{ClN}_4\text{O}$   $[\text{M}+\text{H}]^+$  315, found 315.

**Step 2: (R)-1-(3-amino-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

A flask was charged with (S)-1-(4-chloro-5-cyano-6-methylpyridin-2-yl)-3-(1-phenylethyl)urea (920mg) and ethanol (6989  $\mu\text{l}$ ) and hydrazine (183  $\mu\text{l}$ ) was added. The  
 20 reaction was heated to 95 °C for 17 hours. LC/MS showed the reaction was mostly but not entirely complete (~15% remaining starting material by LC/MS integration). The reaction was heated for 5 additional hours. After cooling, HCl (1N, 14.6 mL) was added and the reaction was stirred for 30 minutes. The reaction was poured into a 500mL separatory funnel  
 25 containing 150mL of concentrated sodium bicarbonate solution. The resulting emulsion was washed 3x with chloroform/IPA (4:1, 100mL portions). The combined organic washings were dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography (0-10% EtOAc/MeOH + 0.1% ammonia) was performed and the active fractions were concentrated to dryness yielding the title compound as a white solid (400mg, 41.1%). MS ESI calc'd for  
 30  $\text{C}_{16}\text{H}_{18}\text{N}_6\text{O}$   $[\text{M}+\text{H}]^+$  311, found 311.  $^1\text{H}$  NMR (ppm500Mhz,  $\text{DMSO-d}_6$ ):  $\delta$  9.30 (s, 1H), 8.74

- 189 -

(d,  $J=0.9\text{Hz}$ , 1H), 8.29 (s, 1H), 8.07 (s, 1H), 7.37-7.32 (m, 5H), 7.28-7.21 (m, 1H), 6.60 (s, 2H), 4.88 (p,  $J=7.0\text{Hz}$ ), 2.47 (s, 3H), 1.42 (d,  $J=6.9\text{Hz}$ , 3H).

**Example 337**

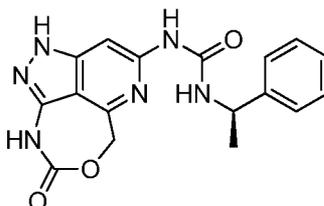
5 **(R)-N-(4-methyl-6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)acetamide**

A conical reaction vial was charged with (R)-1-(3-amino-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (101 mg, 0.325 mmol) and tetrahydrofuran (3000  $\mu\text{l}$ ) was injected. To the resulting solution was added pyridine (132  $\mu\text{l}$ , 1.627 mmol) and acetic anhydride (95  $\mu\text{l}$ , 1.009 mmol). The reaction was stirred for 1 hour and no conversion was observed. Acetyl chloride (116  $\mu\text{l}$ , 1.627 mmol) was injected and the reaction became heterogenous.

10 Dichloromethane (3mL) was added to give a homogenous reaction solution. The reaction was stirred at ambient temperature for 30 minutes. Solvent was removed on the rotovap. Dioxane (3 ml) was added followed by 1N sodium hydroxide (0.256 ml, 0.256 mmol) and the reaction was heated to 50  $^{\circ}\text{C}$  for 30 minutes. Reversed phase HPLC was performed directly on the

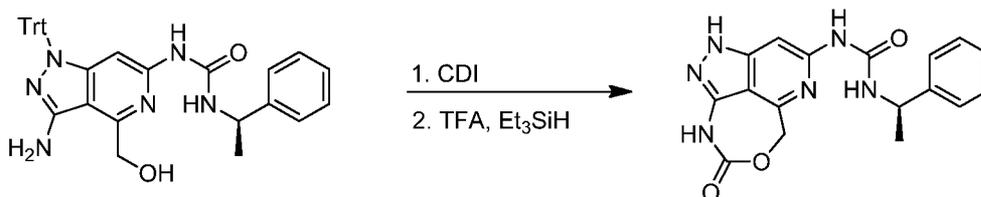
15 crude reaction mixture (5-40% ACN/Water, 30mm Focus Gradient). The active fractions were frozen and concentrated on the lyophilizer, the residue was dissolved in methanol filtered through immobilized bicarbonate and the filtrate was concentrated to give the title compound. MS ESI calc'd for  $\text{C}_{18}\text{H}_{20}\text{N}_6\text{O}_2$   $[\text{M}+\text{H}]^+$  353, found 353.  $^1\text{H}$  NMR (ppm, 500Mhz,  $\text{DMSO-d}_6$ ):  $\delta$  12.72 (s, 1H), 10.01 (s, 1H), 9.26-8.75 (m, 1H), 8.00 (s, 1H), 7.69-7.13 (m, 6H), 5.09-4.69

20 (m, 1H), 3.31 (s, 3H), 2.06 (s, 3H), 1.39 (d,  $J=6.9\text{Hz}$ , 1H).

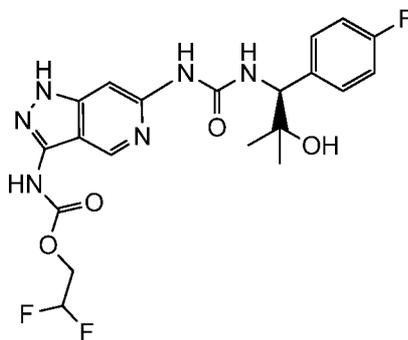
**Example 368**

**(R)-1-(8-oxo-2,6,8,9-tetrahydro-7-oxa-1,2,5,9-tetraazabenzocd]azulen-4-yl)-3-(1-phenylethyl)urea**

- 190 -

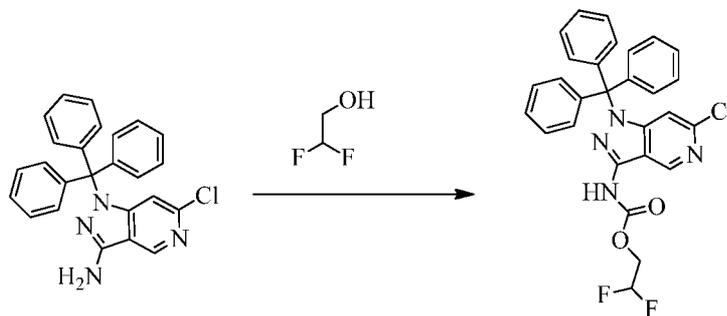


A 20 ml scintillation vial was charged with (R)-1-(3-amino-4-(hydroxymethyl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (15 mg, 0.026 mmol) and CDI (6.42 mg, 0.040 mmol). Acetonitrile (3 ml) was added, the vial was capped and the contents was heated to 60 °C for 16 h. The reaction mixture was concentrated and the resulting residue subjected to TFA (1 ml) hydrolysis for 30 minutes at room temperature. Triethylsilane (8.43  $\mu$ l, 0.053 mmol) was added drop wise and the reaction mixture stirred for an additional 5 minutes. The volatiles were removed *in vacuo* and the resulting residue submitted for purification by mass-triggered HPLC to afford (R)-1-(8-oxo-2,6,8,9-tetrahydro-7-oxa-1,2,5,9-tetraazabenzoc[d]azulen-4-yl)-3-(1-phenylethyl)urea, TFA (3.1 mg, 6.65  $\mu$ mol, 25.2 % yield) as a white solid. MS ESI calc'd. For  $C_{17}H_{17}N_6O_3$   $[M+H]^+$  353, found 353.  $^1H$  NMR (ppm, 500 MHz, DMSO- $d_6$ ):  $\delta$  12.47 (s, 1 H); 10.99 (s, 1 H); 9.05 (s, 1 H); 7.49 (s, 1 H); 7.33 (d, J = 4.7 Hz, 4 H); 7.23 (s, 1 H); 5.34 (s, 2 H); 4.84 (t, J = 7.3 Hz, 1 H); 1.38-1.41 (m, 3 H).

**Example 406**

15

**2,2-difluoroethyl [6-({[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]carbamate**



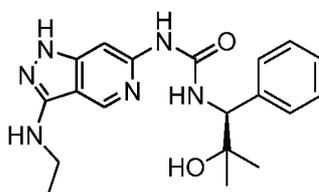
**Step 1: 2,2-difluoroethyl (6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate**

- 191 -

CDI (395 mg, 2.434 mmol) was added to a stirred, room temperature mixture of 6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (500 mg, 1.217 mmol) 6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine and imidazole (331 mg, 4.87 mmol) in tetrahydrofuran (12 mL), and the mixture was stirred at room temperature for overnight. 2,2-Difluoroethanol (0.231 mL, 3.65 mmol) was added to the mixture, and the resultant mixture was kept stirring at room temperature for 2h before the reaction mixture was heated up to 60 °C for overnight. The mixture was cooled and concentrated, and the residue was loaded directly purified with silica gel column chromatography eluting with EtOAc/isohexane = 25%, to give 2,2-difluoroethyl (6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate (570 mg, 1.098 mmol, 90 % yield) as a white solid. MS ESI calc'd. for C<sub>28</sub>H<sub>22</sub>ClF<sub>2</sub>N<sub>4</sub>O<sub>2</sub> [M + H]<sup>+</sup> 519, found 519.

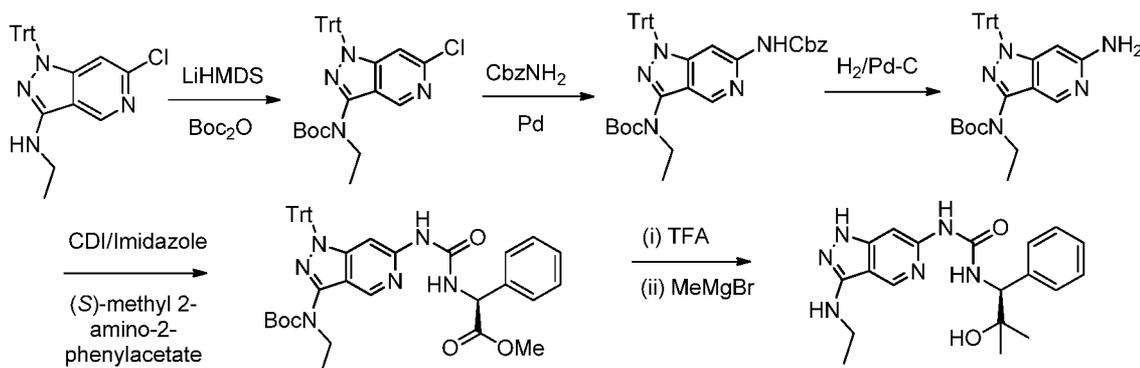
**Step 2 and 3:** Follow the same procedure in Scheme 2, steps 2 and 3 as exemplified in Example 1, 2,2-difluoroethyl [6-({[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]carbamoyl} amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]carbamate (Example 406) can be prepared from 2,2-difluoroethyl (6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)carbamate.

### Example 420



### 1-(3-Ethylamino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-hydroxy-2-methyl-1-phenylpropyl)-urea

20



**Step 1: Synthesis of tert-butyl (6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)(ethyl)carbamate :**

- 192 -

At 0 °C, to a solution of 6-chloro-N-ethyl-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (1.0 g, 2.2 mmol) in *anhydrous* THF (20 mL) was added LiHMDS (1.0 M solution in toluene, 4.5 mL, 4.5 mmol) and the contents were stirred at the same temperature. After 15 min, Boc<sub>2</sub>O (0.58 g, 2.7 mmol) was added at the same temperature and the contents were allowed to warm  
5 to ambient temperature. After 2h (TLC analysis indicated consumption of starting material), H<sub>2</sub>O (10 mL) was added and stirred for 5 min. The organic contents were extracted with EtOAc (3 x 25 mL) and the EtOAc layer washed with brine (1 x 20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvents were removed under reduced pressure. The residue thus obtained was purified by a filter column to afford the title compound (0.8 g, 70% yield). MS ESI calc'd. for  
10 C<sub>32</sub>H<sub>31</sub>ClN<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup> 539; Found 539.

**Step 2: Synthesis of tert-butyl (6-(((benzyloxy)carbonyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)(ethyl)carbamate:**

Under inert atmosphere, to a solution of tert-butyl (6-chloro-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)(ethyl)carbamate **2** (0.52 g, 0.92 mmol) in *anhydrous* 1,4-dioxane (8.0 mL) was  
15 added benzyl carbamate (0.42 g, 2.76 mmol), brettphos pre catalyst (0.04 g, 0.046 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.9 g, 2.76 mmol) and the contents were heated in a sealed tube at 100 °C. After 5 h, the reaction mixture was brought back to ambient temperature and the volatiles were removed under reduced pressure. The residue thus obtained was purified by a flash column chromatography to afford the title compound (0.5 g, 83% yield). MS ESI calc'd. for  
20 C<sub>40</sub>H<sub>39</sub>N<sub>5</sub>O<sub>4</sub> [M+H]<sup>+</sup> 654; Found 654.

**Step 3: Synthesis of tert-butyl (6-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)(ethyl)carbamate:**

To a solution of tert-butyl (6-(((benzyloxy)carbonyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)(ethyl)carbamate (0.2 g, 0.31 mmol) in MeOH (50 mL) was added Pd on  
25 carbon (10%, 0.2 g) and the contents were stirred under an atmosphere of H<sub>2</sub> (3.0 Kg/cm<sup>2</sup>). After 5 h, the suspension was filtered through a pad of celite, and the solvent was evaporated under reduced pressure to afford the title compound (0.12 g, 75% yield) and was taken directly for the next step. MS ESI calc'd. for C<sub>32</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub> [M+H]<sup>+</sup> 520; Found 520.

- 193 -

**Step 4: Synthesis of (S)-methyl 2-(3-(3-((tert-butoxycarbonyl)(ethyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)ureido)-2-phenylacetate:**

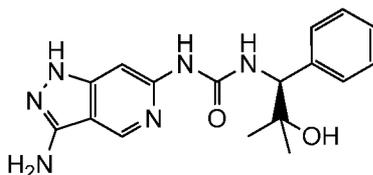
To a solution of tert-butyl (6-amino-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-yl)(ethyl)carbamate (0.2 g, 0.385 mmol) in *anhydrous* 1,4-dioxane (3 mL) was added CDI (0.31 g, 1.92 mmol) followed by the addition of imidazole (0.132 g, 1.92 mmol) and the contents were stirred at ambient temperature. After 16 h (the completion of the reaction was confirmed by quenching small aliquot of the reaction mixture with MeOH and mass obtained corresponds to the methyl carbamate) DIPEA (0.247 g, 1.92 mmol) and (S)-methyl 2-amino-2-phenylacetate (0.194 g, 0.962 mmol) were added and stirred. After 14 h, the reaction mixture was quenched with H<sub>2</sub>O and the organic contents were extracted with EtOAc (3x20 mL), dried over *anhydrous* Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue thus obtained was purified by preparative HPLC to afford the title compound. MS ESI calc'd. for C<sub>42</sub>H<sub>42</sub>N<sub>6</sub>O<sub>5</sub> [M+H]<sup>+</sup> 711; Found 711.

**Steps 5 and 6: Synthesis of 1-(3-Ethylamino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-hydroxy-2-methyl-1-phenyl-propyl)-urea:**

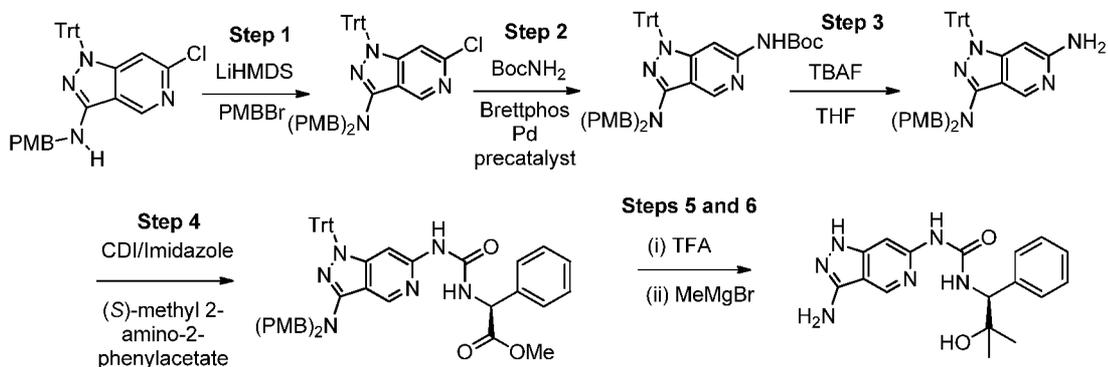
To the solution of (S)-methyl 2-(3-(3-((tert-butoxycarbonyl)(ethyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)ureido)-2-phenylacetate (0.078 g, 0.109 mmol) in *anhydrous* CH<sub>2</sub>Cl<sub>2</sub>(1mL) was added TFA (1mL) followed by Et<sub>3</sub>SiH (2 drops). The resultant mixture was stirred at ambient temperature. After 2 h of stirring, solvent was removed under reduced pressure, the residue (TFA salt) thus obtained was triturated in diethyl ether to afford the compound which was taken as such for next step. At 0°C, to the solution of [3-(3-Ethylamino-1H-pyrazolo[4,3-c]pyridin-6-yl)-ureido]-phenyl-acetic acid methyl ester TFA salt (0.06 g, 0.163 mmol) in *anhydrous* THF was added methyl magnesium bromide (1 M solution in toluene, 1.63 mL, 1.63 mmol) and resultant mixture was allowed to warm and stirred at ambient temperature. After 10 h, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl solution (5 mL), and the organic contents were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The volatiles were removed under reduced pressure and the residue thus obtained was further purified by prep HPLC to afford the title compound. <sup>1</sup>H NMR (ppm, 400 MHz, CD<sub>3</sub>OD): δ 8.69 (s, 1H), 7.44-7.39 (m, 2H), 7.33-7.29 (m, 2H), 7.26-7.23 (m, 1H), 6.99 (s, 1H), 4.78 (s, 1H), 3.36 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.30 (s, 3H), 1.16 (s, 3H). MS ESI calc'd. for C<sub>19</sub>H<sub>24</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 369; Found 369.

- 194 -

## Example 425



**1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]urea**



5

**Step 1: Synthesis of 6-chloro-N,N-bis(4-methoxybenzyl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine :**

At 0 °C, to a solution of 6-chloro-N-(4-methoxybenzyl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (2.0 g, 3.78 mmol) in *anhydrous* THF (30 mL) was added LiHMDS (1.0 M solution in Toluene, 7.56 mL, 7.56 mmol) and the contents were stirred at the same temperature. After 15 min, PMBBBr (0.92 g, 4.53 mmol) was added at the same temperature and the contents were allowed to warm to ambient temperature. After 3h, H<sub>2</sub>O (10 mL) was added and stirred for 5 min. The organic contents were extracted with EtOAc (3 x 40 mL) and the EtOAc layer washed with brine (1 x 20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvents were removed under reduced pressure. The residue thus obtained was purified by a filter column to afford the title compound (1.0 g, 41% yield). MS ES calc'd. for C<sub>41</sub>H<sub>35</sub>ClN<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup> 651; Found 651.

15

**Step 2: Synthesis of tert-butyl (3-(bis(4-methoxybenzyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)carbamate:**

Under inert atmosphere, to a solution of 6-chloro-N,N-bis(4-methoxybenzyl)-1-trityl-1H-pyrazolo[4,3-c]pyridin-3-amine (0.5 g, 0.77 mmol) in *anhydrous* 1,4-dioxane (10.0 mL) was added *tert*-Butyl carbamate (0.26 g, 2.3 mmol), brettphos pre catalyst (0.03 g, 0.004 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.75 g, 2.3 mmol) and the contents were heated in a sealed tube at 100 °C. After 6 h, the reaction mixture was brought back to ambient temperature and the volatiles

20

- 195 -

were removed under reduced pressure. The residue thus obtained was purified by a flash column chromatography to afford the title compound (0.4 g, 71% yield). MS ES calc'd. for  $C_{46}H_{45}N_5O_4$   $[M+H]^+$  732; Found 732.

**5 Step 3: Synthesis of 3-N,N-bis(4-methoxybenzyl)-1-trityl-1H-pyrazolo[4,3-c]pyridine-3,6-diamine:**

To a solution of (3-(bis(4-methoxybenzyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)carbamate (0.4 g, 0.55 mmol) in THF (8 mL) was added TBAF (1.0 M solution in THF, 10 mL) and the contents were heated to reflux. After 12 h, the reaction was cooled back to ambient temperature, quenched with 1N HCl (5 mL) and stirred at ambient temperature for 1h.  
10 The reaction mixture was further diluted with EtOAc (25 mL) and the organic layer was separated. The organic layer was washed with brine (1 x 20 mL), dried over anhydrous  $Na_2SO_4$  and the solvents were removed under reduced pressure. The residue thus obtained was purified by a filter column to afford the title compound. MS ES calc'd. for  $C_{41}H_{37}N_5O_2$   $[M+H]^+$  632; Found 632.

**15 Step 4: Synthesis of Methyl (S)-2-(3-(3-(bis(4-methoxybenzyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)ureido)-2-phenylacetate:**

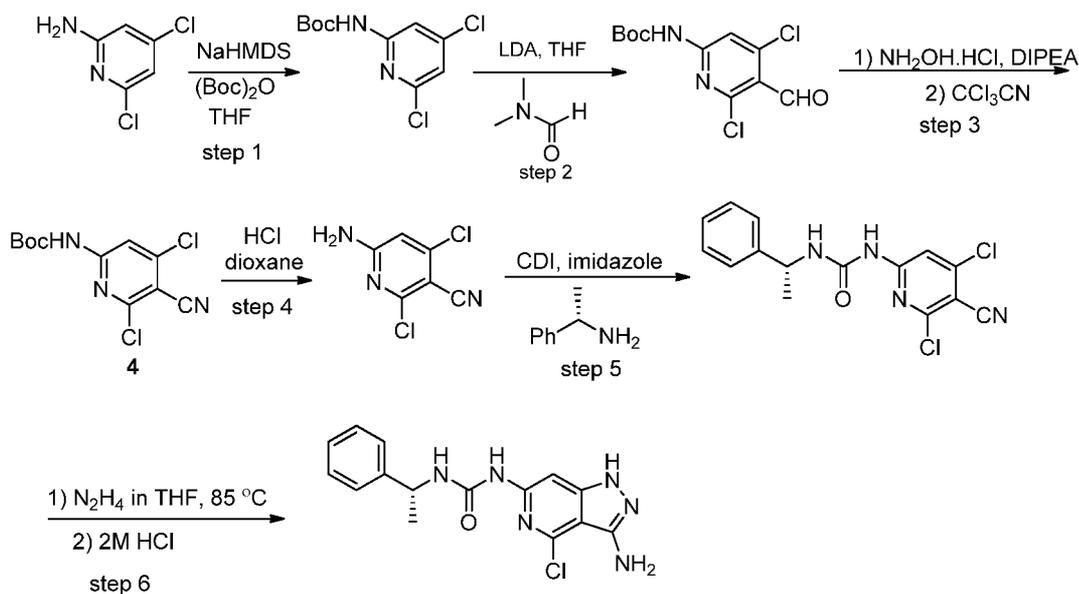
To a solution of 3-N,N-bis(4-methoxybenzyl)-1-trityl-1H-pyrazolo[4,3-c]pyridine-3,6-diamine (0.1 g, 0.16 mmol) in *anhydrous* 1,4-dioxane (3 mL) was added CDI (0.13 g, 0.79 mmol) followed by the addition of imidazole (0.05 g, 0.78 mmol) and the contents were stirred  
20 at ambient temperature. After 16 h, DIPEA (0.12 mL, 0.64 mmol) and (S)-methyl-2-amino-2-phenylacetate (0.064 g, 0.32 mmol) were added and stirred. After 2 h, the reaction mixture was quenched with  $H_2O$  and the organic contents were extracted with EtOAc (2x20 mL), dried over *anhydrous*  $Na_2SO_4$  and concentrated. The residue thus obtained was purified by preparative HPLC to afford the title compound MS ES calc'd. for  $C_{51}H_{46}N_6O_5$   $[M+H]^+$  823;  
25 Found 823.

**Steps 5 and 6: Synthesis of (S)-1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-hydroxy-2-methyl-1-phenylpropyl)urea:**

To the solution of (S)-2-(3-(3-(bis(4-methoxybenzyl)amino)-1-trityl-1H-pyrazolo[4,3-c]pyridin-6-yl)ureido)-2-phenylacetate (0.05 g, 0.06 mmol) was added TFA (2mL) followed  
30 by  $Et_3SiH$  (2 drops). The resultant mixture was stirred at 80 °C. After 3 h of stirring, solvent was removed under reduced pressure, the residue (TFA salt) thus obtained was triturated in diethyl ether to afford the compound which was taken as such for next step. At 0°C, to the solution methyl (S)-2-(3-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)ureido)-2-phenylacetate

- 196 -

(0.05 g, 0.146 mmol) in *anhydrous* THF was added methyl magnesium bromide (3 M solution in Et<sub>2</sub>O, 0.5 mL, 1.5 mmol) and resultant mixture was allowed to warm and stirred at ambient temperature. After 10 h, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl solution (5 mL), and the organic contents were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The volatiles were removed under reduced pressure and the residue thus obtained was further purified by prep HPLC to afford the title compound. <sup>1</sup>H NMR (ppm, 400 MHz, CD<sub>3</sub>OD): δ 8.73 (s, 1H), 7.42-7.40 (m, 2H), 7.35-7.30 (m, 3H), 7.28 (s, 1H), 4.80 (s, 1H) 1.31 (s, 3H), 1.17 (s, 3H). MS ES calc'd. for C<sub>17</sub>H<sub>20</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 341; Found 341.

**Example 444**

10

**Step 1: tert-butyl (4,6-dichloropyridin-2-yl)carbamate**

To a stirred solution of 4,6-dichloropyridin-2-amine (5.0 g, 30.6 mmol) in THF (100.0 mL) was added NaHMDS (67.5 mL, 1M solution in THF, 67.0 mmol) at -78 °C followed by Boc anhydride (8.08 g, 36.7 mmol) and allowed to warm to room temperature over 12 h. After confirming the completion of starting material by TLC, the reaction mixture was quenched with saturated ammonium chloride solution extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated under reduced pressure to get crude product which was purified by column chromatography (hexanes:ethyl acetate=9:1) to afford desired product. <sup>1</sup>H NMR (ppm, 400 MHz, DMSO-d<sub>6</sub>): δ 10.48 (s, 1H), 7.85 (s, 1H), 7.36 (s, 1H), 1.46 (s, 9H), MS ES calc'd. for C<sub>10</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 263, Found: 263.

20

- 197 -

**Step 2: tert-butyl (4,6-dichloro-5-formylpyridin-2-yl)carbamate**

To a stirred solution of diisopropylethylamine (7.4 mL, 53.2 mmol) in THF was added n-BuLi (18.8 mL, 47.1 mmol, 2.5 M solution in hexanes) at -78 °C, and allowed to stir at 0 °C of 30 minutes. The reaction mixture was again cooled to -78 °C and a solution compound  
5 *tert*-butyl (4,6-dichloropyridin-2-yl)carbamate (4.0 g, 15.2 mmol) in THF (20.0 mL) was added dropwise and stirred for 1 h at the same temperature. After 1 h, DMF (8.08 g, 36.7 mmol) was added at the same temperature and stirred for 30 minutes. After confirming the completion of starting material by TLC, the reaction mixture was quenched with saturated ammonium chloride solution extracted with ethyl acetate. The organic layer was washed with  
10 brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated under reduced pressure to get crude product which was purified by column chromatography (hexanes:ethyl acetate=4:1) to afford product. <sup>1</sup>H NMR (ppm, 400 MHz, DMSO-d<sub>6</sub>): δ 10.95 (s, 1H), 10.22 (s, 1H), 7.95 (s, 1H), 1.47 (s, 9H).

**Step 3: tert-butyl (4,6-dichloro-5-cyanopyridin-2-yl)carbamate**

To a stirred solution of compound *tert*-butyl (4,6-dichloro-5-formylpyridin-2-yl)carbamate (3.0 g, 10.3 mmol) in THF (30.0 mL) was added diisopropylethylamine (2.76 mL, 15.4 mmol) followed by hydroxylamine hydrochloride (0.78 g, 11.3 mmol) at 0 °C and was stirred at room temperature for 3 h. After confirming the completion of starting material by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate. The  
20 organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated under reduced pressure to get crude product. To the crude product was added trichloroacetonitrile (30.0 mL) and was heated at 85 °C for 2 h. After confirming the completion of starting material by TLC, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography  
25 (hexanes:ethyl acetate=9:1) to afford product. <sup>1</sup>H NMR (ppm, 400 MHz, DMSO-d<sub>6</sub>): δ 11.08 (s, 1H), 8.02 (s, 1H), 1.46 (s, 9H), MS ES calc'd. for C<sub>11</sub>H<sub>11</sub>C<sub>12</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup> 288; Found 288.

**Step 4: 6-amino-2,4-dichloronicotinonitrile**

To a solution of *tert*-butyl (4,6-dichloro-5-cyanopyridin-2-yl)carbamate (2.1 g, 7.2 mmol) in dichloromethane (30.0 mL) was added TFA (3.0 mL) at 0 °C and stirred at the room  
30 temperature for 3 h. After confirming the completion of starting material by TLC, the reaction mixture was concentrated and the crude product was purified by column chromatography (dichloromethane:methanol = 9:1) to afford titled compound. <sup>1</sup>H NMR (ppm, 400 MHz,

- 198 -

DMSO- $d_6$ ):  $\delta$  7.81 (bs, 2H), 6.59 (s, 1H), MS ES calc'd. for  $C_6H_3C_{12}N_3 [M+H]^+$  188; Found 188.

**Step 5: (R)-1-(4,6-dichloro-5-cyanopyridin-2-yl)-3-(1-phenylethyl)urea**

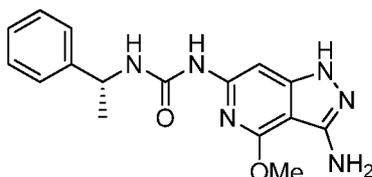
To a stirred solution of compound 6-amino-2,4-dichloronicotinonitrile (0.26 g, 1.37 mmol) in chloroform (7.0 mL) was added diisopropylethylamine (0.49 mL, 2.75 mmol) followed by imidazole (0.47 g, 6.87 mmol) and CDI (1.15 g, 6.87 mmol) at 0 °C and allowed to stir at room temperature for 12 h. After the clear solution is formed (R)-(+)-phenyl ethyl amine (1.08 g, 8.9 mmol) was added at room temperature and stirred for 2 h. After confirming the completion of starting material by TLC, the reaction mixture was concentrated under reduced pressure and dissolved in ethyl acetate and then washed with water. The organic layer was washed with brine, dried over anhydrous  $Na_2SO_4$ , filtered, concentrated under reduced pressure to get crude product which was purified by column chromatography (hexanes:ethyl acetate=7:3) to afford desired product.  $^1H$  NMR (ppm, 400 MHz, DMSO- $d_6$ ):  $\delta$  10.07 (s, 1H), 8.03 (s, 1H), 7.37-7.32 (m, 5H), 7.28-7.24 (m, 1H), 4.84 (t,  $J = 8.00$  Hz, 1H), 1.41 (d,  $J = 8.00$  Hz, 3H). MS ES calc'd. for  $C_{15}H_{12}Cl_2N_4O [M+H]^+$  335; Found 335.

**Step 6: (R)-1-(3-amino-4-chloro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

To a stirred solution of compound (R)-1-(4,6-dichloro-5-cyanopyridin-2-yl)-3-(1-phenylethyl)urea (0.10 g, 0.29 mmol) in ethanol (8.0 mL) was added hydrazine hydrate (0.59 mL, 0.59 mmol, 1M solution in THF) and stirred at 80 °C for 2 h. After the precipitation of white solid, the reaction mixture was cooled to room temperature and a 2M solution of HCl in water (0.29 mL, 0.59 mmol) was added stirred at same temperature for 2 h. After confirming the completion of reaction by TLC, the reaction mixture was concentrated under reduced pressure to give crude product which was purified by preparative HPLC to afford (R)-1-(3-amino-4-chloro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea.  $^1H$  NMR (ppm, 400 MHz, DMSO- $d_6$ ):  $\delta$  11.88 (s, 1H), 9.05 (s, 1H), 7.44 (s, 1H), 7.36-7.32 (m, 4H), 7.23 (d,  $J = 8.00$  Hz, 2H), 5.42 (s, 2H), 4.84 – 4.82 (m, 1H), 1.38 (d,  $J = 8.00$  Hz, 3H), MS ES calc'd. for  $C_{15}H_{15}ClN_6O [M+H]^+$  331; Found 331.

- 199 -

## Example 452

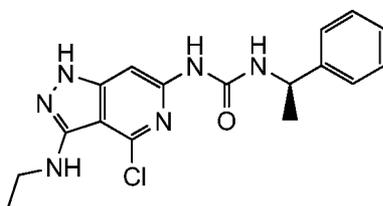


**1-(3-amino-4-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea**  
**(R)-1-(3-amino-4-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea**

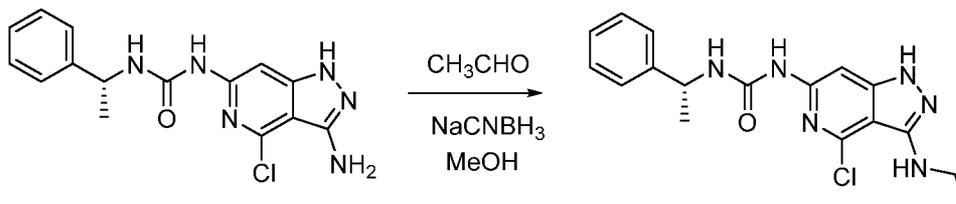
5 To a stirred solution of (R)-1-(3-amino-4-chloro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (0.12 g, 0.36 mmol) in methanol (3.0 mL) was added sodium methoxide (0.78 mL, 3.62 mmol, 25 % solution in MeOH) and stirred at 120 °C for 1 h in a microwave reactor. After confirming the completion of reaction by TLC, the reaction mixture was  
 10 acidified with 1.5N HCl and concentrated under reduced pressure and crude product which was purified by preparative HPLC to afford (R)-1-(3-amino-4-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea. <sup>1</sup>H NMR (ppm, 400 MHz, DMSO-d<sub>6</sub>): δ 11.48 (s, 1H), 8.76 (s, 1H), 7.94 (s, 1H), 7.35-7.33 (m, 4H), 7.26-7.21 (m, 1H), 6.86 (d, *J* = 8.00 Hz, 1H), 5.12 (s, 2H), 4.88 – 4.85 (m, 1H), 3.87 (s, 3H), 1.41 (d, *J* = 8.00 Hz, 3H), MS ES calc'd. for C<sub>16</sub>H<sub>18</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 327; Found 327.

15

## Example 454



**1-[4-chloro-3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea**



20 To a stirred solution of (R)-1-(3-amino-4-chloro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (0.06 g, 0.18 mmol) in methanol (2.0 mL) was added aqueous acetaldehyde (0.025 mL, 35 wt. % in water, 0.20 mmol) followed by sodium cyanoborohydride (0.03 g, 0.54 mmol) and stirred at room temperature for 12 h. After confirming the completion of reaction by TLC, the reaction mixture was acidified with 1.5 N HCl and concentrated under reduced pressure. The crude product was dissolved in ethyl acetate, washed with 10 % NaOH followed

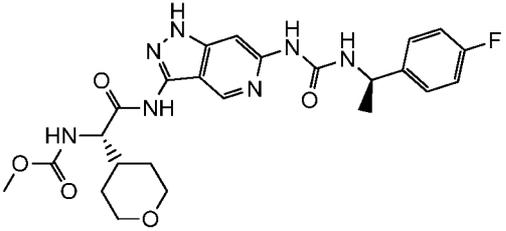
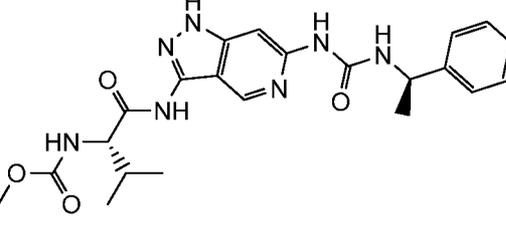
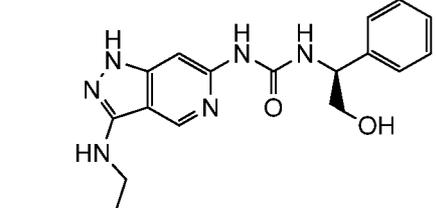
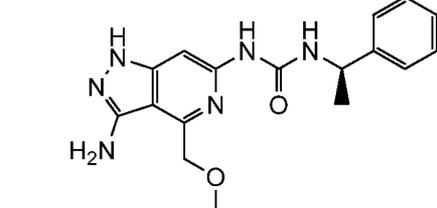
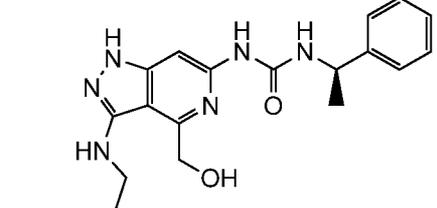
- 200 -

by water and brine solution. The organic layer was concentrated under reduced pressure and crude product was purified by preparative HPLC to afford (R)-1-(4-chloro-3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea (0.021 g, 32.0 %). <sup>1</sup>H NMR (ppm, 400 MHz, DMSO-d<sub>6</sub>): δ 11.92 (s, 1H), 9.05 (s, 1H), 7.44 (s, 1H), 7.37-7.32 (m, 4H), 7.26-7.22 (m, 2H), 5.44 (t, *J* = 5.6 Hz, 1H), 4.84 (m, 1H), 3.28-3.23 (m, 2H), 1.39 (d, *J* = 8.00 Hz, 3H), 1.20 (t, *J* = 6.8 Hz, 3H). MS ES calc'd. for C<sub>17</sub>H<sub>19</sub>ClN<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup> 359; Found: 359.

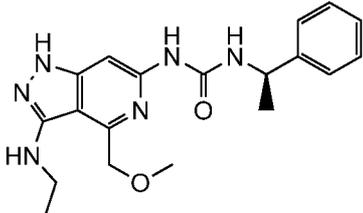
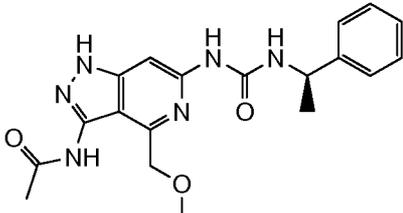
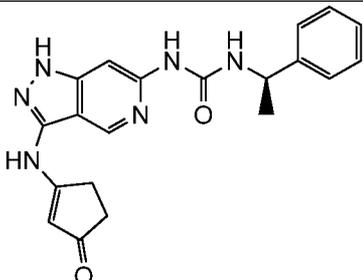
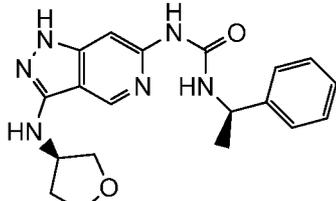
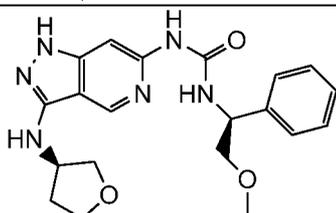
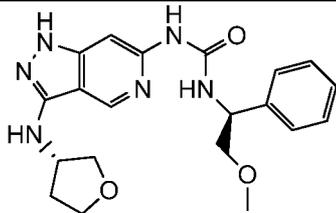
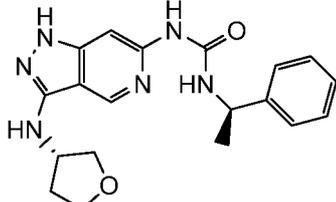
The Table below provides data for compounds of this invention.

No.	Structure	IUPAC Name	Exact Mass [M+H] <sup>+</sup>	Route Used
61		1-{3-[(6-methylpyridin-3-yl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 388, found 388	Following a similar procedure in Example 121
62		1-{3-[(2-methylpyridin-4-yl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 388, found 388	Following a similar procedure in Example 121
63		1-[3-(6,7-dihydro[1,3]thiazolo[4,5-c]pyridin-5(4H)-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-(4-fluorophenyl)ethyl]urea	Calc'd 438, found 438	Scheme 1
64		1-[3-(6,7-dihydro[1,3]thiazolo[4,5-c]pyridin-5(4H)-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S,2R)-2-hydroxy-1-phenylpropyl]urea	Calc'd 450, found 450	Scheme 1

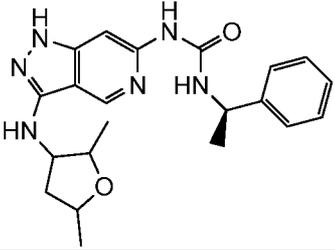
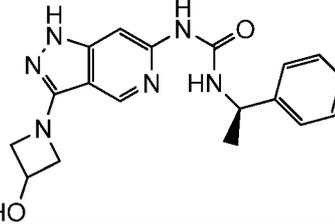
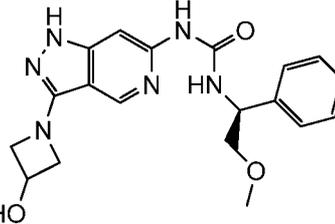
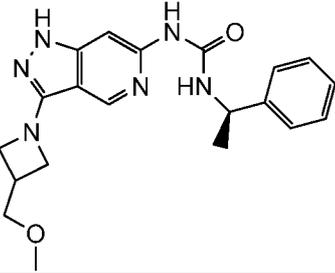
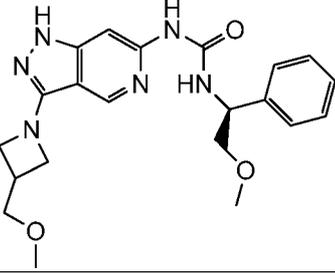
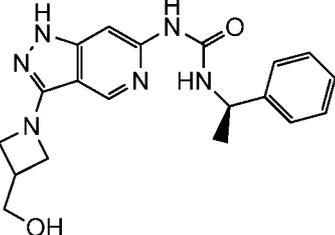
- 201 -

65		methyl [(1S)-2-{{6-((1R)-1-(4-fluorophenyl)ethyl)carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl}amino]-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl]carbamate	Calc'd 514, found 514	Scheme 14, Example 321 using corresponding carboxylic acid (with coupling condition in Scheme 11, step 1) instead of chloroformate
66		methyl [(1S)-1-{{6-((1R)-1-(4-fluorophenyl)ethyl)carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl}carbamoyl]-2-methylpropyl]carbamate	Calc'd 472, found 472	Scheme 14, Example 321 using corresponding carboxylic acid (with coupling condition in Scheme 11, step 1) instead of chloroformate
67		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-hydroxy-1-phenylethyl]urea	Calc'd 341, found 341	Scheme 1
68		1-[3-amino-4-(hydroxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 327, found 327	Example 68
69		1-[3-amino-4-(methoxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 341, found 341	Example 69
70		1-[3-(ethylamino)-4-(hydroxymethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 355, found 355	Followed similar procedure in Example 71

- 202 -

71		1-[3-(ethylamino)-4-(methoxymethyl)-1H-pyrazolo[4,3-c]-pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 369, found, 369	Example 71
72		N-[4-(methoxymethyl)-6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]-pyridin-3-yl]-acetamide	Calc'd 383, found 383	Example 72
73		1-{3-[(3-oxocyclopent-1-en-1-yl)amino]-1H-pyrazolo[4,3-c]-pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 377, found 377	Example 73
74		1-[(1R)-1-phenylethyl]-3-{3-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[4,3-c]-pyridin-6-yl}urea	Calc'd 367, found 367	Scheme 1 Example 1
75		1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[4,3-c]-pyridin-6-yl}urea	Calc'd 397, found 397	Scheme 1 Example 1
76		1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[4,3-c]-pyridin-6-yl}urea	Calc'd 397, found 397	Scheme 1 Example 1
77		1-[(1R)-1-phenylethyl]-3-{3-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[4,3-c]-pyridin-6-yl}urea	Calc'd 367, found 367	Scheme 1 Example 1

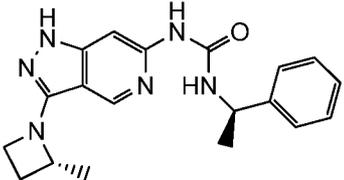
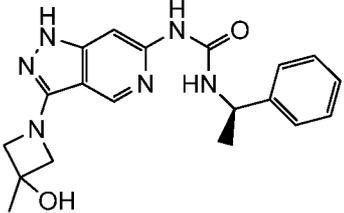
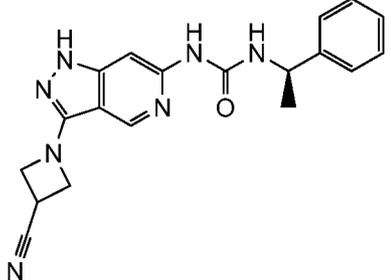
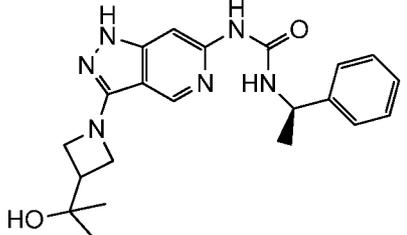
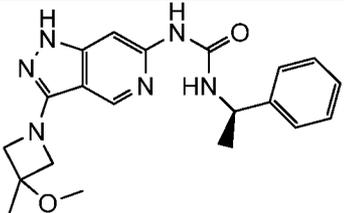
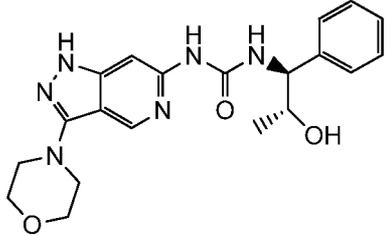
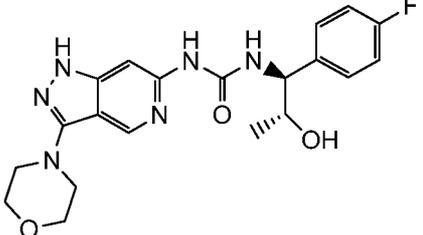
- 203 -

78		1-(3-((2,5-dimethyltetrahydrofuran-3-yl)amino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-((R)-1-phenylethyl)urea	Calc'd 395, found 395	Scheme 1 Example 1 with Intermediate 78A
79		1-[3-(3-hydroxyazetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 353, found 353	Scheme 1 Example 1
80		1-[3-(3-hydroxyazetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 383, found 383	Scheme 1 Example 1
81		1-{3-[3-(methoxymethyl)azetidin-1-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 381, found 381	Scheme 1 Example 1
82		1-{3-[3-(methoxymethyl)azetidin-1-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 411, found 411	Scheme 1 Example 1
83		1-{3-[3-(hydroxymethyl)azetidin-1-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 367, found 367	Scheme 1 Example 1

- 204 -

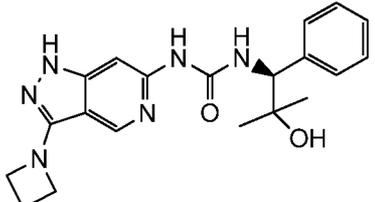
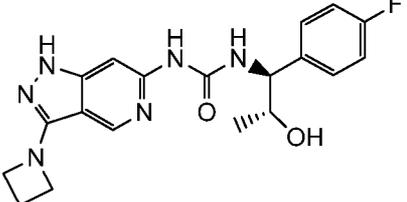
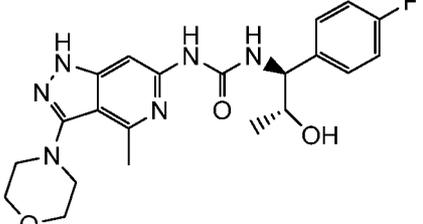
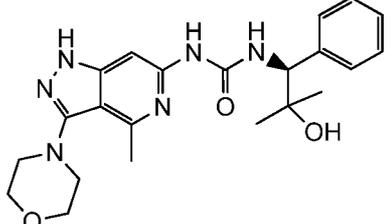
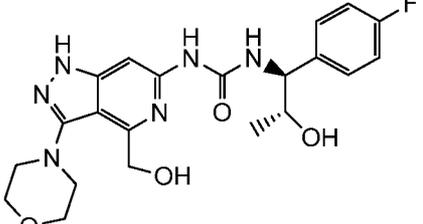
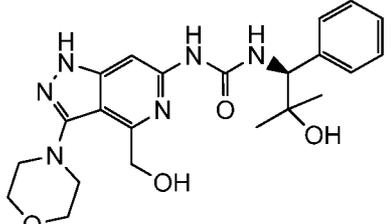
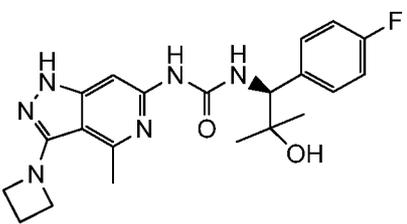
84		1-(3-{{(3R,4R)-4-fluorotetrahydrofuran-3-yl}amino}-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 385, found 385	Scheme 1 Example 39/40
85		1-(3-{{(3S,4S)-4-fluorotetrahydrofuran-3-yl}amino}-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 385, found 385	Scheme 1 Example 39/40
86		1-[(1R)-1-phenylethyl]-3-(3-{{(1S)-1-pyridin-2-ylethyl}amino}-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 402, found 402	Scheme 1 Example 39/40
87		1-[(1R)-1-phenylethyl]-3-(3-{{(1R)-1-pyridin-2-ylethyl}amino}-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 402, found 402	Scheme 1 Example 39/40
88		1-(3-{{(3R,4S)-4-fluorotetrahydrofuran-3-yl}amino}-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 385, found 385	Scheme 1 Example 1
89		1-[3-(2-oxa-7-azaspiro[3.5]non-7-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 407, found 407	Scheme 1 Example 1
90		1-{3-[(2S)-2-methylazetididin-1-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 351, found 351	Scheme 1 Example 39/40

- 205 -

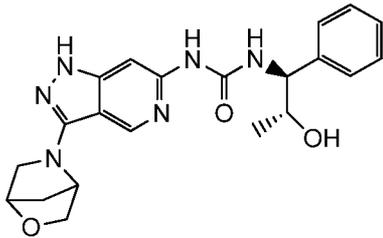
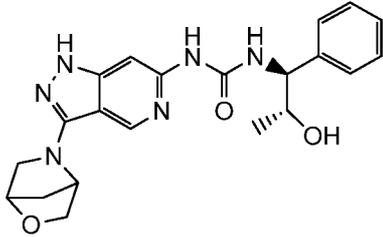
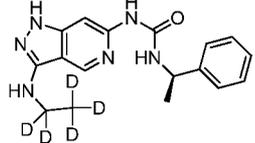
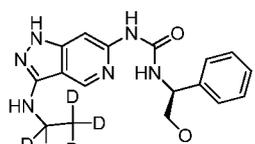
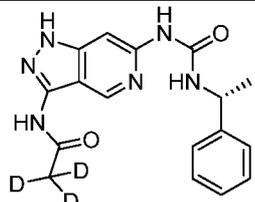
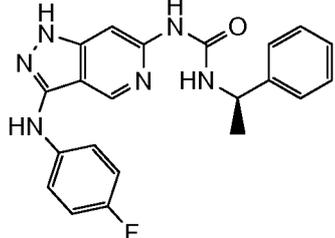
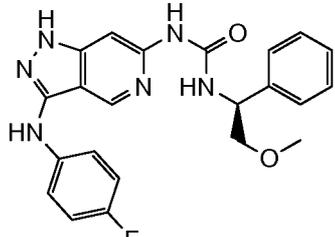
91		1-{3-[(2R)-2-methylazetidin-1-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]-urea	Calc'd 351, found 351	Scheme 1 Example 39/40
92		1-[3-(3-hydroxy-3-methylazetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 367, found 367	Scheme 1 Example 1
93		1-[3-(3-cyanoazetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 362, found 362	Scheme 1 Example 1
94		1-{3-[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]-urea	Calc'd 395, found 395	Scheme 1 Example 1
95		1-[3-(3-methoxy-3-methylazetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 381, found 381	Scheme 1 Example 1
96		1-[(1S,2R)-2-hydroxy-1-phenylpropyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-ylurea	Calc'd 397, found 397	Scheme 1 Example 1
97		1-[(1S,2R)-1-(4-fluorophenyl)-2-hydroxypropyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-ylurea	Calc'd 415, found 415	Scheme 1 Example 39/40

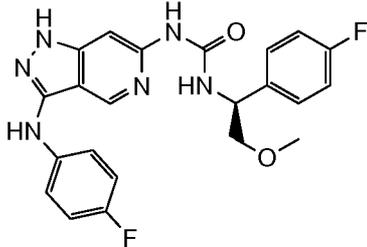
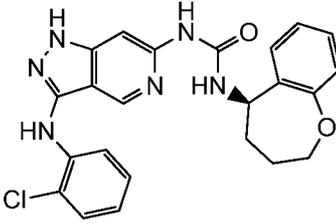
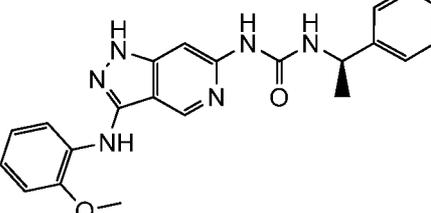
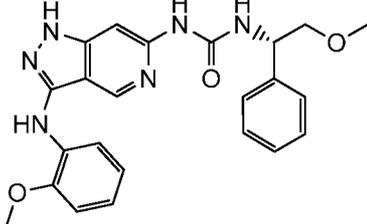
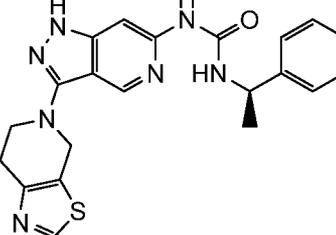
- 206 -

98		1-[(1S,2S)-1-(4-fluorophenyl)-2-hydroxypropyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]-pyridin-6-yl)urea	Calc'd 415, found 415	Scheme 1 Example 39/40
99		1-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-3-{3-[2-(trifluoromethyl)-morpholin-4-yl]-1H-pyrazolo[4,3-c]-pyridin-6-yl}urea	Calc'd 479, found 479	Scheme 1 Example 1
100		1-(3-azetidin-1-yl)-1H-pyrazolo[4,3-c]-pyridin-6-yl)-3-[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]urea	Calc'd 399, found 399	Scheme 1 Example 1
101		1-[3-azetidin-1-yl-4-(hydroxymethyl)-1H-pyrazolo[4,3-c]-pyridin-6-yl]-3-[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]urea	Calc'd 429, found 429	Scheme 1 Example 1 with Intermediate 101A
102		1-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-3-{3-[(2S,6R)-2-methyl-6-(trifluoromethyl)morpholin-4-yl]-1H-pyrazolo[4,3-c]-pyridin-6-yl}urea	Calc'd 493, found 493	Scheme 1 Example 1
103		1-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-3-{3-[(2R,6R)-2-methyl-6-(trifluoromethyl)morpholin-4-yl]-1H-pyrazolo[4,3-c]-pyridin-6-yl}urea	Calc'd 493, found 493	Scheme 1 Example 1

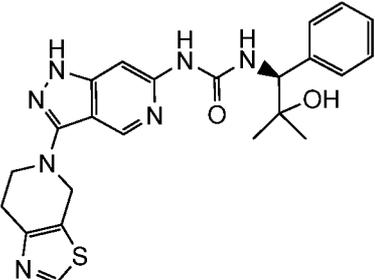
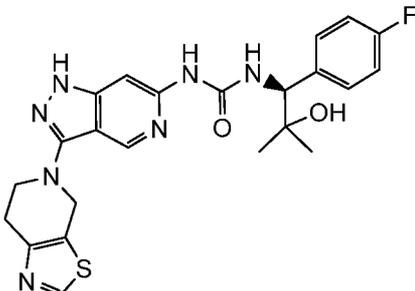
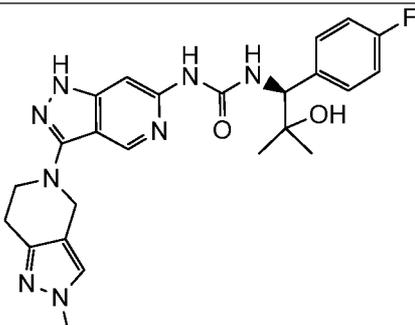
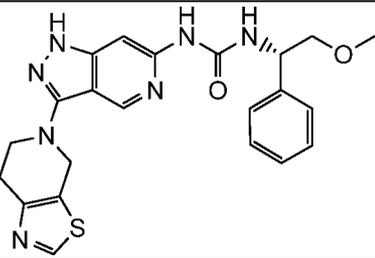
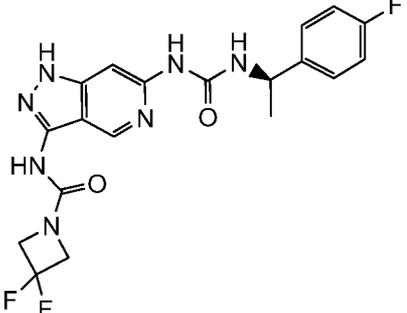
104		1-(3-azetidin-1-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]urea	Calc'd 381, found 381	Scheme 1 Example 1
105		1-(3-azetidin-1-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S,2R)-1-(4-fluorophenyl)-2-hydroxypropyl]urea	Calc'd 385, found 385	Scheme 1 Example 1
106		1-[(1S,2R)-1-(4-fluorophenyl)-2-hydroxypropyl]-3-(4-methyl-3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 429, found 429	Example 106
107		1-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-3-(4-methyl-3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 425, found 425	Followed similar procedure in Example 106
108		1-[(1S,2R)-1-(4-fluorophenyl)-2-hydroxypropyl]-3-[4-(hydroxymethyl)-3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 445, found 445	Example 108
109		1-[4-(hydroxymethyl)-3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]urea	Calc'd 441, found 441	Followed similar procedure in Example 108
110		1-(3-azetidin-1-yl-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]urea	Calc'd 413, found 413	Followed similar procedure in Example 106

- 208 -

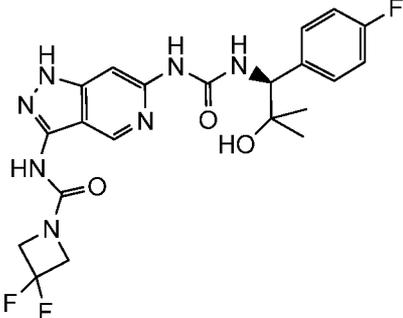
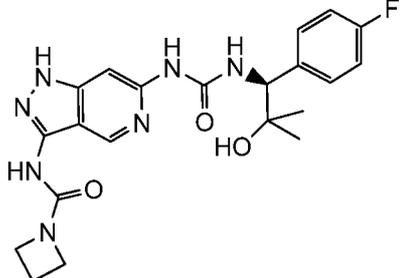
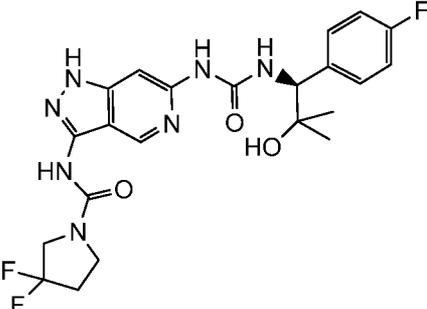
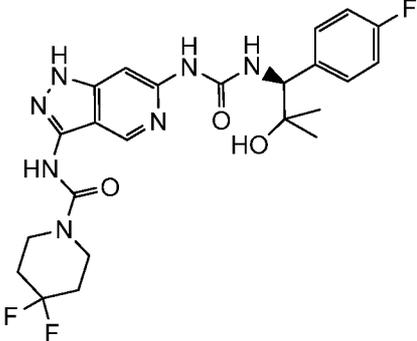
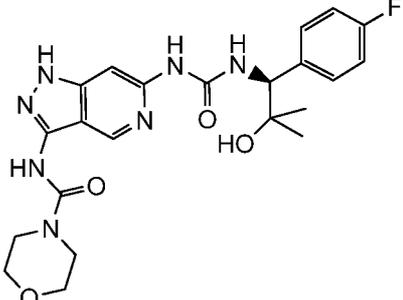
111		1-[(1S,2R)-2-hydroxy-1-phenylpropyl]-3-[3-(2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 409, found 409	Followed similar procedure in Example 106
112		1-[(1S,2R)-2-hydroxy-1-phenylpropyl]-3-[3-(2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 409, found 409	Followed similar procedure in Example 106
113		(R)-1-(3-((ethyl-D5)amino))-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea	Calc'd 330, found 330	Scheme 1
114		(S)-1-(3-((ethyl-D5)amino))-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-methoxy-1-phenylethyl)urea	Calc'd 360, found 360	Scheme 1
115		(R)-N-(6-(3-(1-phenylethyl)ureido))-1H-pyrazolo[4,3-c]pyridin-3-yl(acetamide-D3)	Calc'd 342, found 342	Scheme 14, Example 321 using acetyl chloride instead of chloroformate
116		1-{3-[(4-fluorophenyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 391, found 391	Following a similar procedure in Example 121.
117		1-{3-[(4-fluorophenyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 421, found 421	Following a similar procedure in Example 121

118		1-{3-[(4-fluorophenyl)-amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1S)-1-(4-fluorophenyl)-2-methoxyethyl]urea	Calc'd 439, found 439	Following a similar procedure in Example 121
119		1-{3-[(2-chlorophenyl)-amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(5R)-2,3,4,5-tetrahydro-1-benzoxepin-5-yl]urea	Calc'd 449, found 449	Following a similar procedure in Example 121
120		1-{3-[(2-chlorophenyl)-amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 437, found 437	Following a similar procedure in Example 121
121		1-{3-[(2-methoxyphenyl)-amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 403, found 403	Example 121
122		1-{3-[(2-methoxyphenyl)-amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 433, found 433	Following a similar procedure in Example 121
123		1-[3-(6,7-dihydro[1,3]thiazolo[5,4-c]pyridin-5(4H)-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 420, found 420	Scheme 1, Example 1

- 210 -

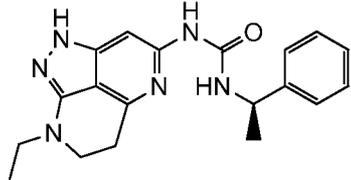
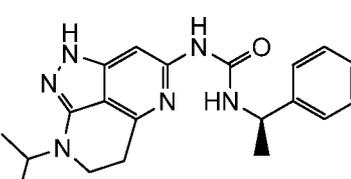
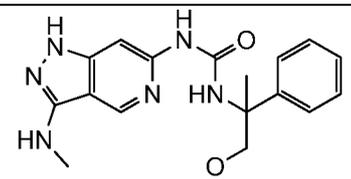
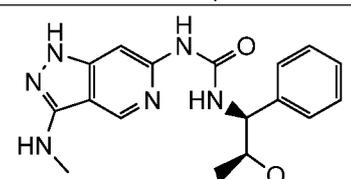
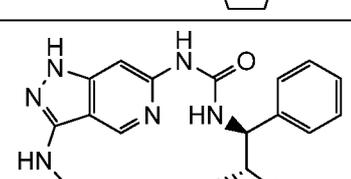
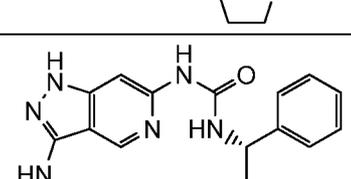
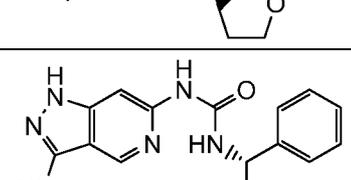
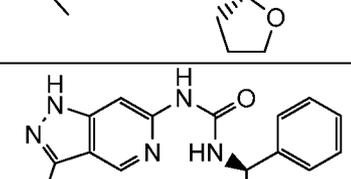
124		1-[3-(6,7-dihydro[1,3]thiazolo[5,4-c]pyridin-5(4H)-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]urea	Calc'd 464, found 464	Scheme 1, Example 1
125		1-[3-(6,7-dihydro[1,3]thiazolo[5,4-c]pyridin-5(4H)-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]urea	Calc'd 482, found 482	Scheme 1, Example 1
126		1-[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]-3-(2'-methyl-2',4',6',7'-tetrahydro-1H-3,5'-bipyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 479, found 479	Scheme 1, Example 1
127		1-[3-(6,7-dihydro[1,3]thiazolo[5,4-c]pyridin-5(4H)-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 450, found 450	Scheme 1, Example 1
128		3,3-difluoro-N-[6-({[(1R)-1-(4-fluorophenyl)ethyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-azetidine-1-carboxamide	Calc'd 434, found 434	Scheme 1, Example 1 with Intermediate 128A

- 211 -

129		3,3-difluoro-N-[6-((1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-azetidine-1-carboxamide	Calc'd 478, found 478	Following a similar procedure in Example 128
130		N-[6-((1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-azetidine-1-carboxamide	Calc'd 442, found 442	Following a similar procedure in Example 128
131		3,3-difluoro-N-[6-((1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-pyrrolidine-1-carboxamide	Calc'd 492, found 492	Following a similar procedure in Example 128
132		4,4-difluoro-N-[6-((1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-piperidine-1-carboxamide	Calc'd 506, found 506	Following a similar procedure in Example 128
133		N-[6-((1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-morpholine-4-carboxamide	Calc'd 472, found 472	Following a similar procedure in Example 128

- 212 -

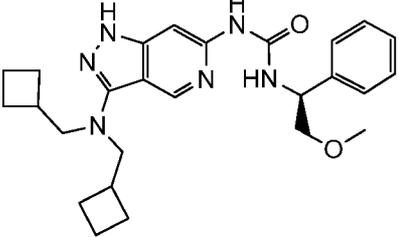
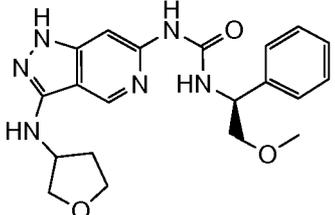
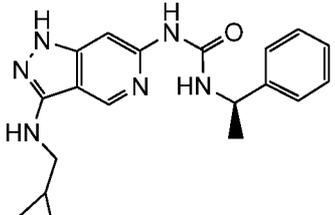
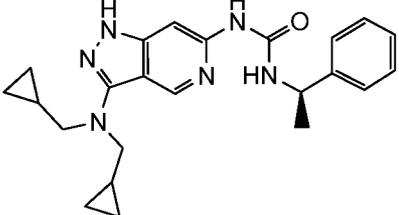
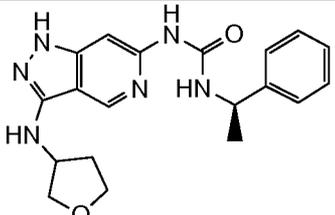
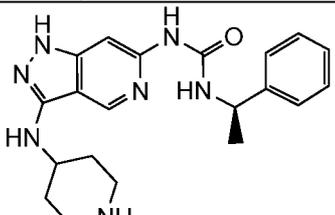
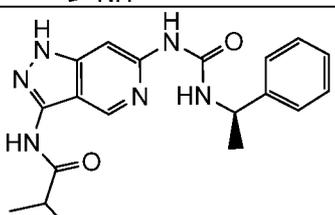
134		3-hydroxy-3-methyl-N-[6-((1R)-1-phenylethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-azetidine-1-carboxamide	Calc'd 410, found 410	Following a similar procedure in Example 128
135		1-[3-(ethylamino)-7-(trifluoromethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 393, found 393	Example 135
136		1-[(1R)-1-phenylethyl]-3-(1,3,4,5-tetrahydropyrazolo[3,4,5-de]-[1,6]-naphthyridin-7-yl)-urea	Calc'd 323, found 323	Example 136
137		1-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-3-(1,3,4,5-tetrahydropyrazolo[3,4,5-de]-[1,6]-naphthyridin-7-yl)urea	Calc'd 367, found 367	Example 137
138		1-[(4R)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de]-[1,6]naphthyridin-7-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 337, found 337	Example 138
139		1-[(4S)-4-methyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de]-[1,6]-naphthyridin-7-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 337, found 337	Example 139
140		1-(3-acetyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de]-[1,6]-naphthyridin-7-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 365, found 365	Example 140

141		1-(3-ethyl-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]-naphthyridin-7-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 351.0, found 351	Example 141
142		1-[3-(1-methylethyl)-1,3,4,5-tetrahydropyrazolo[3,4,5-de][1,6]-naphthyridin-7-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 365, found 365	Example 142
143		1-(2-methoxy-1-methyl-1-phenylethyl)-3-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 355, found 355	Scheme 1
144		1-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(S)-phenyl[(2S)-tetrahydrofuran-2-yl]methyl]urea	Calc'd 367, found 367	Example 144
145		1-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(S)-phenyl[(2R)-tetrahydrofuran-2-yl]methyl]urea	Calc'd 367, found 367	Example 144
146		1-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(R)-phenyl[(2S)-tetrahydrofuran-2-yl]methyl]urea	Calc'd 367, found 367	Example 144
147		1-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(R)-phenyl[(2R)-tetrahydrofuran-2-yl]methyl]urea	Calc'd 367, found 367	Example 144
148		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(S)-phenyl[(2S)-tetrahydrofuran-2-yl]methyl]urea	Calc'd 381, found 381	Scheme 1 With intermediate 148A

- 214 -

149		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-{{(S)-phenyl[(2R)-tetrahydrofuran-2-yl]methyl}urea	Calc'd 381, found 381	Scheme 1 With intermediate 149A
150		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-{{(R)-phenyl[(2R)-tetrahydrofuran-2-yl]methyl}urea	Calc'd 381, found 381	Scheme 1 With intermediate 150A
151		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-{{(R)-phenyl[(2S)-tetrahydrofuran-2-yl]methyl}urea	Calc'd 381, found 381	Scheme 1 With intermediate 151A
152		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-{{(S)-phenyl[(2S)-tetrahydrofuran-2-yl]methyl}urea	Calc'd 353, found 353	Scheme 2 With intermediate 148A
153		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-{{(S)-phenyl[(2R)-tetrahydrofuran-2-yl]methyl}urea	Calc'd 353, found 353	Scheme 2 With intermediate 149A
154		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-{{(R)-phenyl[(2R)-tetrahydrofuran-2-yl]methyl}urea	Calc'd 353, found 353	Scheme 2 With intermediate 150A
155		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-{{(R)-phenyl[(2S)-tetrahydrofuran-2-yl]methyl}urea	Calc'd 353, found 353	Scheme 2 With intermediate 151A
156		1-{3-[(cyclobutylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 395, found 395	Scheme 8 Method C / Example 316

- 215 -

157		1-{3-[bis(cyclobutylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 463, found 463	Scheme 8, Method C / example 316
158		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(tetrahydrofuran-3-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 397, found 397	Scheme 8, Method C / example 316
159		1-{3-[(cyclopropylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 351, found 351	Scheme 8, Method B / example 316
160		1-{3-[bis(cyclopropylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 405, found 405	Scheme 8, Method B / example 316
161		1-[(1R)-1-phenylethyl]-3-[3-(tetrahydrofuran-3-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 367, found 367	Scheme 8, Method A / example 316
162		1-[(1R)-1-phenylethyl]-3-[3-(piperidin-4-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 380, found 380	Scheme 8, Method A / example 316
163		2-methyl-N-[6-({[(1R)-1-phenylethyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]propanamide	Calc'd 367, found 367	Scheme 10, Method A / Example 47

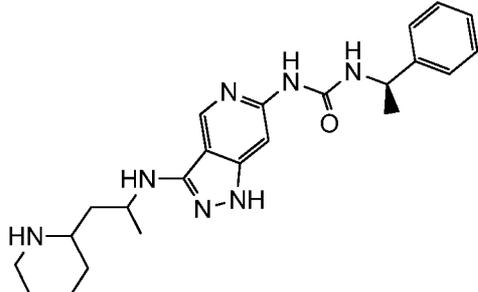
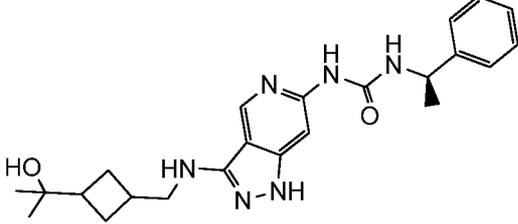
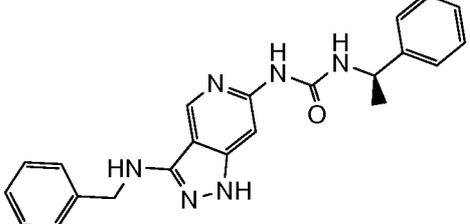
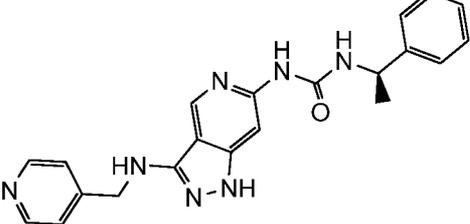
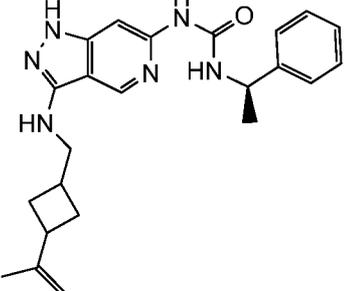
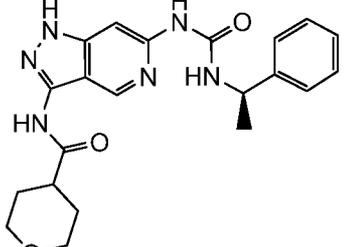
- 216 -

164		1-[(1R)-1-phenylethyl]-3-[3-(piperidin-3-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 380, found 380	Scheme 8, Method A / example 316
165		1-[(1R)-1-phenylethyl]-3-[3-[(piperidin-4-ylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 394, found 394	Scheme 8, Method A / example 316
166		1-[(1R)-1-phenylethyl]-3-[3-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 395, found 395	Scheme 8, Method A / example 316
167		1-[(1R)-1-phenylethyl]-3-[3-[(tetrahydro-2H-pyran-3-ylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 395, found 395	Scheme 8, Method A / example 316
168		1-[3-(azetidin-3-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 352, found 352	Scheme 8, Method A / example 316
169		1-(3-{3-(dimethylamino)cyclobutyl}amino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 394, found 394	Scheme 8, Method A / example 316

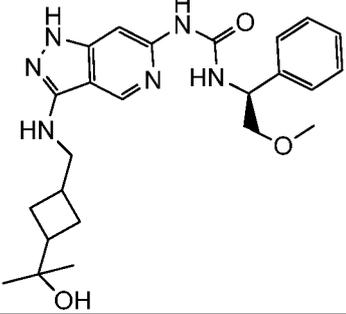
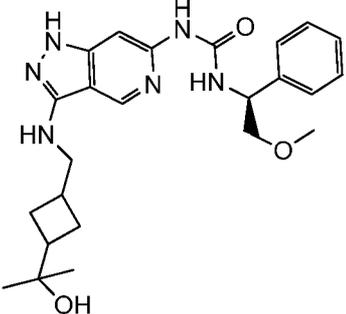
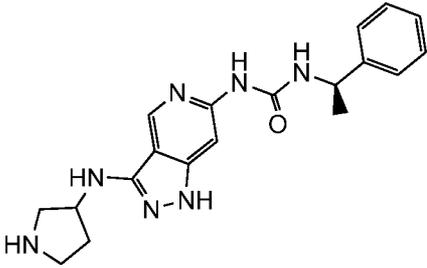
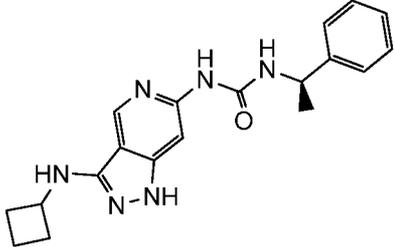
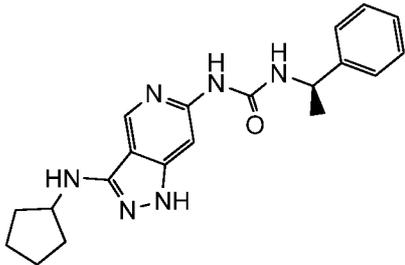
- 217 -

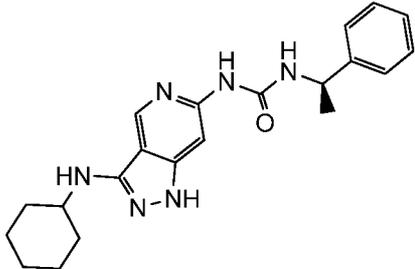
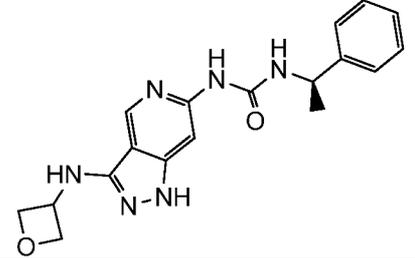
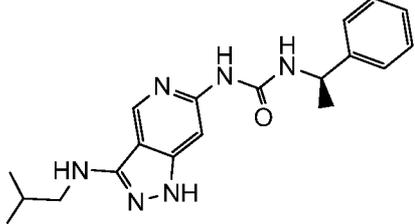
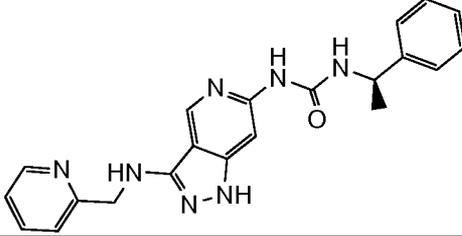
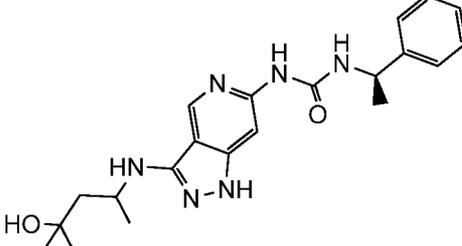
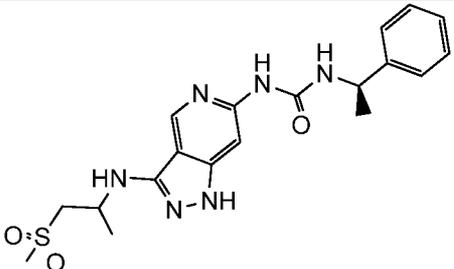
170		1-(3-{{(3-methoxy-cyclobutyl)methyl} amino})-1H-pyrazolo[4,3-c]-pyridin-6-yl)-3-{{(1R)-1-phenylethyl}urea	Calc'd 395, found 395	Scheme 8, Method A / example 316
171		1-{{(1R)-1-phenylethyl}}-3-(3-{{1-(tetrahydro-2H-pyran-4-yl)ethyl}amino})-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 409, found 409	Scheme 8, Method A / example 316
172		1-(3-{{4-(dimethylamino)-cyclohexyl}amino})-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-{{(1R)-1-phenylethyl}urea	Calc'd 422, found 422	Scheme 8, Method A / example 316
173		1-(3-{{(3-methyl-4,5-dihydro-isoxazol-5-yl)-methyl}amino})-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-{{(1R)-1-phenylethyl}urea	Calc'd 394, found 394	Scheme 8, Method A / example 316
174		1-{{(1R)-1-phenylethyl}}-3-3-{{tetrahydro-2H-pyran-3-yl}amino}-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 381, found 381	Scheme 8, Method A / example 316
175		1-3-{{(1-methyl-2-morpholin-4-ylethyl)amino}}-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-{{(1R)-1-phenylethyl}urea	Calc'd 424, found 424	Scheme 8, Method A / example 316

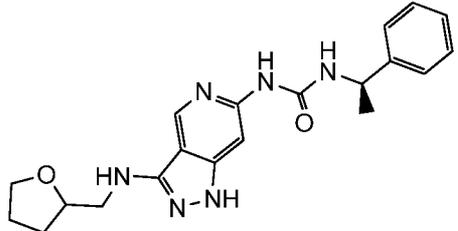
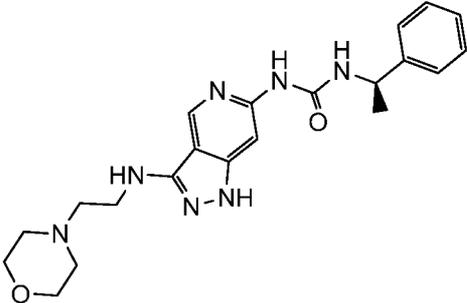
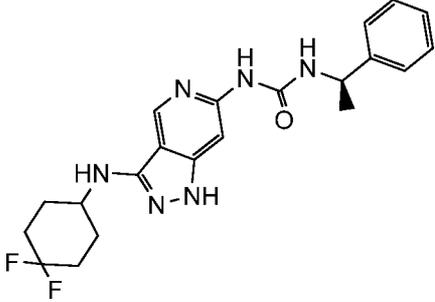
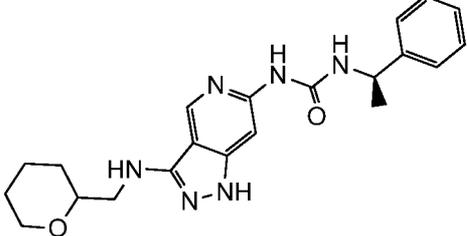
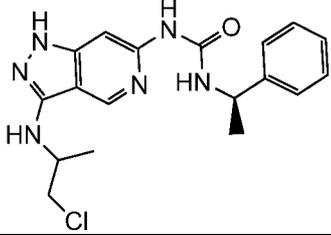
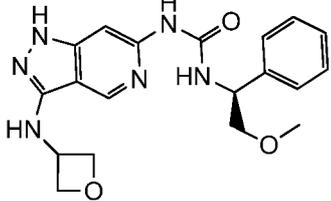
- 218 -

176		1-{3-[(1-methyl-2-piperidin-2-ylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 422, found 422	Scheme 8, Method A / example 316
177		1-[3-({3-(1-hydroxy-1-methylethyl)cyclobutyl}methyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 423, found 423	Scheme 8, Method A / example 316
178		1-[3-(benzylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 387, found 387	Scheme 8, Method A / example 316
179		1-[(1R)-1-phenylethyl]-3-{3-[(pyridin-4-ylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 388, found 388	Scheme 8, Method A / example 316
180		1-[3-({3-(1-methylethenyl)cyclobutyl}methyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 405, found 405	Scheme 8, Method A / example 316
181		N-[6-({[(1R)-1-phenylethyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-tetrahydro-2H-pyran-4-carboxamide	Calc'd 409, found 409	Scheme 10, Method B /Example 318

- 219 -

182		1-[3-({[3-(1-hydroxy-1-methylethyl)-cyclobutyl]methyl}amino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 453, found 453	Scheme 8, Method D/ example 316
183		1-[3-({[3-(1-hydroxy-1-methylethyl)-cyclobutyl]methyl}amino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 453, found 453	Scheme 8, Method D/ example 316
184		1-[(1R)-1-phenylethyl]-3-[3-(pyrrolidin-3-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 366, found 366	Scheme 8, Method A/ example 316
185		1-[3-(cyclobutylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 351, found 351	Scheme 8, Method A/ example 316
186		1-[3-(cyclopentylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 365, found 365	Scheme 8, Method A/ example 316

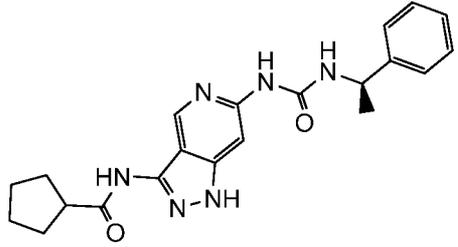
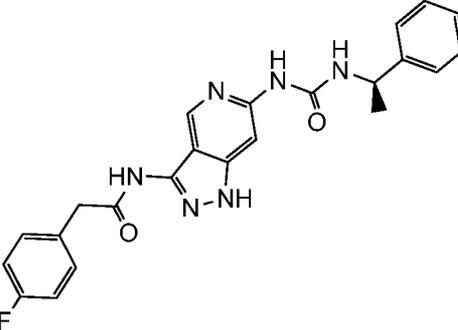
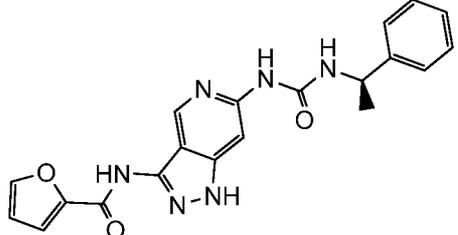
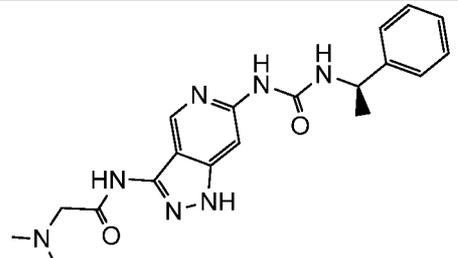
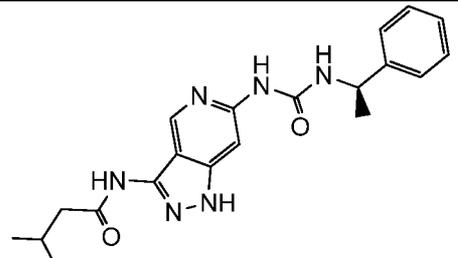
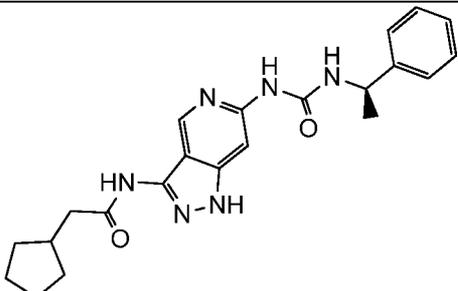
187		1-[3-(cyclohexylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 379, found 379	Scheme 8, Method A/ example 316
188		1-[3-(oxetan-3-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 353, found 353	Scheme 8, Method A/ example 316
189		1-[3-[(2-methylpropyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 353, found 353	Scheme 8, Method A/ example 316
190		1-[(1R)-1-phenylethyl]-3-{3-[(pyridin-2-ylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 388, found 388	Scheme 8, Method A/ example 316
191		1-[3-[(3-hydroxy-1,3-dimethylbutyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 397, found 397	Scheme 8, Method A/ example 316
192		1-[3-[[1-methyl-2-(methylsulfonyl)ethyl]amino]-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 417, found 417	Scheme 8, Method A/ example 316

193		1-[(1R)-1-phenylethyl]-3-{3-[(tetrahydrofuran-2-ylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 381, found 381	Scheme 8, Method A/ example 316
194		1-{3-[(2-morpholin-4-ylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 410, found 410	Scheme 8, Method A/ example 316
195		1-{3-[(4,4-difluorocyclohexyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 415, found 415	Scheme 8, Method A/ example 316
196		1-[(1R)-1-phenylethyl]-3-{3-[(tetrahydro-2H-pyran-2-ylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 395, found 395	Scheme 8, Method A/ example 316
197		1-{3-[(2-chloro-1-methylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 373, found 373	Scheme 8, Method A/ example 316
198		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(oxetan-3-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 383, found 383	Scheme 8, Method D/ example 316

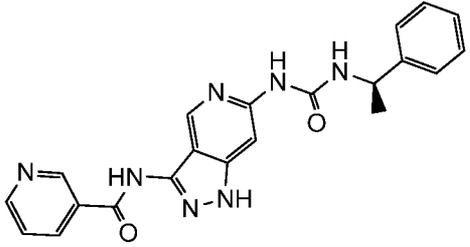
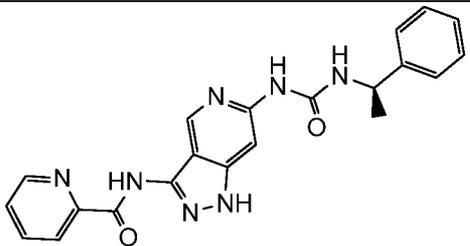
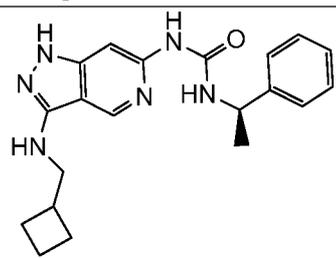
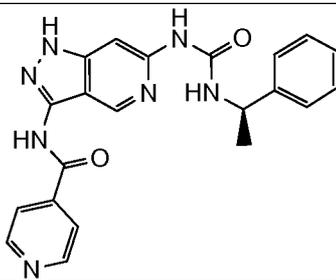
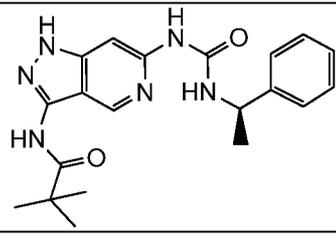
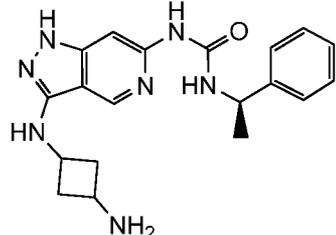
- 222 -

199		3,3,3-trifluoro-N-[6-((1R)-1-phenylethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]propanamide	Calc'd 407, found 407	Scheme 10, Method B / Example 318
200		4-methyl-N-[6-((1R)-1-phenylethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-1,2,3-thiadiazole-5-carboxamide	Calc'd 423, found 423	Scheme 10, Method B / Example 318
201		N-[6-((1R)-1-phenylethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]cyclobutane-carboxamide	Calc'd 379, found 379	Scheme 10, Method B / Example 318
202		2-phenyl-N-[6-((1R)-1-phenylethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]acetamide	Calc'd 415, found 415	Scheme 10, Method B / Example 318
203		2-cyclohexyl-N-[6-((1R)-1-phenylethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]acetamide	Calc'd 421, found 421	Scheme 10, Method B / Example 318
204		N-[6-((1R)-1-phenylethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]cyclohexane-carboxamide	Calc'd 407, found 407	Scheme 10, Method B / Example 318

- 223 -

205		N-[6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-cyclopentane-carboxamide	Calc'd 393, found 393	Scheme 10, Method B / Example 318
206		2-(4-fluorophenyl)-N-[6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-acetamide	Calc'd 433, found 433	Scheme 10, Method B / Example 318
207		N-[6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-furan-2-carboxamide	Calc'd 391, found 391	Scheme 10, Method B / Example 318
208		N~2~,N~2~-dimethyl-N-[6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-glycinamide	Calc'd 382, found 382	Scheme 10, Method B / Example 318
209		3-methyl-N-[6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-butanamide	Calc'd 381, found 381	Scheme 10, Method B / Example 318
210		2-cyclopentyl-N-[6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-acetamide	Calc'd 407, found 407	Scheme 10, Method B / Example 318

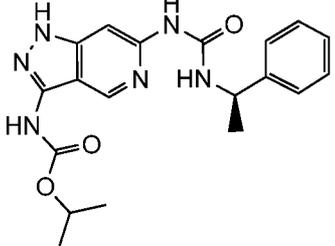
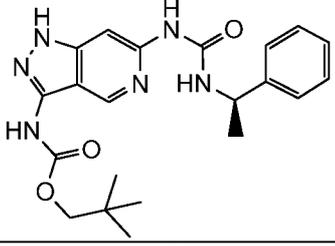
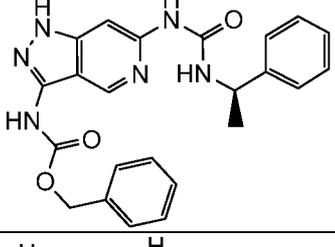
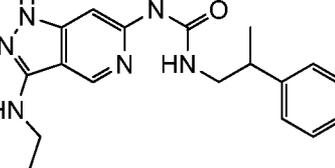
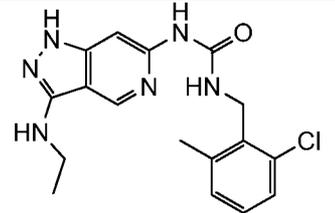
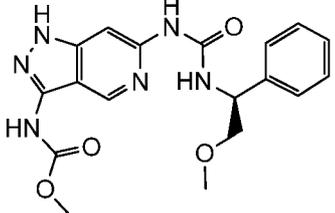
- 224 -

211		N-[6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-pyridine-3-carboxamide	Calc'd 402, found 402	Scheme 10, Method B / Example 318
212		N-[6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-pyridine-2-carboxamide	Calc'd 402, found 402	Scheme 10, Method B / Example 318
213		1-{3-[(cyclobutylmethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 365, found 365	Scheme 8, Method D/ example 316
214		N-[6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-pyridine-4-carboxamide	Calc'd 402, found 402	Scheme 10, Method B / Example 318
215		2,2-dimethyl-N-[6-({[(1R)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-propanamide	Calc'd 381, found 381	Scheme 10, Method B / Example 318
216		1-{3-[(3-amino-cyclobutyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 366, found 366	Scheme 8, Method A/ example 316

- 225 -

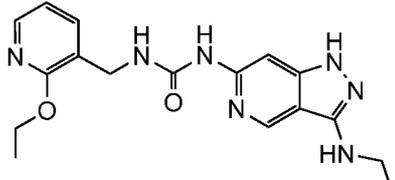
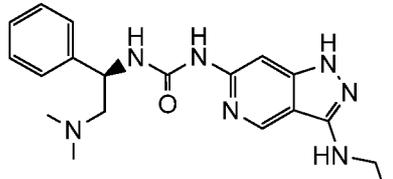
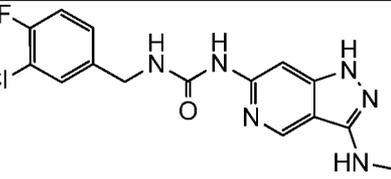
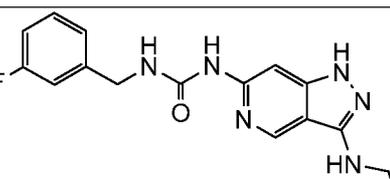
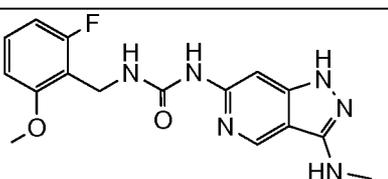
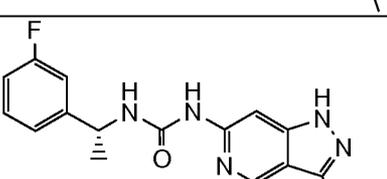
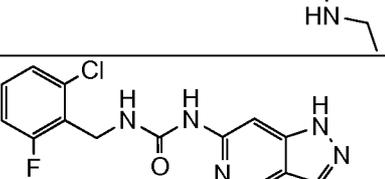
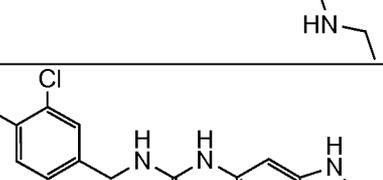
217		tert-butyl [6- ({(1R)-1- phenylethyl}- carbamoyl)amino)- 1H-pyrazolo[4,3- c]pyridin-3-yl]- carbamate	Calc'd 397, found 397	Scheme 9, example 315
218		1-(1-methylethyl)- 3-[6-({(1R)-1- phenylethyl}- carbamoyl)amino)- 1H-pyrazolo[4,3- c]pyridin-3-yl]urea	Calc'd 382, found 382	Scheme 12, Example 313
219		2-methylpropyl [6- ({(1R)-1- phenylethyl}- carbamoyl)amino)- 1H-pyrazolo[4,3- c]pyridin-3-yl]- carbamate	Calc'd 397, found 397	Scheme 9, example 315
220		methyl[6-({(1R)- 1-phenylethyl}- carbamoyl)amino)- 1H-pyrazolo[4,3- c]pyridin-3-yl]- carbamate	Calc'd 355, found 355	Scheme 9, example 315
221		2-methoxyethyl [6- ({(1R)-1-phenyl- ethyl}carbamoyl)- amino)-1H- pyrazolo[4,3-c]- pyridin-3-yl]- carbamate	Calc'd 399, found 399	Scheme 9, example 315
222		phenyl[6-({(1R)- 1-phenylethyl}- carbamoyl)amino)- 1H-pyrazolo[4,3- c]pyridin-3-yl]- carbamate	Calc'd 417, found 417	Scheme 9, example 315

- 226 -

223		1-methylethyl[6-((1R)-1-phenylethyl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 383, found 383	Scheme 9, example 315
224		2,2-dimethylpropyl [6-((1R)-1-phenylethyl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 411, found 411	Scheme 9, example 315
225		benzyl [6-((1R)-1-phenylethyl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 431, found 431	Scheme 9, example 315
226		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-(2-phenylpropyl)-urea	Calc'd 339, found 339	Scheme 1, Example 1
227		1-(2-chloro-6-methylbenzyl)-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 359, found 359	Scheme 1, Example 1
228		1-[2-(difluoromethoxy)benzyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 377, found 377	Scheme 1, Example 1
229		methyl [6-((1S)-2-methoxy-1-phenylethyl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 385, found 385	Scheme 9, example 315

- 227 -

230		1-[(1R)-1-cyclohexylethyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 331, found 331	Scheme 1, Example 1
231		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-(1,2,5-thiadiazol-3-ylmethyl)urea	Calc'd 319, found 319	Scheme 1, Example 1
232		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-(1,2,3,4-tetrahydroquinolin-3-yl)urea	Calc'd 352, found 352	Scheme 1, Example 1
233		1-(3,4-dihydro-2H-chromen-3-yl)-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 353, found 353	Scheme 1, Example 1
234		1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 353, found 353	Scheme 1, Example 1
235		1-(2,3-dihydro-1-benzofuran-3-yl)-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 339, found 339	Scheme 1, Example 1
236		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(S)-(1-hydroxycyclopentyl)(phenyl)methyl]urea	Calc'd 395, found 395	Scheme 1, Example 1
237		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-(2-phenylcyclopentyl)urea	Calc'd 365, found 365	Scheme 1, Example 1

238		1-[(2-ethoxy-pyridin-3-yl)-methyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 356, found 356	Scheme 1, Example 1
239		1-[(1R)-2-(dimethylamino)-1-phenylethyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 368, found 368	Scheme 1, Example 1
240		1-(3-chloro-4-fluorobenzyl)-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 363, found 363	Scheme 1, Example 1
241		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-(3-fluorobenzyl)-urea	Calc'd 329, found 329	Scheme 1, Example 1
242		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-(2-fluoro-6-methoxybenzyl)-urea	Calc'd 359, found 359	Scheme 1, Example 1
243		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-(3-fluorophenyl)ethyl]urea	Calc'd 343, found 343	Scheme 1, Example 1
244		1-(2-chloro-6-fluorobenzyl)-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 363, found 363	Scheme 1, Example 1
245		1-[(1R)-1-(3-chloro-4-fluorophenyl)ethyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 377, found 377	Scheme 1, Example 1

- 229 -

246		1-[(1R)-1-(3-chlorophenyl)ethyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 359, found 359	Scheme 1, Example 1
247		1-[(1R)-1-(4-chlorophenyl)propyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 373, found 373	Scheme 1, Example 1
248		1-[(1R)-1-(3,4-dichlorophenyl)ethyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 393, found 393	Scheme 1, Example 1
249		1-[(1R)-1-(4-chlorophenyl)ethyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 359, found 359	Scheme 1, Example 1
250		1-{[2-(dimethylamino)pyridin-3-yl]methyl}-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 355, found 355	Scheme 1, Example 1
251		1-[1-(3,4-difluorophenyl)ethyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 361, found 361	Scheme 1, Example 1
252		1-[(1R)-1-(4-chloro-3-methylphenyl)ethyl]-3-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 373, found 373	Scheme 1, Example 1

- 230 -

253		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(3S,4R)-1-methyl-4-phenylpyrrolidin-3-yl]urea	Calc'd 380, found 380	Scheme 1, Example 1
254		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-phenylpropyl)urea	Calc'd 311, found 311	Scheme 2, Example 43
255		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-cyclohexylethyl]urea	Calc'd 303, found 303	Scheme 2, Example 43
256		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1,2,3,4-tetrahydroquinolin-3-yl)urea	Calc'd 324, found 324	Scheme 2, Example 43
257		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(3,4-dihydro-2H-chromen-3-yl)urea	Calc'd 325, found 325	Scheme 2, Example 43
258		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea	Calc'd 325, found 325	Scheme 2, Example 43
259		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2,3-dihydro-1-benzofuran-3-yl)urea	Calc'd 311, found 311	Scheme 2, Example 43
260		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(S)-(1-hydroxycyclopentyl)-(phenyl)methyl]urea	Calc'd 367, found 367	Scheme 2, Example 43

- 231 -

261		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-phenylcyclopentyl)urea	Calc'd 337, found 337	Scheme 2, Example 43
262		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(2-ethoxypyridin-3-yl)methyl]urea	Calc'd 328, found 328	Scheme 2, Example 43
263		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-2-(dimethylamino)-1-phenylethyl]urea	Calc'd 340, found 340	Scheme 2, Example 43
264		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(3-chloro-4-fluorobenzyl)urea	Calc'd 335, found 335	Scheme 2, Example 43
265		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(3-fluorobenzyl)urea	Calc'd 301, found 301	Scheme 2, Example 43
266		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-chloro-6-methylbenzyl)urea	Calc'd 331, found 331	Scheme 2, Example 43
267		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[2-(difluoromethoxy)benzyl]urea	Calc'd 349, found 349	Scheme 2, Example 43
268		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-methoxybenzyl)urea	Calc'd 313, found 313	Scheme 2, Example 43
269		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(2-fluoro-6-methoxybenzyl)urea	Calc'd 331, found 331	Scheme 2, Example 43

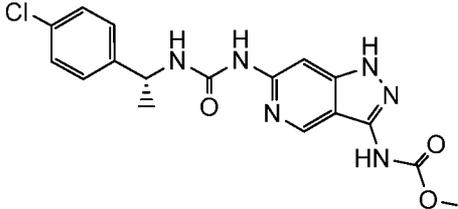
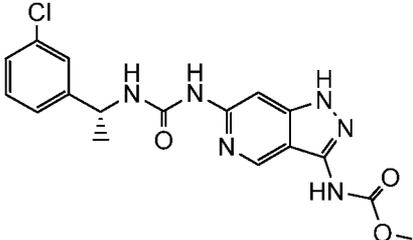
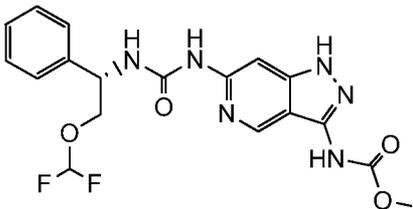
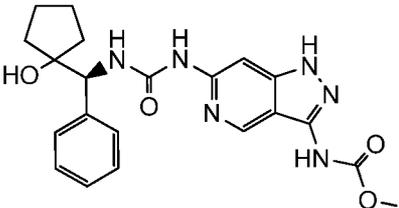
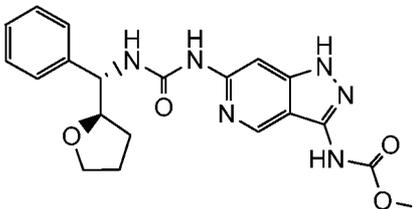
- 232 -

270		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-(3-fluorophenyl)ethyl]urea	Calc'd 315, found 315	Scheme 2, Example 43
271		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-(3-chloro-4-fluorophenyl)ethyl]urea	Calc'd 349, found 349	Scheme 2, Example 43
272		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-(3-chlorophenyl)ethyl]urea	Calc'd 331, found 331	Scheme 2, Example 43
273		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-(4-chlorophenyl)propyl]urea	Calc'd 345, found 345	Scheme 2, Example 43
274		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[[2-(dimethylamino)pyridin-3-yl]methyl]urea	Calc'd 327, found 327	Scheme 2, Example 43
275		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[1-(3,4-difluorophenyl)ethyl]urea	Calc'd 333, found 333	Scheme 2, Example 43
276		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-(4-chloro-3-methylphenyl)ethyl]urea	Calc'd 345, found 345	Scheme 2, Example 43
277		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(3S,4R)-1-methyl-4-phenylpyrrolidin-3-yl]urea	Calc'd 352, found 352	Scheme 2, Example 43

- 233 -

278		1-[(3-chloro- pyridin-2-yl)- methyl]-3-[3- (ethylamino)-1H- pyrazolo[4,3-c]- pyridin-6-yl]urea	Calc'd 346, found 346	Scheme 13, Example 320
279		1-[3-(ethylamino)- 1H-pyrazolo[4,3- c]pyridin-6-yl]-3- [(3-fluoropyridin-2- yl)methyl]urea	Calc'd 330, found 330	Scheme 13, Example 320
280		1-[3-(ethylamino)- 1H-pyrazolo[4,3- c]pyridin-6-yl]-3- [1-(6-methyl- pyridin-3-yl)- ethyl]urea	Calc'd 340, found 340	Scheme 13, Example 320
281		1-[3-(ethylamino)- 1H-pyrazolo[4,3- c]pyridin-6-yl]-3- [1-(4-methyl- pyridin-2-yl)- ethyl]urea	Calc'd 340, found 340	Scheme 13, Example 320
282		1-[3-(ethylamino)- 1H-pyrazolo[4,3- c]pyridin-6-yl]-3- [1-(6-fluoropyridin- 3-yl)ethyl]urea	Calc'd 344, found 344	Scheme 13, Example 320
283		1-[3-(ethylamino)- 1H-pyrazolo[4,3- c]pyridin-6-yl]-3- (1-pyridin-3- ylethyl)urea	Calc'd 326, found 326	Scheme 13, Example 320
284		1-[3-(ethylamino)- 1H-pyrazolo[4,3- c]pyridin-6-yl]-3- [1-(5-fluoropyridin- 2-yl)ethyl]urea	Calc'd 344, found 344	Scheme 13, Example 320
285		methyl [6-({[(1S)- 1-(4-fluorophenyl)- 2-methoxyethyl]- carbonyl} amino)- 1H-pyrazolo[4,3- c]pyridin-3-yl]- carbamate	Calc'd 403, found 403	Scheme 14, Example 321

- 234 -

286		methyl [6-({[(1R)-1-(4-chlorophenyl)ethyl]carbamoyl}-amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]carbamate	Calc'd 389, found 389	Scheme 14, Example 321
287		methyl [6-({[(1R)-1-(3-chlorophenyl)ethyl]carbamoyl}-amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]carbamate	Calc'd 389, found 389	Scheme 14, Example 321
288		methyl [6-({[(1S)-2-(difluoromethoxy)-1-phenylethyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]carbamate	Calc'd 421, found 421	Scheme 14, Example 321
289		methyl [6-({[(S)-(1-hydroxycyclopentyl)(phenyl)methyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]carbamate	Calc'd 425, found 425	Scheme 14, Example 321
290		methyl {6-[(S)-phenyl[(2R)-tetrahydrofuran-2-yl]methyl]carbamoyl}amino-1H-pyrazolo[4,3-c]pyridin-3-yl}carbamate	Calc'd 411, found 411	Scheme 14, Example 321

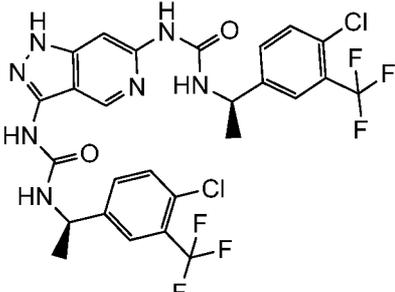
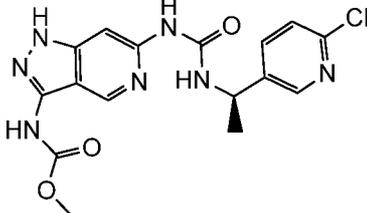
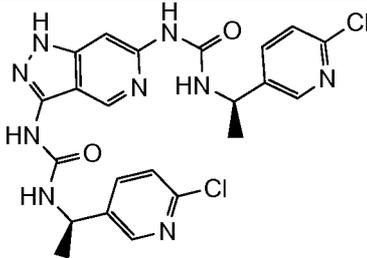
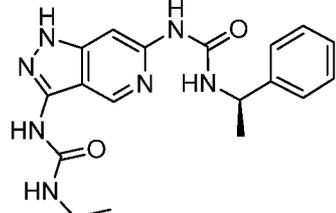
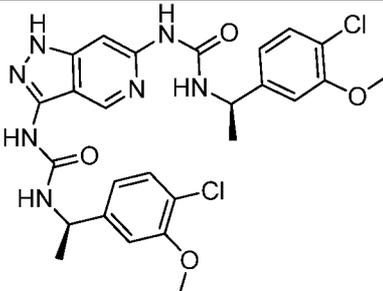
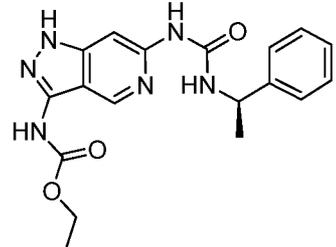
291		methyl[6- ({(3S,4R)-1- methyl-4-phenyl- pyrrolidin-3- yl]carbamoyl)- amino)-1H- pyrazolo[4,3- c]pyridin-3-yl]- carbamate	Calc'd 410, found 410	Scheme 14, Example 321
292		methyl [6-({(1R)- 1-cyclohexylethyl]- carbamoyl]amino)- 1H-pyrazolo[4,3- c]pyridin-3-yl]- carbamate	Calc'd 361, found 361	Scheme 14, Example 321
293		methyl {6- [(1,2,3,4- tetrahydroquinolin- 3-yl)carbamoyl]- amino}-1H- pyrazolo[4,3-c]- pyridin-3-yl]- carbamate	Calc'd 382, found 382	Scheme 14, Example 321
294		methyl {6-[(3,4- dihydro-2H- chromen-3- yl)carbamoyl]amino ]-1H-pyrazolo[4,3- c]pyridin-3-yl]- carbamate	Calc'd 383, found 383	Scheme 14, Example 321
295		methyl (6-({(4R)- 3,4-dihydro-2H- chromen-4- yl)carbamoyl]- amino)-1H- pyrazolo[4,3-c]- pyridin-3-yl)- carbamate	Calc'd 383, found 383	Scheme 14, Example 321
296		methyl [6-({[2- (difluoromethoxy)benzyl] carbamoyl]a mino)-1H- pyrazolo[4,3-c]- pyridin-3-yl]- carbamate	Calc'd 407, found 407	Scheme 14, Example 321

- 236 -

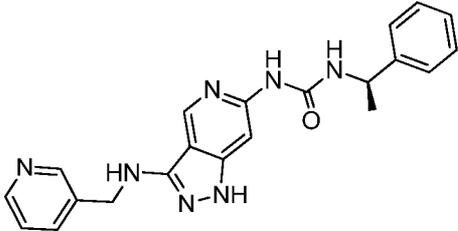
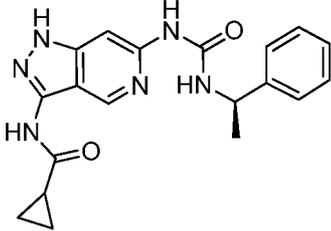
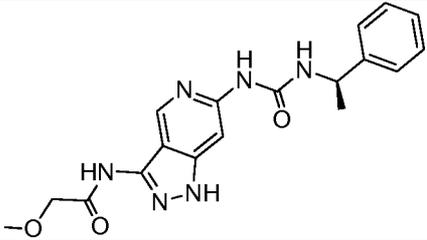
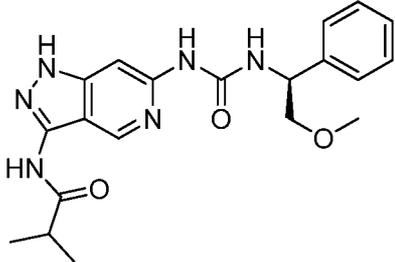
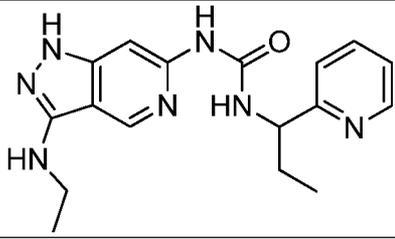
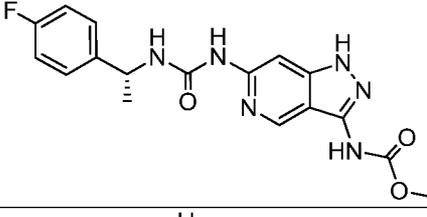
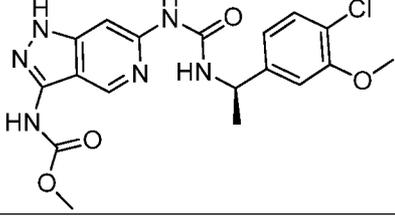
297		methyl (6-{{(2-methoxybenzyl)carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl)-carbamate	Calc'd 371, found 371	Scheme 14, Example 321
298		methyl (6-{{(2-fluoro-6-methoxybenzyl)carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl)-carbamate	Calc'd 389, found 389	Scheme 14, Example 321
299		methyl [6-({(1R)-1-(3-fluorophenyl)ethyl}carbamoyl)amino)-1H-pyrazolo[4,3-c]pyridin-3-yl)-carbamate	Calc'd 373, found 373	Scheme 14, Example 321
300		methyl [6-({(1R)-1-(3-chloro-4-fluorophenyl)ethyl}carbamoyl)amino)-1H-pyrazolo[4,3-c]pyridin-3-yl)-carbamate	Calc'd 407, found 407	Scheme 14, Example 321
301		methyl [6-({(1R)-1-(4-chlorophenyl)propyl}carbamoyl)amino)-1H-pyrazolo[4,3-c]pyridin-3-yl)-carbamate	Calc'd 403, found 403	Scheme 14, Example 321
302		methyl [6-({(1R)-1-(3,4-dichlorophenyl)ethyl}carbamoyl)amino)-1H-pyrazolo[4,3-c]pyridin-3-yl)-carbamate	Calc'd 423, found 423	Scheme 14, Example 321
303		methyl [6-({[1-(3,4-difluorophenyl)ethyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl)-carbamate	Calc'd 391, found 391	Scheme 14, Example 321

- 237 -

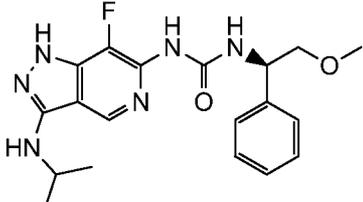
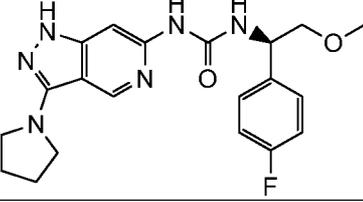
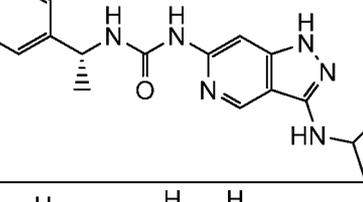
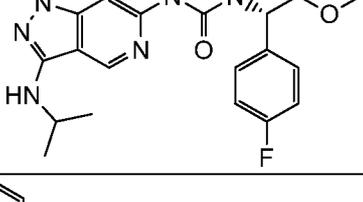
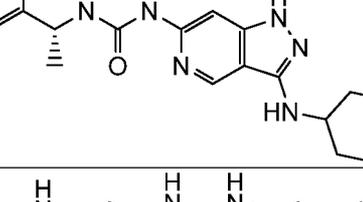
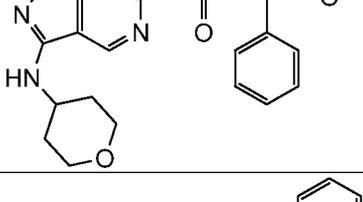
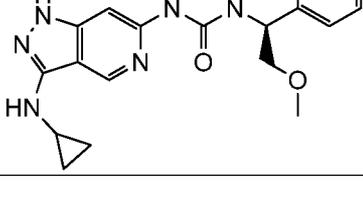
304		methyl [6-((1R)-1-(4-chloro-3-methylphenyl)ethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 403, found 403	Scheme 14, Example 321
305		methyl [6-((1R)-1-(2-fluorophenyl)ethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 373, found 373	Scheme 14, Example 321
306		methyl [6-((1R)-1-(4-chloro-3-fluorophenyl)ethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 407, found 407	Scheme 15, Example 322
307		methyl [6-((1R)-1-(4-chloro-3-hydroxyphenyl)ethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 405, found 405	Scheme 15, Example 322
308		N',N'''-1H-pyrazolo[4,3-c]pyridine-3,6-diylbis{1-[(1R)-1-(4-chloro-3-hydroxyphenyl)ethyl]urea}	Calc'd 544, found 544	Scheme 15, Example 314
309		methyl {6-[(1R)-1-[4-chloro-3-(trifluoromethyl)phenyl]ethyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 457, found 457	Scheme 15, Example 322

310		N',N'''-1H-pyrazolo[4,3-c]pyridine-3,6-diylbis(1-((1R)-1-[4-chloro-3-(trifluoromethyl)phenyl]ethyl)urea)	Calc'd 648, found 648	Scheme 15, Example 314
311		methyl [6-({[(1R)-1-(6-chloropyridin-3-yl)ethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 390, found 390	Scheme 15, Example 322
312		N',N'''-1H-pyrazolo[4,3-c]pyridine-3,6-diylbis{1-[(1R)-1-(6-chloropyridin-3-yl)ethyl]urea}	Calc'd 514, found 514	Scheme 15, Example 314
313		(R)-1-(3-(3-ethylureido)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-phenylethyl)urea	Calc'd 368, found 368	Example 313
314		1,1'-(1H-pyrazolo[4,3-c]pyridine-3,6-diyl)bis(3-((R)-1-(4-chloro-3-methoxyphenyl)ethyl)urea)	Calc'd 572.4, found 572	Example 314
315		(R)-ethyl (6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)-carbamate	Calc'd 369, found 369	Example 315

- 239 -

316		(R)-1-(1-phenylethyl)-3-(3-((pyridin-3-yl-methyl)amino)-1H-pyrazolo[4,3-c]-pyridin-6-yl)urea	Calc'd 388, found 388	Example 316
317		(R)-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)-cyclopropane-carboxamide	Calc'd 365, found 365	Example 317
318		(R)-2-methoxy-N-(6-(3-(1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)-acetamide	Calc'd 369, found 369	Example 318
319		(S)-N-(6-(3-(2-methoxy-1-phenylethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)-isobutyramide	Calc'd 397, found 397	Scheme 11, Example 317
320		1-(3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-(1-(pyridin-2-yl)propyl)urea	Calc'd 340, found 340	Example 320
321		(R)-methyl (6-(3-(1-(4-fluorophenyl)ethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)-carbamate	Calc'd 373, found 373	Example 321
322		(R)-methyl (6-(3-(1-(4-chloro-3-methoxyphenyl)ethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)-carbamate	Calc'd 420, found 420	Example 322

- 240 -

323		1-{7-fluoro-3-[(1-methylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-2-methoxy-1-phenylethyl]urea	Calc'd 387, found 387	Scheme 5
324		1-[(1R)-1-(4-fluorophenyl)-2-methoxyethyl]-3-(3-pyrrolidin-1-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 399, found 399	Scheme 1
325		1-{3-[(1-methylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 339, found 339	Scheme 1
326		1-[(1S)-1-(4-fluorophenyl)-2-methoxyethyl]-3-{3-[(1-methylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 387, found 387	Scheme 1
327		1-[(1R)-1-phenylethyl]-3-[3-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 381, found 381	Scheme 1
328		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 411, found 411	Scheme 1
329		1-[3-(cyclopropylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 367, found 367	Scheme 1

- 241 -

330		1-[3-(cyclopropylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 337, found 337	Scheme 1
331		1-[3-(ethylamino)-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 339, found 339	Example 331
332		1-[4-methyl-6-({[(1R)-1-phenylethyl]carbamoyl}-amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]proline	Calc'd 409, found 409	Scheme 1
333		1-(3-amino-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-1-phenylethyl]urea	Calc'd 311, found 311	Example 333
334		1-[3-(ethylamino)-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 369, found 369	Scheme 1
335		1-(3-amino-4-methyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 341, found 341	Scheme 1
336		1-[4-methyl-3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 325, found 325	Similar procedure in Example 331

- 242 -

337		N-[4-methyl-6-((1R)-1-phenylethyl)carbamoyl]-1H-pyrazolo[4,3-c]pyridin-3-yl]-acetamide	Calc'd 353, found 353	Example 337
338		methyl [4-methyl-6-((1R)-1-phenylethyl)carbamoyl]-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 369, found 369	Similar procedure in Example 337
339		(R)-1-(1-(4-fluorophenyl)-2-methoxyethyl)-3-(3-morpholino-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 415, found 415	Scheme 1, Example 1
340		(R)-1-(1-(4-fluorophenyl)ethyl)-3-(3-(isopropylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 357, found 357	Scheme 1, Example 1
341		1-[(1R)-1-phenylethyl]-3-{3-[(2,2,2-trifluoroethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 379, found 379	Scheme 1, Example 1
342		1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(2,2,2-trifluoroethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 409, found 409	Scheme 1, Example 1

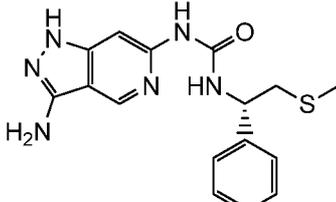
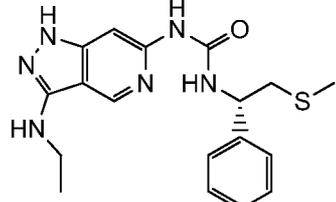
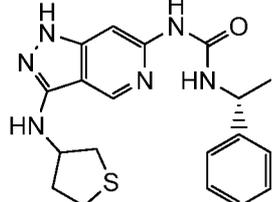
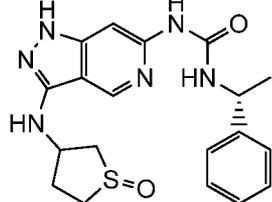
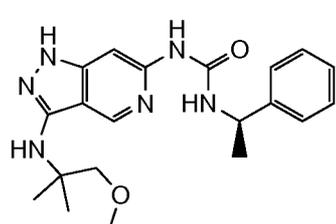
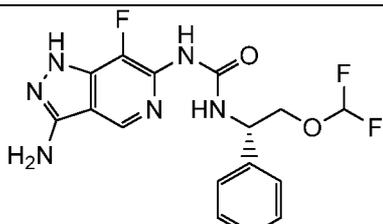
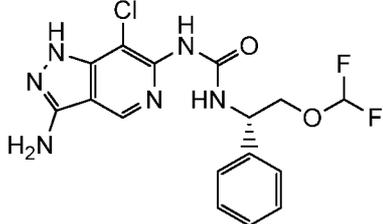
- 243 -

343		1-[(1R)-1-(4-chlorophenyl)ethyl]-3-[3-(methylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 345, found 345	Scheme 1, Example 1
344		1-[(1R)-1-pyridin-2-ylpropyl]-3-(3-pyrrolidin-1-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 366, found 366	Scheme 1, Example 9 with chiral resolution.
345		1-[(1S)-1-pyridin-2-ylpropyl]-3-(3-pyrrolidin-1-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 366, found 366	Scheme 1, Example 9 with chiral resolution.
346		1-[3-(cyclobutylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 381, found 381	Scheme 1, Example 1
347		N,N-dimethyl-N-[2-[[6-({[(1R)-1-phenylethyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-glycinamide	Calc'd 382, found 382	Scheme 1, Example 1
348		N,N-dimethyl-N-[3-[[6-({[(1R)-1-phenylethyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-beta-alaninamide	Calc'd 396, found 396	Scheme 1, Example 1
349		N-methyl-N-[6-({[(1R)-1-phenylethyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-acetamide	Calc'd 353, found 353	Scheme 5/ Step 1, Example 10

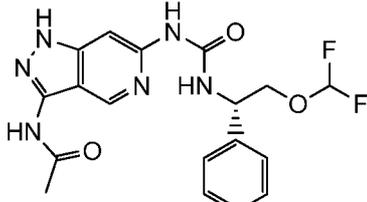
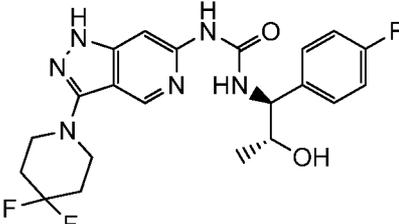
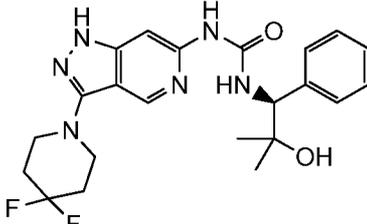
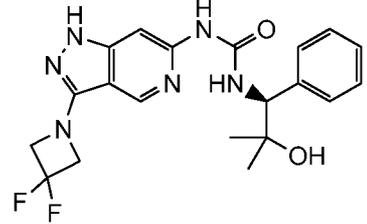
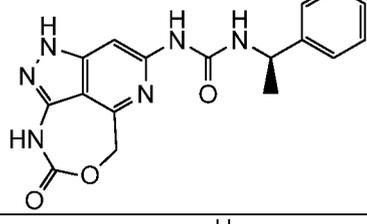
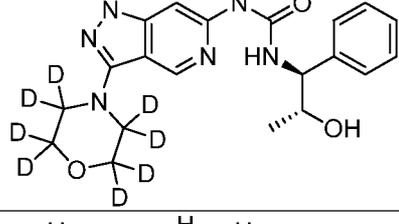
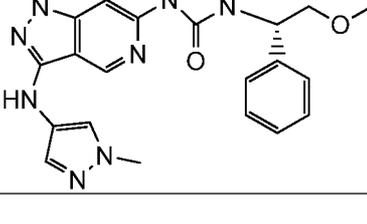
- 244 -

350		N-ethyl-N-[6- ({(1R)-1-phenyl- ethyl]carbamoyl}- amino)-1H- pyrazolo[4,3-c]- pyridin-3-yl]- acetamide	Calc'd 367, found 367	Scheme 5/ Step 1, Example 10
351		1-[3-(tert- butylamino)-1H- pyrazolo[4,3-c]- pyridin-6-yl]-3- [(1R)-1- phenylethyl]urea	Calc'd 353, found 353	Scheme 1, Example 1 with Intermediate 351A
352		1-(3-amino-1H- pyrazolo[4,3-c]- pyridin-6-yl)-3- [(1S)-2- (difluoromethoxy)- 1-phenylethyl]urea	Calc'd 363, found 363	Scheme 1 Example 1
353		1-[(1S)-2- (difluoromethoxy)- 1-phenylethyl]-3- [3-(ethylamino)- 1H-pyrazolo[4,3- c]pyridin-6-yl]urea	Calc'd 391, found 391	Scheme 1 Example 1
354		1-(3-[(1S)-2,2- difluoro-1-methyl- ethyl]amino)-1H- pyrazolo[4,3-c]- pyridin-6-yl)-3- [(1R)-1- phenylethyl]urea	Calc'd 375, found 375	Scheme 8, Method A with chrial resolution.
355		1-(3-[(1R)-2,2- difluoro-1-methyl- ethyl]amino)-1H- pyrazolo[4,3-c]- pyridin-6-yl)-3- [(1R)-1- phenylethyl]urea	Calc'd 375, found 375	Scheme 8, Method A with chrial resolution
356		1-[3-[(1- methylcyclo- butyl)amino]-1H- pyrazolo[4,3-c]- pyridin-6-yl]-3- [(1R)-1- phenylethyl]urea	Calc'd 365, found 365	Scheme 1, Example 1 with Intermediate prepared according to procedure of intermediate 351A

- 245 -

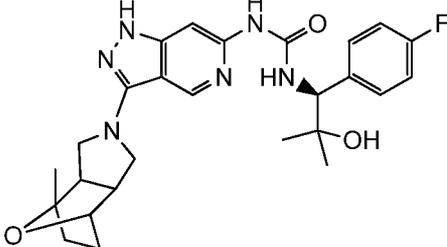
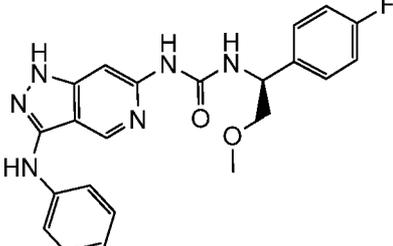
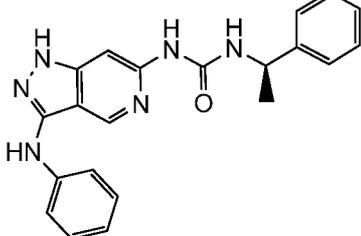
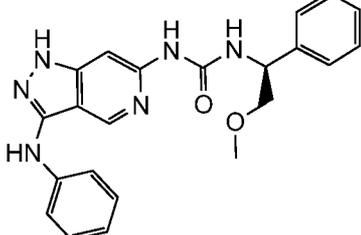
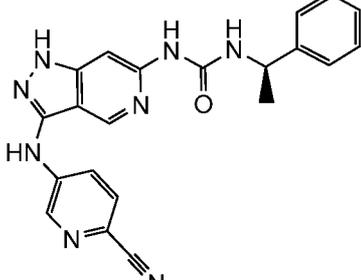
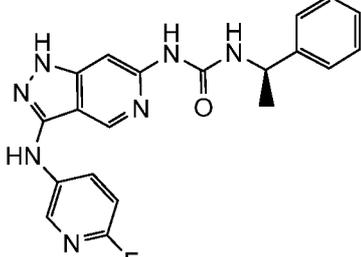
357		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-2-(methylsulfanyl)-1-phenylethyl]urea	Calc'd 343, found 343	Scheme 1, Example 1
358		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-(methylsulfanyl)-1-phenylethyl]urea	Calc'd 371, found 371	Scheme 1, Example 1
359		1-[(1R)-1-phenylethyl]-3-[3-(tetrahydrothiophen-3-ylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 383, found 383	Scheme 8, Method A
360		1-{3-[(1-oxidotetrahydrothiophen-3-yl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 399, found 399	Scheme 8 Method A (byproduct from Example 359)
361		1-{3-[(2-methoxy-1,1-dimethylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 383, found 383	Scheme 1, Example 1 (with Intermediate prepared according to procedure of intermediate 351A)
362		1-(3-amino-7-fluoro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-2-(difluoromethoxy)-1-phenylethyl]urea	Calc'd 381, found 381	Scheme 6, example 5a
363		1-(3-amino-7-chloro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-2-(difluoromethoxy)-1-phenylethyl]urea	Calc'd 397, found 397	Scheme 6, example 5a

- 246 -

364		N-[6-({[(1S)-2-(difluoromethoxy)-1-phenylethyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-acetamide	Calc'd 405, found 405	Scheme 3, example 47
365		1-[3-(4,4-difluoropiperidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S,2R)-1-(4-fluorophenyl)-2-hydroxypropyl]urea	Calc'd 449, found 449	Scheme 1 Example 1
366		1-[3-(4,4-difluoropiperidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]urea	Calc'd 445, found 445	Scheme 1 Example 1
367		1-[3-(3,3-difluoroazetidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]urea	Calc'd 417, found 417	Scheme 1 Example 1
368		1-(8-oxo-2,6,8,9-tetrahydro-7-oxa-1,2,5,9-tetraazabenzocdiazulen-4-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 353, found 353	Example 368
369		1-((1S,2R)-2-hydroxy-1-phenylpropyl)-3-(3-(morpholino-D8)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 405, found 405	Scheme 1, Example 1
370		1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(1-methyl-1H-pyrazol-4-yl)-amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 407, found 407	Scheme 1

- 247 -

371		1-{3-[(2-methoxyethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 385, found 385	Scheme 1
372		1-[(1S)-1-(4-fluorophenyl)-2-methoxyethyl]-3-{3-[(1-methyl-1H-pyrazol-4-yl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 425, found 425	Scheme 1
373		1-[(1S)-1-(4-fluorophenyl)-2-methoxyethyl]-3-{3-[(2-methoxyethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 403, found 403	Scheme 1
374		1-[(1R)-1-(4-fluorophenyl)ethyl]-3-{3-[(2-methoxyethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 373, found 373	Scheme 1
375		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-2-hydroxy-1-phenylethyl]urea	Calc'd 313, found 313	Scheme 2
376		1-[(1R)-1-(4-fluorophenyl)ethyl]-3-[3-(4-methyloctahydro-2H-4,7-epoxyisoindol-2-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 451, found 451	Scheme 1, Example 1

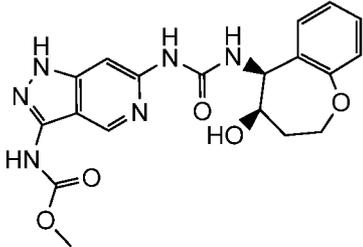
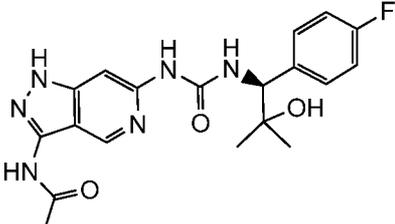
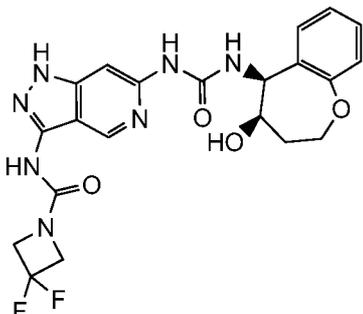
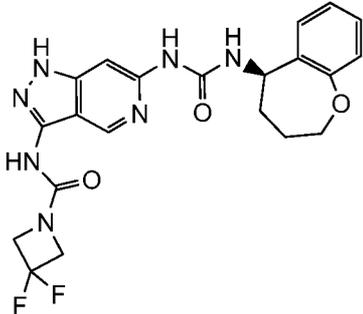
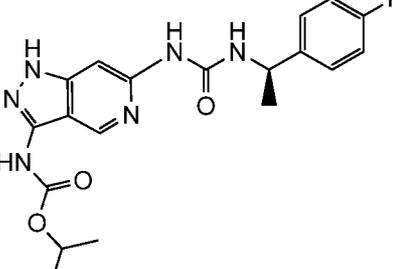
377		1-[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]-3-[3-(4-methyloctahydro-2H-4,7-epoxyisoindol-2-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 495, found 495	Scheme 1, Example 1
378		1-[(1S)-1-(4-fluorophenyl)-2-methoxyethyl]-3-[3-(phenylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 421, found 421	similar procedure in Example 121
379		1-[3-(phenylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 373, found 373	similar procedure in Example 121
380		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(phenylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 403, found 403	similar procedure in Example 121
381		1-[3-[(6-cyanopyridin-3-yl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 399, found 399	similar procedure in Example 121
382		1-[3-[(6-fluoropyridin-3-yl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 392, found 392	similar procedure in Example 121

- 249 -

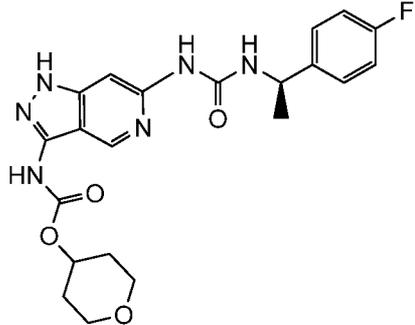
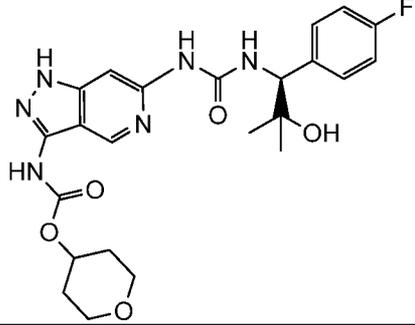
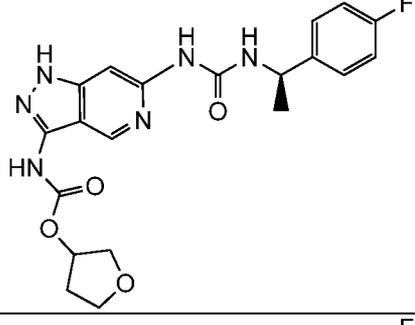
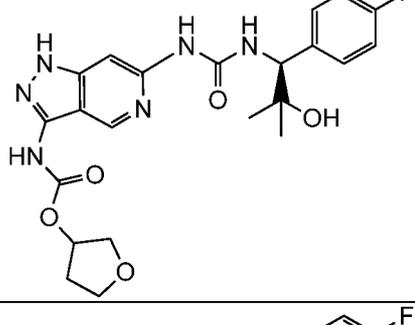
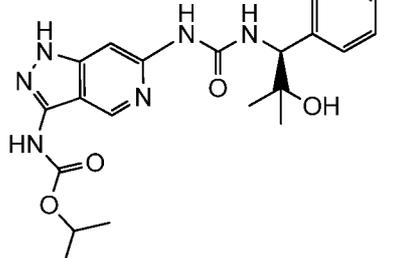
383		1-{3-[(2-cyanophenyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 428, found 428	similar procedure in Example 121
384		1-{3-[(2-fluorophenyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 421, found 421	similar procedure in Example 121
385		methyl [6-({(S)-(1-hydroxycyclobutyl)(phenyl)methyl} carbamoyl) amino]-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 411, found 411	Scheme 14, Example 321
386		methyl [6-({(S)-(4-fluorophenyl)(1-hydroxycyclobutyl)methyl} carbamoyl) amino]-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 429, found 429	Scheme 14, Example 321
387		1-[3-(6,7-dihydro[1,3]thiazolo[5,4-c]pyridin-5(4H)-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S,2R)-2-hydroxy-1-phenylpropyl]urea	Calc'd 450, found 450	Scheme 1, Example 1
388		1-[3-(6,7-dihydro[1,3]thiazolo[5,4-c]pyridin-5(4H)-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S,2S)-2-hydroxy-1-phenylpropyl]urea	Calc'd 450, found 450	Scheme 1, Example 1

- 250 -

389		methyl [6-({[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 399, found 399	Scheme 14, Example 321
390		methyl [6-({[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]-carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 417, found 417	Scheme 14, Example 321
391		1-[(1R)-1-(4-fluorophenyl)ethyl]-3-(2'-methyl-2',4',6',7'-tetrahydro-1H-3,5'-bipyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 435, found 435	Scheme 1, Example 1
392		methyl [6-({[(3,4-dichlorophenyl)(1,3-oxazol-5-yl)methyl]carbamoyl}amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 476, found 476	Scheme 14, Example 321
393		1-[(1S,2R)-2-hydroxy-1-phenylpropyl]-3-(2'-methyl-2',4',6',7'-tetrahydro-1H-3,5'-bipyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 447, found 447	Scheme 1, Example 1

394		methyl [6-((4R,5S)-4-hydroxy-2,3,4,5-tetrahydro-1-benzoxepin-5-yl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 413, found 413	Scheme 14, Example 321
395		N-[6-((1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-acetamide	Calc'd 401, found 401	Scheme 14, Example 321 using acetyl chloride instead of chloro- formate.
396		3,3-difluoro-N-[6-((4R,5S)-4-hydroxy-2,3,4,5-tetrahydro-1-benzoxepin-5-yl)-carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-azetidine-1-carboxamide	Calc'd 474, found 474	Following a similar procedure in Example 128
397		3,3-difluoro-N-(6-((5R)-2,3,4,5-tetrahydro-1-benzoxepin-5-yl)-carbamoyl)amino)-1H-pyrazolo[4,3-c]pyridin-3-yl)-azetidine-1-carboxamide	Calc'd 458, found 458	Following a similar procedure in Example 128
398		1-methylethyl [6-((1R)-1-(4-fluorophenyl)ethyl)carbamoyl]amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 401, found 401	Following a similar procedure in Example 406

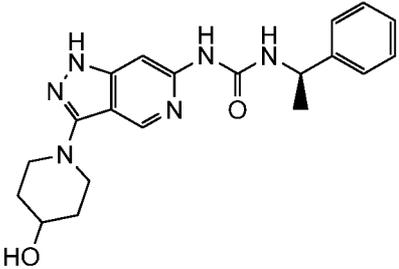
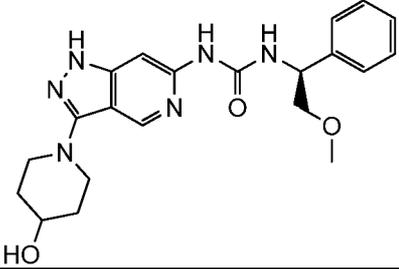
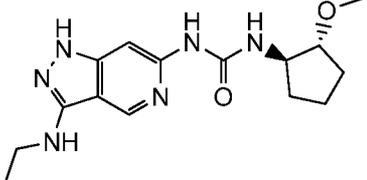
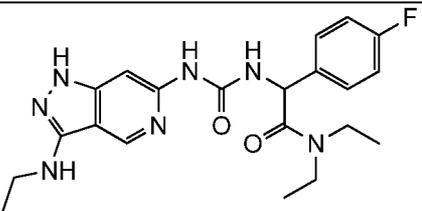
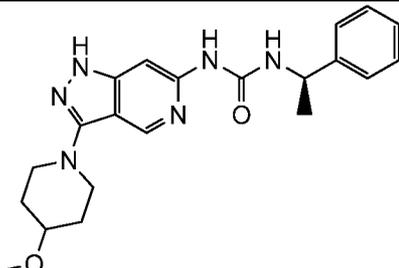
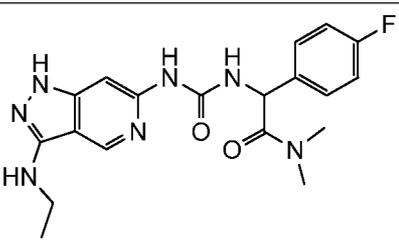
- 252 -

399		tetrahydro-2H-pyran-4-yl [6-({[(1R)-1-(4-fluorophenyl)ethyl] carbamoyl} amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 443, found 443	Following a similar procedure in Example 406
400		tetrahydro-2H-pyran-4-yl [6-({[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl] carbamoyl} amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 487, found 487	Following a similar procedure in Example 406
401		tetrahydrofuran-3-yl [6-({[(1R)-1-(4-fluorophenyl)ethyl] carbamoyl} amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 429, found 429	Following a similar procedure in Example 406
402		tetrahydrofuran-3-yl [6-({[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl] carbamoyl} amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 473, found 473	Following a similar procedure in Example 406
403		1-methylethyl [6-({[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl] carbamoyl} amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 445, found 445	Following a similar procedure in Example 406

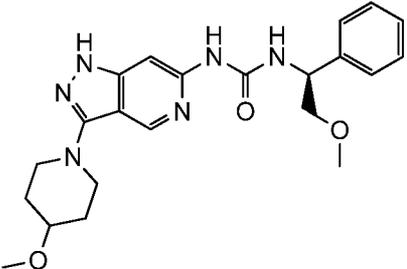
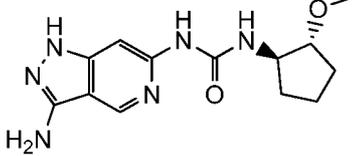
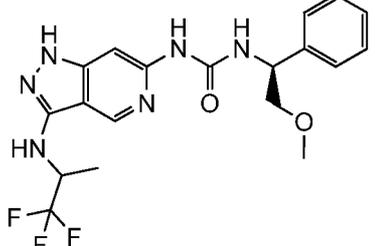
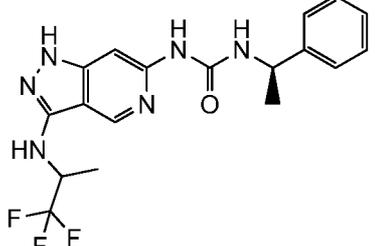
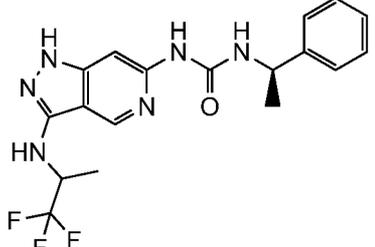
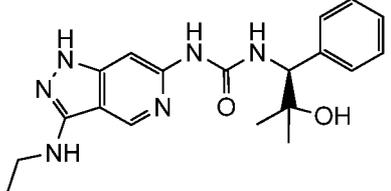
- 253 -

404		2-hydroxyethyl [6-({[(1R)-1-(4-fluorophenyl)ethyl] carbamoyl} amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 403, found 403	Following a similar procedure in Example 406
405		2,2-difluoroethyl [6-({[(1R)-1-(4-fluorophenyl)ethyl] carbamoyl} amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 423, found 423	Following a similar procedure in Example 406
406		2,2-difluoroethyl [6-({[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl] carbamoyl} amino)-1H-pyrazolo[4,3-c]pyridin-3-yl]-carbamate	Calc'd 467, found 467	Following a similar procedure in Example 406
407		1-[(1R)-1-phenylethyl]-3-{3-[(2,2,2-trifluoro-1-methylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 393, found 393	Scheme 1
408		1-[3-(2-oxopyrrolidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 365, found 365	Scheme 1

- 254 -

409		1-[3-(4-hydroxypiperidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 381, found 381	Scheme 1
410		1-[3-(4-hydroxypiperidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-1-phenylethyl]urea	Calc'd 411, found 411	Scheme 1
411		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R,2R)-2-methoxycyclopentyl]urea	Calc'd 319, found 319	Scheme 1
412		N,N-diethyl-2-({[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-carbamoyl}amino)-2-(4-fluorophenyl)acetamide	Calc'd 428, found 428	Scheme 1
413		1-[3-(4-methoxypiperidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 395, found 395	Scheme 1
414		2-({[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-carbamoyl}amino)-2-(4-fluorophenyl)-N,N-dimethylacetamide	Calc'd 400, found 400	Scheme 1

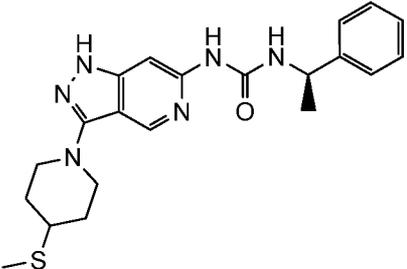
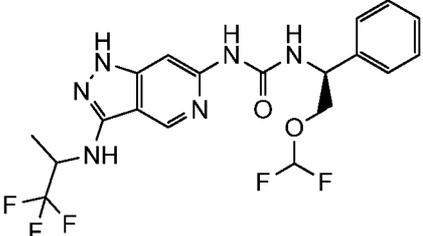
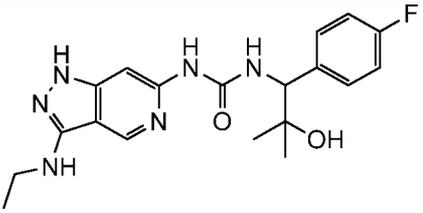
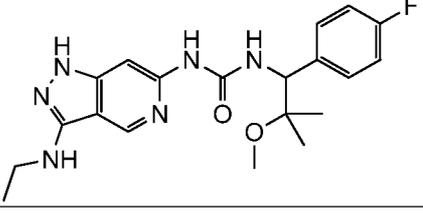
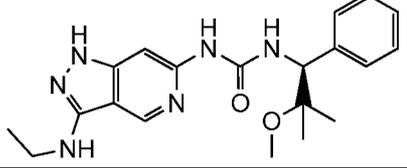
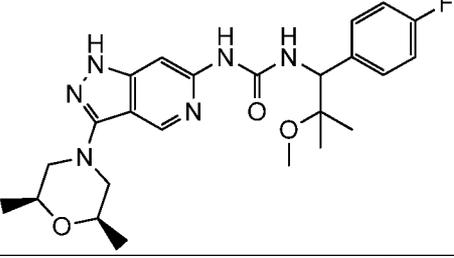
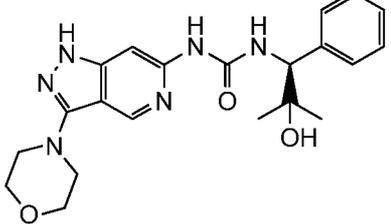
- 255 -

415		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(4-methoxypiperidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 425, found 425	Scheme 1
416		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R,2R)-2-methoxy-cyclopentyl]urea	Calc'd 291, found 291	Scheme 2
417		1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(2,2,2-trifluoro-1-methylethyl)-amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 423, found 423	Scheme 1
418		1-[(1R)-1-phenylethyl]-3-{3-[(2,2,2-trifluoro-1-methylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 393, found 393	Scheme 1
419		1-[(1R)-1-phenylethyl]-3-{3-[(2,2,2-trifluoro-1-methylethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 393, found 393	Scheme 1
420		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]urea	Calc'd 369, found 369	Example 420

- 256 -

421		1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(2,2,2-trifluoro-1-methylethyl)-amino]-1H-pyrazolo[4,3-c]-pyridin-6-yl}urea	Calc'd 423, found 423	Scheme 1
422		1-[(1S)-2-methoxy-1-phenylethyl]-3-{3-[(2,2,2-trifluoro-1-methylethyl)-amino]-1H-pyrazolo[4,3-c]-pyridin-6-yl}urea	Calc'd 423, found 423	Scheme 1
423		1-[3-(4-cyanopiperidin-1-yl)-1H-pyrazolo[4,3-c]-pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 390, found 390	Scheme 1
424		1-[3-(4-hydroxy-4-methylpiperidin-1-yl)-1H-pyrazolo[4,3-c]-pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 395, found 395	Scheme 1
425		1-(3-amino-1H-pyrazolo[4,3-c]-pyridin-6-yl)-3-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]urea	Calc'd 341, found 341	Example 425
426		1-[(1S)-2-(difluoromethoxy)-1-phenylethyl]-3-[3-(4-methoxypiperidin-1-yl)-1H-pyrazolo[4,3-c]-pyridin-6-yl]urea	Calc'd 461, found 461	Scheme 1

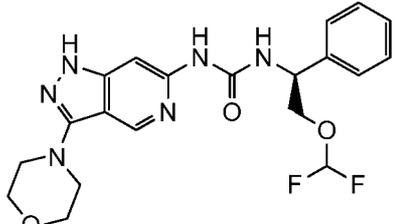
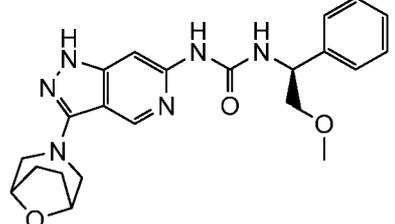
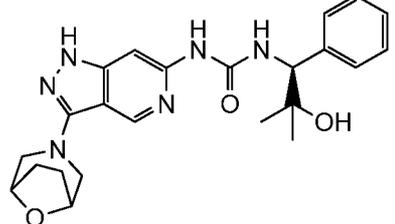
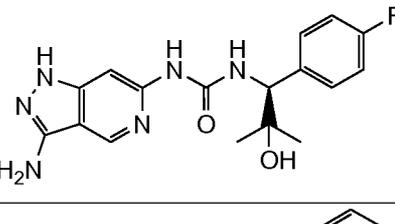
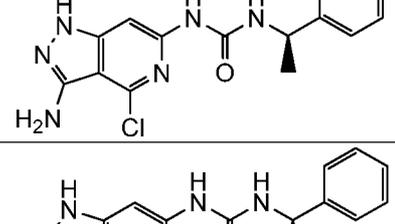
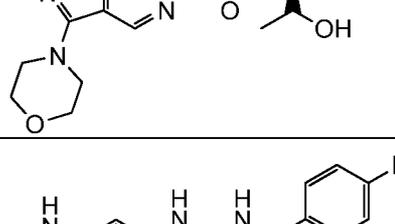
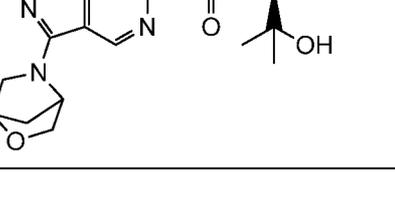
- 257 -

427		1-{3-[4-(methylsulfanyl)pyrrolidin-1-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[(1R)-1-phenylethyl]urea	Calc'd 411, found 411	Scheme 1
428		1-[(1S)-2-(difluoromethoxy)-1-phenylethyl]-3-{3-[(2,2,2-trifluoroethyl)amino]-1H-pyrazolo[4,3-c]pyridin-6-yl}urea	Calc'd 459, found 459	Scheme 1
429		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]urea	Calc'd 387, found 387	Scheme 1
430		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[1-(4-fluorophenyl)-2-methoxy-2-methylpropyl]urea	Calc'd 401, found 401	Scheme 1
431		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-2-methoxy-2-methyl-1-phenylpropyl]urea	Calc'd 383, found 383	Scheme 1
432		1-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1H-pyrazolo[4,3-c]pyridin-6-yl}-3-[1-(4-fluorophenyl)-2-methoxy-2-methylpropyl]urea	Calc'd 471, found 471	Scheme 1
433		1-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 411, found 411	Scheme 1

- 258 -

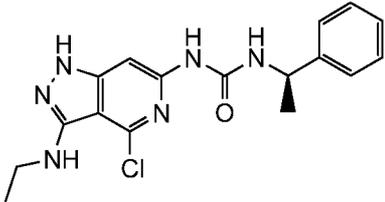
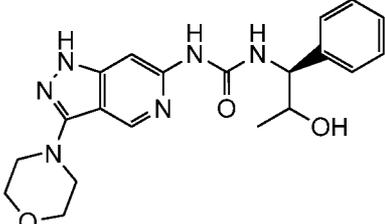
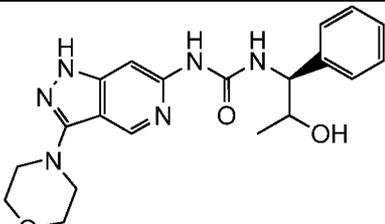
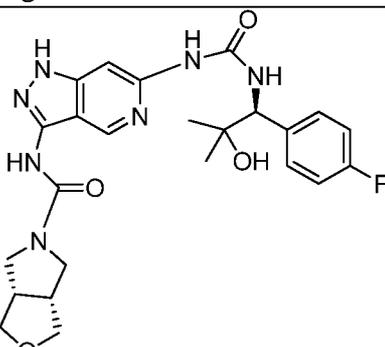
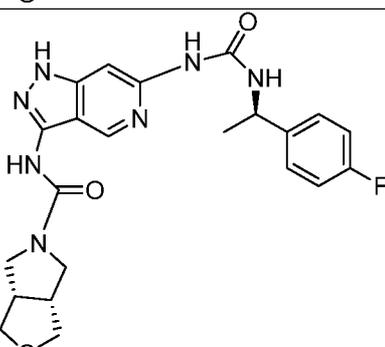
434		1-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-3-{3-[(2,2,2-trifluoro-1-methylethyl)-amino]-1H-pyrazolo[4,3-c]-pyridin-6-yl}urea	Calc'd 437, found 437	Scheme 1
435		1-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1H-pyrazolo[4,3-c]-pyridin-6-yl}-3-[1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]urea	Calc'd 457, found 457	Scheme 1
436		1-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-1H-pyrazolo[4,3-c]-pyridin-6-yl}-3-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]urea	Calc'd 439, found 439	Scheme 1
437		1-[(1S)-2-hydroxy-1-phenylethyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 383, found 383	Scheme 1
438		1-[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]-pyridin-6-yl)urea	Calc'd 429, found 429	Scheme 1
439		1-[(1S)-2-hydroxy-1-phenylethyl]-3-[3-(8-oxa-3-azabicyclo[3.2.1]-oct-3-yl)-1H-pyrazolo[4,3-c]-pyridin-6-yl]urea	Calc'd 409, found 409	Scheme 1

- 259 -

440		1-[(1S)-2-(difluoromethoxy)-1-phenylethyl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 433, found 433	Scheme 1
441		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 423, found 423	Scheme 1
442		1-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-3-[3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 437, found 437	Scheme 1
443		1-(3-amino-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]urea	Calc'd 359, found 359	Scheme 2
444		1-(3-amino-4-chloro-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 331, found 331	Example 444
445		1-[(1S,2R)-2-hydroxy-1-phenylpropyl]-3-(3-morpholin-4-yl-1H-pyrazolo[4,3-c]pyridin-6-yl)urea	Calc'd 397, found 397	Scheme 1
446		1-[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]-3-[3-(2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 441, found 441	Scheme 1

447		1-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-3-[3-(2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 423, found 423	Scheme 1
448		1-[3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]urea	Calc'd 387, found 387	Scheme 1
449		1-[3-(2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 379, found 379	Scheme 1
450		1-[(1S)-2-hydroxy-1-phenylethyl]-3-[3-(2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 395, found 395	Scheme 1
451		1-[(1S)-2-methoxy-1-phenylethyl]-3-[3-(2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]urea	Calc'd 409, found 409	Scheme 1
452		1-(3-amino-4-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)-3-[(1R)-1-phenylethyl]urea	Calc'd 327, found 327	Example 452
453		1-[3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 393, found 393	Scheme 1

- 261 -

454		1-[4-chloro-3-(ethylamino)-1H-pyrazolo[4,3-c]pyridin-6-yl]-3-[(1R)-1-phenylethyl]urea	Calc'd 359, found 359	Example 454
455		1-[(1S)-2-hydroxy-1-phenylpropyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-ylurea	Calc'd 397, found 397	Scheme 1
456		1-[(1S)-2-hydroxy-1-phenylpropyl]-3-(3-morpholin-4-yl)-1H-pyrazolo[4,3-c]pyridin-6-ylurea	Calc'd 397, found 397	Scheme 1
457		(3aR,6aS)-N-(6-(3-((S)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl)-ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)-tetrahydro-1H-furo[3,4-c]pyrrole-5(3H)-carboxamide	Calc'd 498, found 498	Following a similar procedure in Example 128
458		(3aR,6aS)-N-(6-(3-((R)-1-(4-fluorophenyl)ethyl)ureido)-1H-pyrazolo[4,3-c]pyridin-3-yl)-tetrahydro-1H-furo[3,4-c]pyrrole-5(3H)-carboxamide	Calc'd 454, found 454	Following a similar procedure in Example 128

## ASSAYS

### Active human ERK2 (hERK2) Activity Assay:

Activated ERK2 activity was determined in an IMAP-FP assay (Molecular Devices).

- Using this assay format, the potency ( $IC_{50}$ ) of each compound was determined from a 10 point (1:3 serial dilution, 3  $\mu$ M starting compound concentration) titration curve using the following

- 262 -

outlined procedure. To each well of a black Corning 384-well plate (Corning Catalog #3575), 7.5 nL of compound (3333 fold dilution in final assay volume of 25  $\mu$ L) was dispensed, followed by the addition of 15  $\mu$ L of kinase buffer (tween containing kinase buffer, Molecular Devices) containing 0.0364 ng/mL (0.833 nM) of phosphorylated active hERK2 enzyme.

- 5 Following a 15 minute compound & enzyme incubation, each reaction was initiated by the addition of 10  $\mu$ L kinase buffer containing 2.45  $\mu$ M ERK2 IMAP substrate peptides (2.25  $\mu$ M-unlabeled IPTTPITTTYFFFK-COOH and 200 nM-labeled IPTTPITTTYFFFK-5FAM (5-carboxyfluorescein)-COOH), and 75  $\mu$ M ATP. The final reaction in each well of 25  $\mu$ L
- 10 consists of 0.5 nM hERK2, 900 nM unlabeled peptide, 80 nM labeled-peptide, and 30  $\mu$ M ATP. Phosphorylation reactions were allowed to proceed for 60 minutes and were immediately quenched by the addition of 60  $\mu$ L IMAP detection beads (1:1000 dilutions) in IMAP binding buffer (Molecular Devices) with 24 mM NaCl. Plates were read on EnVision reader after 60 minutes binding equilibration using Fluorescence Polarization protocol (Perkin Elmer).

- The AERK2 IC<sub>50</sub> in nanomolar (nM) for the compounds of Examples 1 to 60 is in
- 15 Table 5.

TABLE 5

Ex	IC <sub>50</sub>						
1	7.85	16	20.6	31	0.40	46	1.79
2	1.13	17	11.8	32	0.37	47	0.66
3	4.87	18	15.19	33	0.67	48	1
4	19.47	19	13.81	34	0.61	49	0.56
5	1.00	20	13.63	35	0.67	50	320.8
6	2295	21	10.4	36	5.25	51	651.6
7	341.6	22	8.75	37	80.9	52	914.1
8	255.2	23	8.69	38	13.94	53	424
9	104.6	24	4.80	39	1.45	54	810
10	42.11	25	4.78	40	0.63	55	88.75
11	30	26	3.29	41	20.18	56	191.1
12	51.6	27	1.20	42	0.20	57	3.05
13	27.99	28	1.00	43	1.07	58	6.43
14	21.83	29	0.82	44	2.81	59	6.47
15	17.29	30	0.40	45	1.67	60	38.82

- 263 -

The AERK2 IC<sub>50</sub> in nanomolar (nM) for the compounds of Examples 61 to 458 is in Table 6.

TABLE 6

Ex	IC <sub>50</sub> (nM)						
61	8.8	161	2.3	261	6.0	361	385
62	14.7	162	165	262	20.7	362	1.3
63	5.8	163	0.6	263	127	363	52.2
64	5.6	164	30.2	264	940	364	0.3
65	365	165	50.2	265	24.5	365	0.9
66	31.6	166	1.7	266	13.8	366	0.4
67	0.7	167	4.2	267	5.3	367	0.6
68	0.5	168	31.7	268	10.7	368	1.1
69	1.5	169	50.2	269	3.3	369	0.4
70	0.6	170	2.7	270	3.2	370	19.7
71	4.4	171	4.1	271	17.3	371	0.7
72	106	172	31.2	272	5.6	372	14.7
73	39.2	173	5.8	273	2.6	373	1.1
74	1.7	174	4.4	274	32.4	374	2.8
75	0.8	175	33.8	275	4.6	375	2.5
76	1.3	176	38.2	276	2.3	376	13.8
77	2.1	177	12.0	277	3.2	377	2.3
78	7.4	178	4.6	278	21.8	378	62.3
79	9.7	179	1.0	279	63.4	379	127
80	5.5	180	17.9	280	143	380	15.5
81	8.5	181	4.3	281	98.3	381	367
82	3.7	182	2.6	282	34.2	382	72.1
83	2.7	183	3.6	283	44.4	383	2280
84	4.4	184	102	284	33.0	384	9.4
85	0.8	185	1.5	285	1.1	385	2.0
86	4.7	186	2.3	286	5.2	386	0.4
87	13.4	187	6.8	287	1.0	387	0.5
88	3.6	188	146	288	0.6	388	34.6
89	9.1	189	1.7	289	0.9	389	0.4
90	14.9	190	9.3	290	0.6	390	0.5
91	52.0	191	64.3	291	1.0	391	0.4
92	27.3	192	79.8	292	19.7	392	2.6
93	9.9	193	14.0	293	5.8	393	0.4
94	25.4	194	28.4	294	26.4	394	0.3
95	14.0	195	10.2	295	55.0	395	0.6
96	0.3	196	27.9	296	2.5	396	0.3
97	0.2	197	3.1	297	2.0	397	4.4
98	0.2	198	0.5	298	1.2	398	52.5
99	0.6	199	1.1	299	1.6	399	19.7
100	1.1	200	1.1	300	2.9	400	1.6
101	0.9	201	0.5	301	1.4	401	15.3
102	2.7	202	0.6	302	0.7	402	2.9

- 264 -

103	1.1	203	3.6	303	3.1	403	1.1
104	1.6	204	5.9	304	3.4	404	5.3
105	2.8	205	1.2	305	7.3	405	21.6
106	0.5	206	0.5	306	1.5	406	1.5
107	0.3	207	4.6	307	1.7	407	2.4
108	0.4	208	27.8	308	461	408	101
109	0.3	209	1.6	309	3.6	409	2.4
110	1.3	210	2.8	310	2454	410	1.2
111	0.5	211	3.1	311	19.1	411	99.3
112	0.5	212	11.7	312	134	412	421
113	1.6	213	2.2	313	5.6	413	4.5
114	0.8	214	2.9	314	732	414	413
115	0.8	215	3.9	315	10.0	415	1.0
116	94.2	216	12.0	316	0.7	416	483
117	18.0	217	47.7	317	1.0	417	0.6
118	57.2	218	25.1	318	2.2	418	3.2
119	60.1	219	32.5	319	0.4	419	2.2
120	27.2	220	354	320	33.0	420	2.1
121	24.5	221	6.6	321	2.6	421	0.6
122	8.4	222	3.6	322	5.2	422	0.8
123	0.4	223	12.4	323	4.1	423	9.7
124	0.3	224	355	324	1.0	424	21.5
125	0.4	225	39.8	325	1.5	425	14.9
126	0.2	226	17.0	326	0.7	426	1.0
127	0.3	227	11.3	327	1.0	427	15.1
128	3.4	228	3.5	328	0.8	428	1.3
129	0.4	229	1.2	329	1.0	429	1.1
130	0.5	230	11.7	330	0.9	430	0.6
131	1.5	231	57.0	331	2.9	431	0.5
132	4.9	232	18.6	332	74.7	432	2.4
133	2.4	233	28.0	333	0.7	433	0.5
134	8.6	234	52.0	334	2.9	434	0.7
135	382	235	334	335	3.0	435	1.6
136	12.2	236	0.7	336	11.8	436	0.8
137	1.3	237	8.3	337	127	437	0.4
138	5.9	238	9.6	338	16.1	438	0.4
139	5.5	239	27.4	339	0.4	439	1.9
140	111	240	14.7	340	1.6	440	0.4
141	15.4	241	11.8	341	2.4	441	0.9
142	1.2	242	2.4	342	0.9	442	0.5
143	167	243	1.7	343	7.8	443	0.7
144	2.0	244	10.8	344	1021	444	1.2
145	2.1	245	6.7	345	13.8	445	0.4
146	115	246	2.4	346	0.4	446	0.8
147	246	247	2.2	347	18.3	447	1.5
148	0.8	248	3.2	348	3.1	448	0.4
149	0.6	249	12.0	349	484	449	6.0
150	359	250	32.0	350	33.3	450	4.3

- 265 -

151	315	251	3.2	351	88.0	451	3.0
152	0.9	252	2.0	352	1.2	452	0.7
153	0.7	253	1.0	353	0.6	453	3.4
154	435	254	57.7	354	2.2	454	11.8
155	495	255	18.1	355	2.9	455	0.3
156	0.7	256	37.5	356	54.1	456	0.4
157	93.2	257	37.1	357	1.4	457	3.7
158	1.1	258	103	358	0.8	458	14.3
159	1.8	259	325	359	1.2		
160	279	260	0.4	360	2.6		

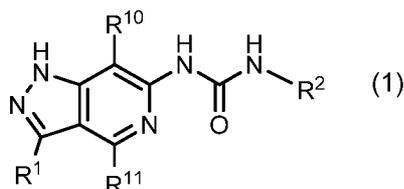
While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

5

- 266 -

**WHAT IS CLAIMED IS:**

1. A compound of the formula:



- 5 or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof, wherein:

$R^1$  is  $-NR^4R^5$ ;

- $R^2$  is selected from the group consisting of: H, (C<sub>6</sub>-C<sub>10</sub>)aryl-(C<sub>1</sub>-C<sub>3</sub>alkyl)-heterocycloalkyl-, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-heterocycloalkyl-(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>1</sub>-C<sub>4</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>1</sub>-C<sub>4</sub>alkyl)heteroaryl, -(C<sub>3</sub>-C<sub>6</sub>cycloalkyl)-(C<sub>6</sub>-C<sub>10</sub>aryl), -heterocycloalkyl-(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), -CH(C<sub>6</sub>-C<sub>10</sub>aryl)((C<sub>1</sub>-C<sub>6</sub>alkyl)N(R<sup>20</sup>)<sub>2</sub>), -CH(C<sub>6</sub>-C<sub>10</sub>aryl)(heterocycloalkyl), -(C<sub>3</sub>-C<sub>6</sub>cycloalkyl-O-(C<sub>1</sub>-C<sub>6</sub>alkyl)), -CH(C<sub>6</sub>-C<sub>10</sub>aryl)C(O)N(R<sup>21</sup>)<sub>2</sub> wherein each R<sup>21</sup> is independently selected, and -fused (heterocycloalkyl)(C<sub>6</sub>-C<sub>10</sub>)aryl wherein said heterocycloalkyl is a 5 to 8 membered ring (including the two atoms common with said aryl) comprising 1-3 heteroatoms selected from the group consisting of: O, S and N, and
- 15 wherein the remaining atoms are carbon;

- and wherein said aryl, heterocycloalkyl, heteroaryl, and cycloalkyl moieties of said R<sup>2</sup> groups are optionally substituted with 1-3 substituents independently selected from the group consisting of: CN, halo, -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -OH, -CF<sub>3</sub>, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -O(halo substituted(C<sub>1</sub>-C<sub>6</sub>alkyl)), -N(R<sup>20</sup>)<sub>2</sub>, aryl and heteroaryl;
- 20

and wherein said alkyl moieties of said R<sup>2</sup> groups are optionally substituted with 1-3 substituents independently selected from the group consisting of: CN, halo, -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -OH and -CF<sub>3</sub>, -O(halo substituted(C<sub>1</sub>-C<sub>6</sub>alkyl)) and -S(C<sub>1</sub>-C<sub>6</sub>alkyl);

- R<sup>4</sup> and R<sup>5</sup> are each independently selected from the group consisting of: H, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>9</sup>, -(C<sub>1</sub>-C<sub>6</sub>alkyl) substituted with 1-3 substituents independently selected from the group consisting of: halo, -OH and -S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl) substituted with 1-3 substituents independently selected from the group consisting of: halo, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, -(C<sub>3</sub>-C<sub>6</sub> cycloalkenyl),
- 25
- 30 -(C<sub>3</sub>-C<sub>6</sub> oxocycloalkenyl), -(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>6</sub>-C<sub>10</sub>aryl) substituted with 1-3 substituents independently selected from the group consisting of: -CN, -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and halo, -(C<sub>1</sub>-

- 267 -

C<sub>6</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)C(O)N(R<sup>20</sup>)<sub>2</sub> wherein each R<sup>20</sup> is independently selected, heteroaryl, heteroaryl substituted with 1-3 substituents independently selected from the group consisting of: -CN, halo and -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)(heteroaryl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)(heteroaryl) substituted with 1-3 substituents independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>3</sub>-C<sub>6</sub>cycloalkyl) substituted with 1-3 substituents independently selected from the group consisting of: -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(hydroxyC<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>2</sub>-C<sub>6</sub>alkenyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)heterocycloalkyl, -C(O)(substituted C<sub>1</sub>-C<sub>6</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>6</sub>alkyl) wherein said substituted alkyl is substituted with a heterocycloalkyl, -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl)NHC(O)O(C<sub>1</sub>-C<sub>6</sub>alkyl), heterocycloalkyl, heterocycloalkyl substituted with 1-3 substituents independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl) and halo, -(C<sub>1</sub>-C<sub>6</sub>alkyl)heterocycloalkenyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)heterocycloalkenyl substituted with 1-3 substituents independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl); or

R<sup>4</sup> and R<sup>5</sup> taken together with the nitrogen to which they are bonded to form a 4-6 membered heterocycloalkyl ring, said ring optionally comprising 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S and N, and said heterocycloalkyl ring optionally comprising a 1-2 carbon bridge, and said ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>6</sub>alkyl), -OH, -SCH<sub>3</sub>, halo, -CF<sub>3</sub>, CN, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-OH and -C(O)OH; or

R<sup>4</sup> and R<sup>5</sup> taken together with the nitrogen to which they are bonded to form a spiro ring comprising two independently selected 4-6 membered heterocycloalkyl rings, wherein one of said rings comprises the nitrogen of the -NR<sup>4</sup>R<sup>5</sup> group, and wherein the other ring of the spiro ring comprises one heteroatom selected from the group consisting of: O, N and S, and wherein each heterocycloalkyl ring optionally comprises 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S and N, and wherein said spiro ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: -OH, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-OH, -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>6</sub>alkyl); or

R<sup>4</sup> and R<sup>5</sup> taken together with the nitrogen to which they are bonded to form a fused bicyclic heterocycloalkyl ring, said ring optionally comprising 1 to 3 additional heteroatoms independently selected from the group consisting of: O, S and N, and said ring optionally comprising a -O- bridge between two ring carbons (i.e., an epoxy bridge), and said ring is

- 268 -

optionally substituted with 1-3 substituents independently selected from the group consisting of: halogen,  $-O(C_1-C_6\text{alkyl})$  and  $-(C_1-C_6\text{ alkyl})$ ; or

$R^4$  and  $R^5$  taken together with the nitrogen to which they are bonded to form a fused bicyclic ring wherein one ring is a heterocycloalkyl ring, and one ring is a heteroaryl ring, said heterocycloalkyl ring optionally comprising 1 to 3 additional heteroatoms independently selected from the group consisting of: O, S and N, and said bicyclic ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: halogen,  $-O(C_1-C_6\text{alkyl})$  and  $-(C_1-C_6\text{ alkyl})$ ; or

$R^4$  and  $R^{11}$  taken together form a 5-8 membered heterocycloalkyl ring, said ring optionally comprising 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S, N, and  $-(C=O)-$ , and said ring is optionally substituted with 1-3 substituents independently selected from  $R^{14}$  group.

$R^8$  and  $R^9$  are each independently selected from the group consisting of:  $-OR^{12}$ ,  $-NHR^{12}$ ,  $-NR^{12}R^{13}$ ,  $-(C_1-C_6\text{alkyl})$ ,  $-(C_1-C_6\text{alkyl})-O-(C_1-C_6\text{alkyl})$ ,  $-(C_3-C_6)\text{cycloalkyl}$ ,  $-(C_1-C_6\text{alkyl})-(C_3-C_6)\text{cycloalkyl}$ , heterocycloalkyl, aryl, heteroaryl,  $-(C_1-C_6\text{alkyl})(C_6-C_{10}\text{aryl})$ , and  $-(C_1-C_6\text{alkyl})(C_3-C_{10}\text{cycloalkyl})$ , fused bicyclic heterocycloalkyl ring, and wherein said heterocycloalkyl is a 4-6 membered ring comprising 1-3 heteroatoms selected from the group consisting of: O, S and N and the remaining ring atoms are carbon, and wherein said aryl is a  $C_6$  to  $C_{10}$  aromatic ring, and wherein said heteroaryl is a 5 to 10 membered ring comprising 1-3 heteroatoms selected from the group consisting of: O, S and N and the remaining ring atoms are carbon, and wherein said  $R^8$  heterocycloalkyl is optionally substituted with 1-3 substituents independently selected from the group consisting of: halo,  $-OH$ , and  $-(C_1-C_6\text{alkyl})$ , and wherein said  $R^8$   $-(C_1-C_6\text{alkyl})$  is optionally substituted with 1-3 substituents independently selected from the group consisting of: halo,  $-NH(C_1-C_6\text{alkyl})$  and  $-N(C_1-C_6\text{alkyl})_2$  wherein each alkyl is independently selected, and wherein said  $R^8$  heteroaryl is optionally substituted with 1-3 substituents independently selected from the group consisting of:  $-(C_1-C_6\text{alkyl})$ , and wherein said  $R^8$  aryl is optionally substituted with 1-3 substituents independently selected from the group consisting of: halo; and

$R^{10}$  is independently selected from the group consisting of: H, halo, CN, OH,  $NH_2$ ,  $-CF_3$ ,  $-O-(C_1-C_6\text{alkyl})$ ,  $-(C_1\text{ to }C_6\text{alkyl})$ ,  $-(C_3-C_6\text{ cycloalkyl})$ , hydroxy substituted  $-(C_1-C_6\text{alkyl})$ ,  $-(C_1-C_6\text{alkyl})-O-(C_1-C_6\text{alkyl})$ ,  $-(C_1-C_6\text{alkyl})-N(C_1-C_6\text{alkyl})_2$  wherein each alkyl is independently selected, and  $-(C_1-C_6\text{alkyl})$ -heterocycloalkyl.

- 269 -

R<sup>11</sup> is independently selected from the group consisting of: H, halo, CN, OH, NH<sub>2</sub>, aryl, heteroaryl, heterocycloalkyl, -NHR<sup>12</sup>, -NR<sup>12</sup>R<sup>13</sup>, -NHC(O)R<sup>8</sup>, -CF<sub>3</sub>, -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub> to C<sub>6</sub>alkyl), -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), hydroxy substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-heterocycloalkyl

each R<sup>12</sup> is independently selected from the group consisting of: (C<sub>1</sub>-C<sub>6</sub>alkyl), (C<sub>3</sub>-C<sub>6</sub>cycloalkyl), ((C<sub>3</sub>-C<sub>6</sub>cycloalkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-), (C<sub>3</sub>-C<sub>6</sub>cycloalkenyl), heterocycloalkyl, (heterocycloalkyl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, (C<sub>6</sub>-C<sub>10</sub>)aryl, (aryl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, heteroaryl, (heteroaryl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl R<sup>12</sup> groups is optionally substituted with 1 to 3 independently selected R<sup>14</sup> groups.

each R<sup>13</sup> is independently selected from the group consisting of: (C<sub>1</sub>-C<sub>6</sub>alkyl), (C<sub>3</sub>-C<sub>6</sub>cycloalkyl), ((C<sub>3</sub>-C<sub>6</sub>cycloalkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-), (C<sub>3</sub>-C<sub>6</sub>cycloalkenyl), heterocycloalkyl, (heterocycloalkyl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, (C<sub>6</sub>-C<sub>10</sub>)aryl, (aryl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, heteroaryl, (heteroaryl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, wherein each of said alkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl R<sup>13</sup> groups is optionally substituted with 1 to 3 independently selected R<sup>14</sup> groups, or

R<sup>12</sup> and R<sup>13</sup> taken together with the nitrogen to which they are bonded to form a 4-8 membered heterocycloalkyl ring, said ring optionally comprising 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S and N, and said ring is optionally substituted with 1-3 substituents independently selected from R<sup>14</sup> group.

each R<sup>14</sup> group is independently selected from the group consisting of halo, -CF<sub>3</sub>, -CN, OH, -OR<sup>15</sup>, (C<sub>1</sub>-C<sub>6</sub>alkyl), (C<sub>3</sub>-C<sub>6</sub>cycloalkyl), (C<sub>3</sub>-C<sub>6</sub>cycloalkenyl), heterocycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, heteroaryl and -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl);

each R<sup>15</sup> is independently selected from the group consisting of: (C<sub>1</sub>-C<sub>6</sub>alkyl), (C<sub>3</sub>-C<sub>6</sub>cycloalkyl), ((C<sub>3</sub>-C<sub>6</sub>cycloalkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-), (C<sub>3</sub>-C<sub>6</sub>cycloalkenyl), heterocycloalkyl, (heterocycloalkyl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, (C<sub>6</sub>-C<sub>10</sub>)aryl, (aryl(C<sub>1</sub>-C<sub>6</sub>alkyl))-, heteroaryl, (heteroaryl(C<sub>1</sub>-C<sub>6</sub>alkyl))- and -C(O)(C<sub>1</sub>-C<sub>6</sub>alkyl);

R<sup>20</sup> is independently selected from the group consisting of H and (C<sub>1</sub>-C<sub>6</sub>alkyl); and

R<sup>21</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl).

- 270 -

2. The compound of Claim 1 wherein:

R<sup>2</sup> is selected from the group consisting of: H, (C<sub>6</sub>-C<sub>10</sub>)aryl-(C<sub>1</sub>-C<sub>3</sub>alkyl)-heterocycloalkyl-, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-heterocycloalkyl-(C<sub>6</sub>-C<sub>10</sub>aryl), -(C<sub>1</sub>-C<sub>4</sub>alkyl)(C<sub>6</sub>-C<sub>10</sub>)aryl, -(C<sub>1</sub>-C<sub>3</sub>alkyl)heteroaryl, -(C<sub>3</sub>-C<sub>6</sub>cycloalkyl)-(C<sub>6</sub>-C<sub>10</sub>aryl), -heterocycloalkyl-(C<sub>6</sub>-C<sub>10</sub>aryl); and wherein said aryl, heterocycloalkyl, heteroaryl, and cycloalkyl moieties of said R<sup>2</sup> groups are optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -OH, -CF<sub>3</sub>, and -(C<sub>1</sub>-C<sub>6</sub>alkyl); and wherein said alkyl moieties of said R<sup>2</sup> groups are optionally substituted with 1-3 substituents independently selected from the group consisting of: halo (e.g., F, Br, and Cl), -O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -OH and -CF<sub>3</sub>;

R<sup>4</sup> and R<sup>5</sup> are each independently selected from the group consisting of: H, -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>9</sup>; or

R<sup>4</sup> and R<sup>5</sup> taken together with the nitrogen to which they are bonded to form a 4-6 membered heterocycloalkyl ring, said ring optionally comprising 1 or 2 additional heteroatoms independently selected from the group consisting of: O, S and N, and said ring is optionally substituted with 1-3 substituents independently selected from the group consisting of: -O(C<sub>1</sub>-C<sub>6</sub>alkyl) and -(C<sub>1</sub>-C<sub>6</sub>alkyl);

R<sup>8</sup> and R<sup>9</sup> are each independently selected from the group consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, -(C<sub>1</sub>-C<sub>6</sub>alkyl)-(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein said heterocycloalkyl is a 4-6 membered ring comprising 1-3 heteroatoms selected from the group consisting of: O, S and N and the remaining ring atoms are carbon, and wherein said aryl is a C<sub>6</sub> to C<sub>10</sub> aromatic ring, and wherein said heteroaryl is a 5 to 10 membered ring comprising 1-3 heteroatoms selected from the group consisting of: O, S and N and the remaining ring atoms are carbon; and

R<sup>10</sup> and R<sup>11</sup> are each independently selected from the group consisting of: H, halo, -(C<sub>1</sub> to C<sub>6</sub>alkyl), -(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), hydroxy substituted -(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-O-(C<sub>1</sub>-C<sub>6</sub>alkyl), -(C<sub>1</sub>-C<sub>6</sub>alkyl)-N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub> wherein each alkyl is independently selected, and -(C<sub>1</sub>-C<sub>6</sub>alkyl)-heterocycloalkyl.

3. The compound of Claim 1 wherein R<sup>1</sup> is selected from the group consisting of: A1 to A18.

4. The compound of Claim 1 wherein R<sup>1</sup> is selected from the group consisting of: -NH<sub>2</sub>, -NHCH<sub>3</sub>, -NHCH<sub>2</sub>CH<sub>3</sub>, -NHCH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>3</sub>, -NHC(O)NHCH<sub>2</sub>CH<sub>3</sub>,

- 271 -

-NHC(O)cyclopropyl, -NHC(O)OCH<sub>3</sub>, -NHC(O)OCH<sub>2</sub>CHF,  
 -NHC(O)CH(CH<sub>3</sub>)<sub>2</sub>NHC(O)OCH<sub>3</sub>, -NH-tetrahydrofuran, -NHC(D<sub>2</sub>)CD<sub>3</sub> (wherein D  
 represents deuterium), -NHC(O)CD<sub>3</sub>, -NHCH<sub>2</sub>cyclobutyl, -NH(CH<sub>2</sub>cyclobutyl)<sub>2</sub>,  
 -NHCH<sub>2</sub>cyclopropyl, -NH(CH<sub>2</sub>cyclopropyl)<sub>2</sub>, -NHC(O)CH(CH<sub>3</sub>)<sub>2</sub>, -NHCH<sub>2</sub>phenyl,  
 5 -NHCH(CH<sub>3</sub>)CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>OH, -NHCH(CH<sub>3</sub>)CH<sub>2</sub>S(O)<sub>2</sub>CH<sub>3</sub>, -NHCH(CH<sub>3</sub>)CH<sub>2</sub>Cl,  
 -NHC(O)CHCF<sub>3</sub>, -NHC(O)cyclobutyl, -NHC(O)CH<sub>2</sub>phenyl, -NHC(O)CH<sub>2</sub>cyclohexyl,  
 -NHC(O)cyclohexyl, -NHC(O)cyclopentyl, -NHC(O)CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,  
 -NHC(O)CH<sub>2</sub>cyclopentyl, -NHC(O)C(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)OC(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)NHCH(CH<sub>3</sub>)<sub>2</sub>,  
 -NHC(O)OCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)OCH<sub>3</sub>, -NHC(O)O(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, -NHC(O)Ophenyl,  
 10 -NHC(O)OCH(CH<sub>3</sub>)<sub>2</sub>, -NHC(O)OCH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, -NHC(O)OCH<sub>2</sub>phenyl,  
 -NHC(O)OCH<sub>2</sub>CH<sub>3</sub>, -NHC(O)cyclopropyl, -NHC(O)CH<sub>2</sub>OCH<sub>3</sub>, -Nhtetrahydropyran,  
 -NHcyclopropyl, -NHCH<sub>2</sub>CF<sub>3</sub>, -NHcyclobutyl, -NHCH<sub>2</sub>C(O)N(CH<sub>3</sub>)<sub>2</sub>,  
 -NH(CH<sub>2</sub>)<sub>2</sub>C(O)N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>3</sub>)C(O)CH<sub>3</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)C(O)CH<sub>3</sub>, -NHC(CH<sub>3</sub>)<sub>3</sub>,  
 -NHCH(CH<sub>3</sub>)CHF<sub>2</sub>, -NHC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NH(CH<sub>2</sub>)<sub>2</sub>OCH<sub>3</sub>, -NHphenyl,  
 15 -NHcyanopyridyl, -NHfluoropyridyl, -NHcyanophenyl, -NHcyclopentyl, -NHcyclohexyl, and  
 A19 to A132.

5. The compound of Claim 1 wherein R<sup>2</sup> is selected from the group consisting of:  
 -(C<sub>1</sub>-C<sub>2</sub>alkyl)phenyl, -CH(phenyl)(C<sub>1</sub>-C<sub>2</sub>alkyl-O-C<sub>1</sub>-C<sub>2</sub>alkyl), -(C<sub>1</sub>-C<sub>2</sub>alkyl)pyridyl,  
 20 -heterocycloalkyl-phenyl, and -(C<sub>1</sub>-C<sub>3</sub>alkyl)-O-C<sub>1</sub>-C<sub>2</sub>alkyl, and wherein said phenyl, pyridyl  
 and heterocycloalkyl groups are optionally substituted with 1-3 substituents independently  
 selected from the group consisting of: -C<sub>1</sub>-C<sub>2</sub>alkyl, F, Cl, and wherein said heterocycloalkyl  
 group is a 5-6 membered ring comprising 1 heteroatom selected from the group consisting of:  
 N, O and S;

25

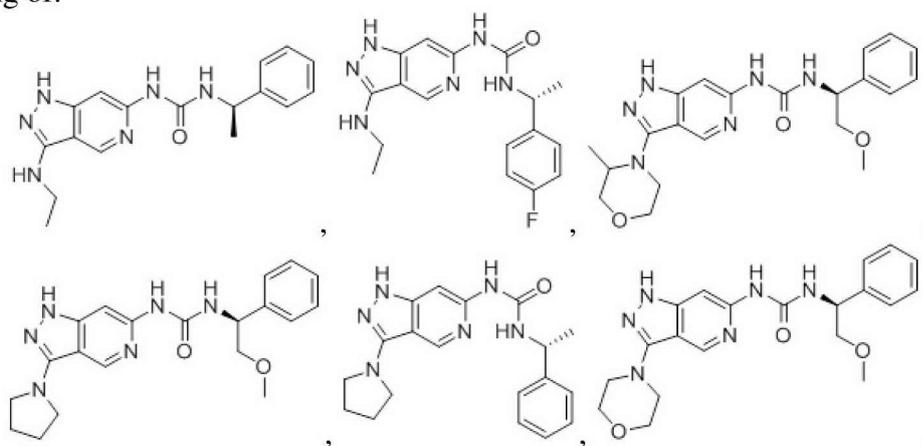
6. The compound of Claim 1 wherein R<sup>2</sup> is selected from the group consisting of:  
 -CH(CH<sub>3</sub>)phenyl, -CH(phenyl)(CH<sub>2</sub>-O-CH<sub>3</sub>), -CH(CH<sub>3</sub>)pyridyl, -pyrrolidinyl-phenyl, -(CH<sub>2</sub>)<sub>2</sub>-  
 O-CH<sub>3</sub>, -CH(CH<sub>3</sub>)CH<sub>2</sub>OCH<sub>3</sub>, -N-methylpyrrolidinyl-phenyl, -CH(CH<sub>3</sub>)(p-F-phenyl), -CH(p-  
 F-phenyl)(CH<sub>2</sub>-O-CH<sub>3</sub>).

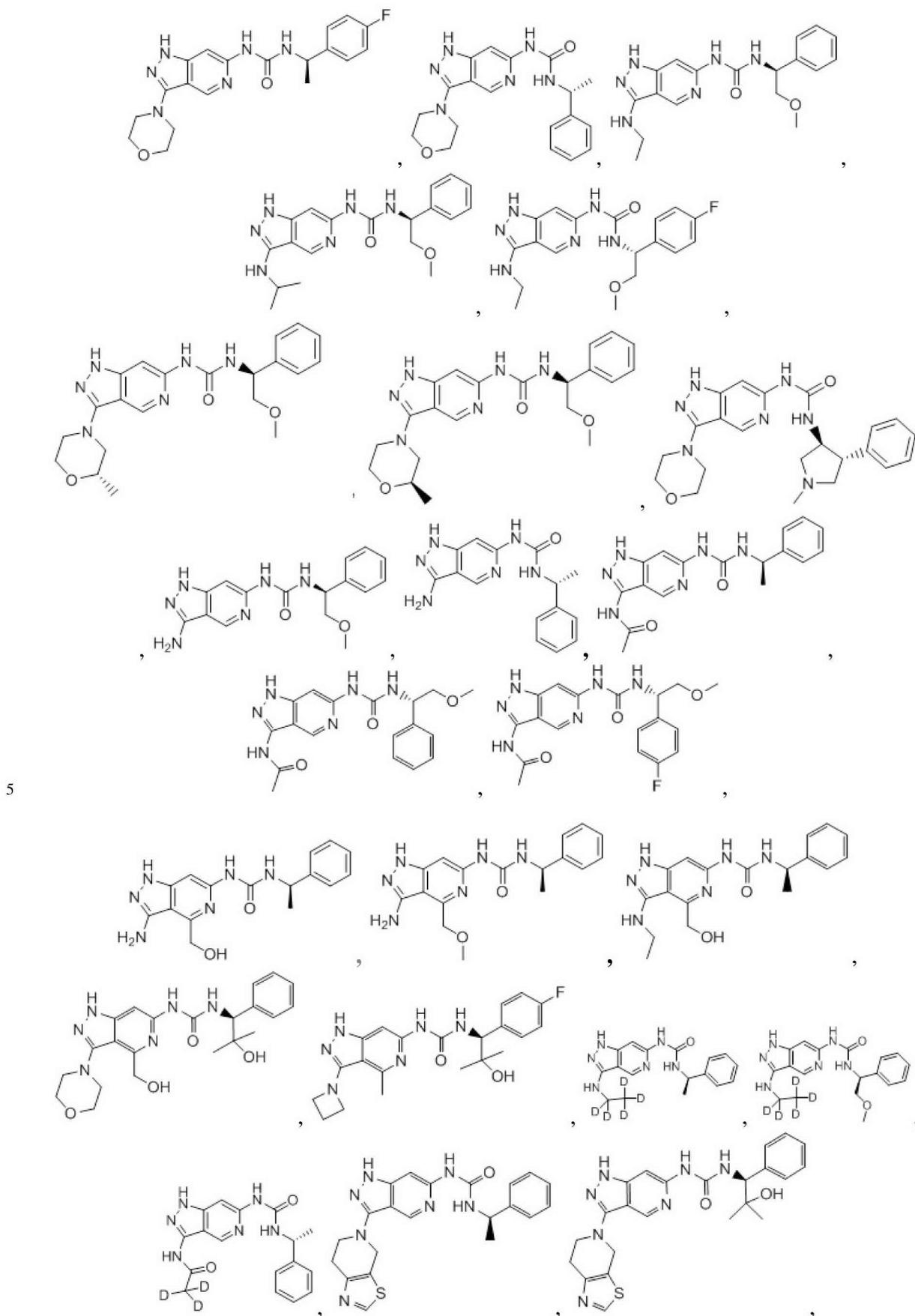
30

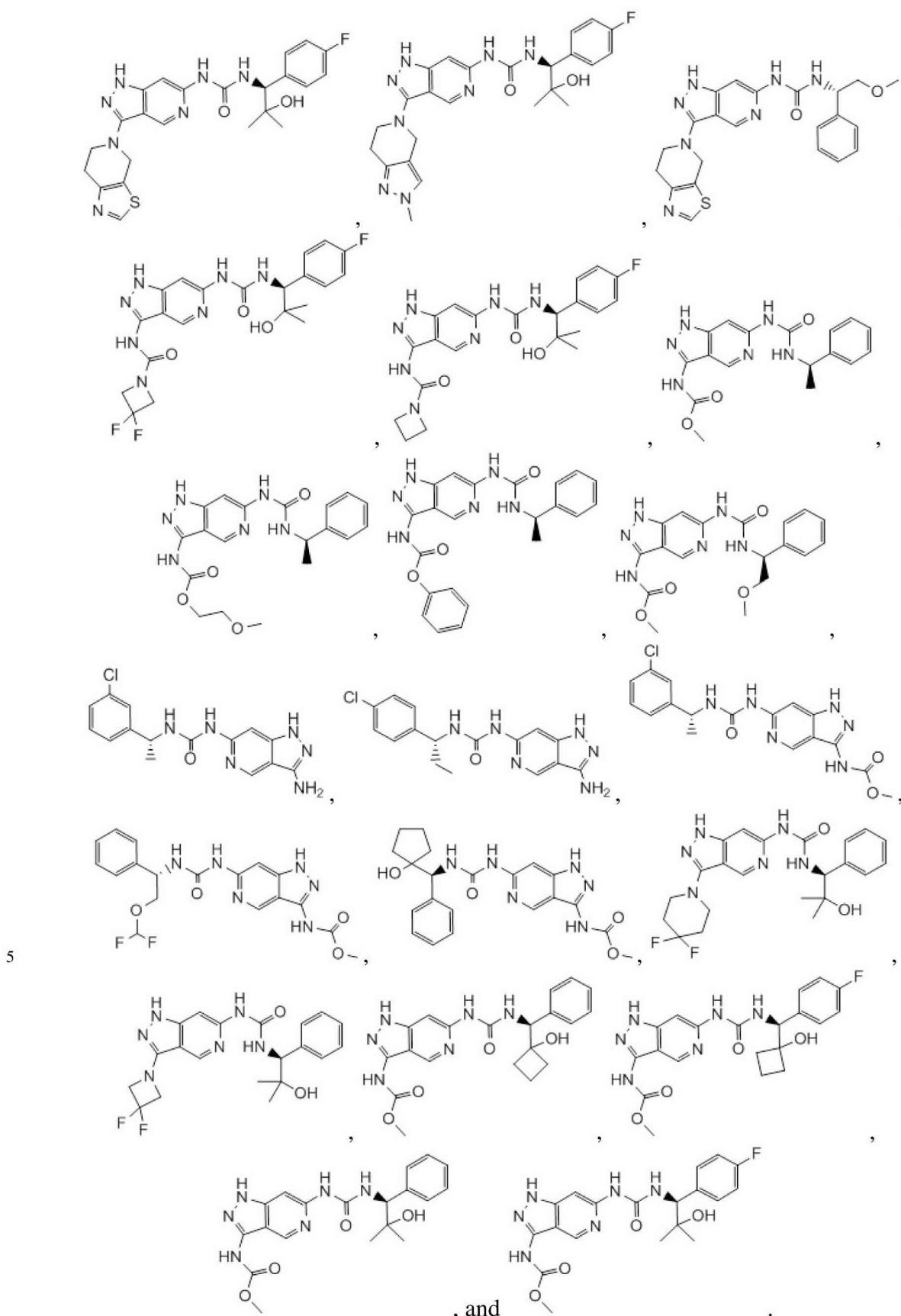
7. The compound of Claim 1 wherein R<sup>4</sup> and/or R<sup>5</sup> is selected from the group  
 consisting of: -(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)R<sup>8</sup> wherein R<sup>8</sup> is -(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)R<sup>8</sup> wherein R<sup>8</sup> is -  
 OR<sup>12</sup> wherein R<sup>12</sup> is a -(C<sub>1</sub>-C<sub>6</sub>alkyl), -C(O)R<sup>8</sup> wherein R<sup>8</sup> is heterocycloalkyl, -C(O)R<sup>8</sup>  
 wherein R<sup>8</sup> is a substituted -heterocycloalkyl.

35

8. The compound of Claim 1 wherein: R<sup>4</sup> and R<sup>5</sup>, taken together with the nitrogen to which they are bonded to, form a 4 to 6 membered heterocycloalkyl ring.
9. The compound of Claim 1 wherein R<sup>4</sup> and R<sup>5</sup>, taken together with the nitrogen to which they are bonded to, form a fused bicyclic ring wherein one ring is a heterocycloalkyl ring, and one ring is a heteroaryl ring.
10. The compound of Claim 1 wherein R<sup>2</sup> is selected from the group consisting of: B1-B90.
11. The compound of Claim 1 wherein R<sup>2</sup> is selected from the group consisting of: B100-B175.
12. The compound of Claim 1 wherein R<sup>10</sup> is selected from the group consisting of: H, Cl, F and -CF<sub>3</sub>, and R<sup>11</sup> is selected from the group consisting of: H, Cl, -CH<sub>3</sub>, -OCH<sub>3</sub>, -CH<sub>2</sub>OH, and -CH<sub>2</sub>OCH<sub>3</sub>.
13. The compound of Claim 1 wherein R<sup>10</sup> is selected from the group consisting of: H, F, Br, Cl, methyl and ethyl; and R<sup>11</sup> is selected from the group consisting of: H, F, Br, Cl, methyl and ethyl.
14. The compound of Claim 1 wherein R<sup>10</sup> is selected from the group consisting of: H, F and methyl, and R<sup>11</sup> is H.
15. The compound of Claim 1 wherein said compound is selected from the group consisting of:







16. A pharmaceutical composition comprising a compound of any one of Claims 1 to 15, or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof, and a pharmaceutically acceptable carrier.

17. A method of treating cancer mediated by inhibiting ERK activity in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one compound of any one of Claims 1 to 15, or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof, or a pharmaceutical composition of Claim 16.

18. The method of Claim 17 wherein said cancer is colorectal cancer or melanoma.

19. A method of treating cancer mediated by inhibiting ERK activity in a patient in need of such treatment, said method comprising administering to said patient an effective amount of at least one compound of any one of Claims 1 to 15, or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof, or a pharmaceutical composition of Claim 16, in combination with an effective amount of at least one chemotherapeutic agent.

20. Use of a compound of any one of Claims 1 to 15, or a pharmaceutically acceptable salt, ester, solvate or prodrug thereof, for the manufacture of a medicament for treating cancer mediated by inhibiting ERK activity.

**Merck Sharpe & Dohme Corp.**

20

**Patent Attorneys for the Applicant/Nominated Person  
SPRUSON & FERGUSON**