(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 March 2008 (20.03.2008)

PCT

(10) International Publication Number
WO 2008/033562 A2

(51) International Patent Classification:
C07D 403/02 (2006.01)

(21) International Application Number:
PCT/US2007/020193

(22) International Filing Date:
14 September 2007 (14.09.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/844,902 15 September 2006 (15.09.2006) US

(71) Applicant *(for all designated States except US)*: **XCOVERY, INC.** [US/US]; 501 South Flagler Drive, Suite 501, West Palm Beach, FL 33401 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LIANG, Congxin** [US/US]; 1037 Vintner Blvd., Palm Beach Gardens, FL 33410 (US). **GAO, Shu** [CN/CN]; 55 Yi Feng Road, Shanghai 201203 (CN). **LI, Zhigang** [CN/CN]; 332 Edison Road, Shanghai 201203 (CN).

(74) Agents: **HSI, Jeffrey, D.** et al.; Edwards Angell Palmer & Dodge LLP, P.O. Box 55874, Boston, MA 02205 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2008/033562 A2

(54) Title: KINASE INHIBITOR COMPOUNDS

(57) Abstract: The invention relates to compounds, compositions comprising the compounds, and methods of using the compounds and compound compositions. The compounds, compositions, and methods described herein can be used for the therapeutic modulation of kinase-mediated processes, and treatment of disease and disease symptoms, particularly those mediated by certain kinase enzymes.

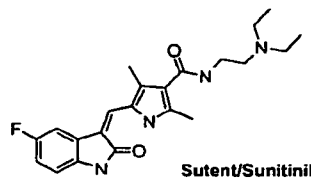
KINASE INHIBITOR COMPOUNDS

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 60/844,902 filed September 15, 2006, the contents of which are incorporated by reference in their entirety.

BACKGROUND

Sunitinib is a potent multi-targeted kinase inhibitor that is efficacious in the treatment of cancers, most notably renal cell carcinoma and GI stroma tumor as approved by FDA. It is also undergoing clinical trials in a number of other cancers. Its structure is an indolinone derivative characterized by a basic diethylaminoethyl side chain. Although Sunitinib is very efficacious, its application is hampered by the side effects. The most common and severe toxicity in clinic is neutropenia and fatigue.



Sutent/Sunitinib/SU11248

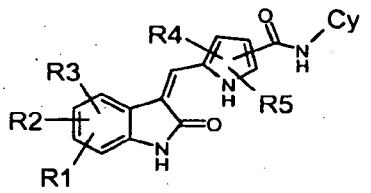
This invention describes a novel class of Sunitinib derivatives with a cyclic side chain replacing the diethylaminiethyl side chain of Sunitinib. They are designed to overcome the fatigue problem of Sunitinib by improving its selectivity. Recently, a proteomic study of a Sunitinib analog, SU6668 found that SU6668 inhibits, among other proteins, AMPK (Godl et al, *Cancer Res* **2005**, 65, 6919). Since AMPK is a key sensor of fuel and energy status in skeletal muscle (see review by Hardie and Sakamoto, *Physiology* **2006**, 21, 48-60), it is hypothesized that inhibition of AMPK might be the cause of the clinically observed fatigue toxicity of Sunitinib. Thus, the cyclic derivatives of Sunitinib are designed to reduce the inhibitory activity of AMPK, thereby alleviating the fatigue problem of Sunitinib

SUMMARY

The invention relates to heterocyclic compounds, compositions comprising the compounds, and methods of using the compounds and compound compositions. The

compounds and compositions comprising them are useful for treating disease or disease symptoms, including those mediated by or associated with kinase enzymes.

In one aspect is a compound of formula (I) or pharmaceutical salt, solvate or hydrate thereof:



I

wherein Cy is a cyclic structure that can be cycloalkyl, heterocyclic, aryl, or heteroaryl, each optionally substituted with Z_1, Z_2 and Z_3;

R_1, R_2, R_3, R_4, and R_5 are each independently:

(1) hydrogen or R_6, where R_6, is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with Z_1, Z_2 and one or more (preferably, one or two) groups Z_3;

(2) –OH or $-OR_6$;

(3) –SH or $-SR_6$;

(4) $-C(O)_2H$, $-C(O)_qR_6$, $-C(O)NR_7R_8$, $-C(O)C(O)NR_7R_8$, or $-O-C(O)_qR_6$, where q is 1 or 2;

(5) $-SO_3H$, $-S(O)_qR_6$, or $-S(O)_qNR_7R_8$;

(6) halo;

(7) cyano;

(8) nitro;

(9) $-Z_4-NR_7R_8$;

(10) $-Z_4-N(R_9)-Z_5-NR_{10}R_{11}$;

(11) $-Z_4-N(R_{12})-Z_5-R_6$;

(12) $-P(O)(OR_6)_2$;

R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are each independently:

(1) hydrogen or R_6;

(2) R_7 and R_8 together with the nitrogen atom to which they are attached may be a heterocycle which is unsubstituted or substituted with Z_1, Z_2 and Z_3; or

(3) any two of R_9, R_{10} and R_{11} together with the nitrogen atoms to which they are attached may be a 3- to 12-membered saturated or unsaturated mono-, bi-, or tri- heterocyclic ring which is unsubstituted or substituted with Z_1, Z_2 and Z_3;

Z_1, Z_2 and Z_3 are each independently:

(1) hydrogen or Z_6, where Z_6 is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (13);

(2) –OH or $-OZ_{16}$;

(3) –SH or $-SZ_{16}$;

(4) $-C(O)_2H$, $C(O)_qZ_{16}$, $-C(O)NZ_{17}Z_{18}$, $-C(O)C(O)NZ_{17}Z_{18}$, or $-O-C(O)_qZ_{16}$, where q is 1 or 2;

(5) $-SO_3H$, $-S(O)_qZ_{16}$, or $-S(O)_qNZ_{17}Z_{18}$;

(6) halo;

(7) cyano;

(8) nitro;

(9) $-Z_4-NZ_{17}Z_{18}$;

(10) $-Z_4-N(Z_{18})-Z_5-NZ_{19}Z_{20}$;

(11) oxo;

(12) $-O-C(O)-Z_{16}$;

(13) any two of Z_1, Z_2, and Z_3 may together be alkylene, alkenylene, aryl, heteroaryl, or heterocyclo completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z_4 and Z_5 are each independently

(1) a single bond;

(2) $-Z_{11}-S(O)_q-Z_{12}-$;

(3) $-Z_{11}-C(O)-Z_{12}-$;

(4) $-Z_{11}-O-Z_{12}-$;

(5) $-Z_{11}-S-Z_{12}-$;

(6) $-Z_{11}-O-C(O)-Z_{12}-$; or

(7) $-Z_{11}-C(O)-O-Z_{12}$;

Z_{11} and Z_{12} are each independently

(1) a single bond;

(2) alkylene;

(3) alkenylene; or

(4) alkynylene;

each Z_{16} is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl, each optionally substituted with one or more of the following groups:

(2) $-OH$ or $-OZ_{21}$;

(3) $-SH$ or $-SZ_{21}$;

(4) $-C(O)_2H$, $C(O)_qZ_{21}$, $-C(O)NZ_{17}Z_{18}$, $-C(O)C(O)NZ_{17}Z_{18}$, or $-O-C(O)_qZ_{21}$, where q is 1 or 2;

(5) $-SO_3H$, $-S(O)_qZ_{21}$, or $-S(O)_qNZ_{17}Z_{18}$;

(6) halo;

(7) cyano;

(8) nitro;

(9) $-Z_4-NZ_{17}Z_{18}$;

(10) $-Z_4-N(Z_{18})-Z_5-NZ_{19}Z_{20}$;

(11) oxo;

(12) $-O-C(O)-Z_{21}$;

each Z_{17} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl;

each Z_{18} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl;

each Z_{19} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl;

each Z_{20} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl;

each Z_{21} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; each Z_{22} is independently is,

(2) –OH or $-OZ_{21}$;

(3) –SH or $-SZ_{21}$;

(4) $-C(O)_2H$, $C(O)_qZ_{21}$, $-C(O)NZ_{21}Z_{21}$, $-C(O)C(O)NZ_{21}Z_{21}$, or $-O-C(O)_qZ_{21}$, where q is 1 or 2;

(5) $-SO_3H$, $-S(O)_qZ_{21}$, or $-S(O)_qNZ_{21}Z_{21}$;

(6) halo;

(7) cyano;

(8) nitro;

(9) $-Z_4-NZ_{21}Z_{21}$;

(10) $-Z_4-N(Z_{21})-Z_5-NZ_{21}Z_{21}$;

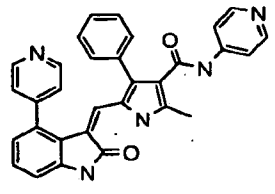
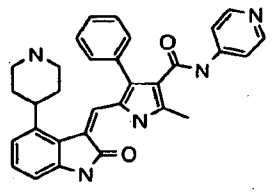
(11) oxo;

(12) $-O-C(O)-Z_{21}$;

where Z_{17} and Z_{18}, or Z_{19} and Z_{20}, together with the nitrogen atom to which they are attached may be a heterocycle which is unsubstituted or substituted with 1, 2, or 3 independent Z_{22}; and

where any two of Z_{18}, Z_{19} or Z_{20} together with the nitrogen atoms to which they are attached may be a 3- to 12-membered saturated or unsaturated mono-, bi-, or tri- heterocyclic ring which is unsubstituted or substituted with 1, 2, or 3 independent Z_{22};

provided said compound is other than a compound of formula IIa or IIb.

IIa  IIb 

Another aspect is the compound of formula (I), or pharmaceutical salt, solvate or hydrate thereof, wherein:

R_1, R_2, R_3, R_4, and R_5 are each independently:

(1) hydrogen or R_6, where R_6, is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with Z_1, Z_2 and one or more (preferably, one or two) groups Z_3;

(2) –OH or $–OR_6$;

(3) –SH or $–SR_6$;

(4) $–C(O)_2H$, $–C(O)_qR_6$, $–C(O)NR_7R_8$, or $–O–C(O)_qR_6$, where q is 1 or 2;

(5) $–SO_3H$, $–S(O)_qR_6$, or $–S(O)_qNR_7R_8$;

(6) halo;

(7) cyano;

(8) nitro;

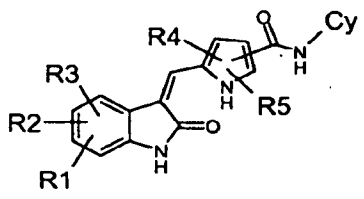
(9) $–Z_4\text{-}NR_7R_8$;

(10) $–Z_4–N(R_9)–Z_5–NR_{10}R_{11}$;

(11) $–Z_4–N(R_{12})–Z_5–R_6$;

(12) $–P(O)(OR_6)_2$.

In one aspect is a compound of formula (I) or pharmaceutical salt, solvate or hydrate thereof:

I 

wherein Cy is a cyclic structure that can be cycloalkyl, heterocyclic, aryl, or heteroaryl, each optionally substituted with Z_1, Z_2 and Z_3;

R_1, R_2, R_3, R_4, and R_5 are each independently:

(1) hydrogen or R_6, where R_6, is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with Z_1, Z_2 and one or more (preferably, one or two) groups Z_3;

(2) –OH or $–OR_6$;

(3) –SH or $–SR_6$;

(4) $–C(O)_2H$, $–C(O)_qR_6$, $–C(O)NR_7R_8$, or $–O–C(O)_qR_6$, where q is 1 or 2;

(5) $–SO_3H$, $–S(O)_qR_6$, or $–S(O)_qNR_7R_8$;

(6) halo;

(7) cyano;

(8) nitro;

(9) $–Z_4\text{-}NR_7R_8$;

(10) $–Z_4–N(R_9)–Z_5–NR_{10}R_{11}$;

(11) $–Z_4–N(R_{12})–Z_5–R_6$;

(12) $–P(O)(OR_6)_2$;

R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are each independently:

(1) hydrogen or R_6;

(2) R_7 and R_8 together with the nitrogen atom to which they are attached may be a heterocycle which is unsubstituted or substituted with Z_1, Z_2 and Z_3; or

(3) any two of R_9, R_{10} and R_{11} together with the nitrogen atoms to which they are attached may be a 3- to 12-membered saturated or unsaturated mono-, bi-, or tri- heterocyclic ring which is unsubstituted or substituted with Z_1, Z_2 and Z_3;

Z_1, Z_2 and Z_3 are each independently:

(1) hydrogen or Z_6, where Z_6 is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups

(i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (13) of the definition of Z_1, Z_2 and Z_3;

(2) –OH or –OZ_6;

(3) –SH or –SZ_6;

(4) –$C(O)_2H$, $C(O)_qZ_6$, –$C(O)NZ_7Z_8$, or –O–$C(O)_qZ_6$, where q is 1 or 2;

(5) –SO_3H, –$S(O)_qZ_6$, or –$S(O)_qNZ_7Z_8$;

(6) halo;

(7) cyano;

(8) nitro;

(9) –Z_4-NZ_7Z_8;

(10) –Z_4–$N(Z_8)$ –Z_5–NZ_9Z_{10};

(11) oxo;

(12) –O-C(O)-Z_6;

(13) any two of Z_1, Z_2, and Z_3 may together be alkylene, alkenylene, aryl, heteroaryl, or heterocyclo completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z_4 and Z_5 are each independently

(1) a single bond;

(2) –Z_{11}-$S(O)_q$-Z_{12}-;

(3) –Z_{11}-C(O)-Z_{12}-;

(4) –Z_{11}-O-Z_{12}-;

(5) –Z_{11}-S-Z_{12}-;

(6) –Z_{11}-O-C(O)-Z_{12}-; or

(7) –Z_{11}-C(O)-O-Z_{12};

Z_7, Z_8, Z_9 and Z_{10} are each independently:

(1) hydrogen or Z_6;

(2) Z_7 and Z_8, or Z_9 and Z_{10}, together with the nitrogen atom to which they are attached may be a heterocycle which is unsubstituted or substituted with Z_1, Z_2 and Z_3; or

(3) any two of Z_8, Z_9 or Z_{10} together with the nitrogen atoms to which they are attached may be a 3- to 12-membered saturated or unsaturated mono-, bi-, or tri- heterocyclic ring which is unsubstituted or substituted with Z_1, Z_2 and Z_3;

Z_{11} and Z_{12} are each independently

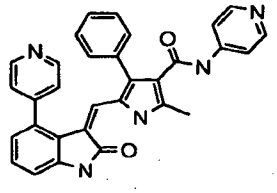
(1) a single bond;

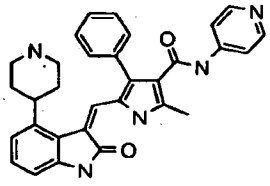
(2) alkylene;

(3) alkenylene; or

(4) alkynylene;

provided said compound is other than a compound of formula IIa or IIb.

IIa 

IIb 

In other aspects, the compounds are those of any of the formulae herein (including any combinations thereof):

wherein Cy is a non-aromatic cycloalkyl or heterocyclic structure that is optionally substituted with Z_1, Z_2 and Z_3;

wherein Cy is a heterocyclic structure that is optionally substituted with Z_1, Z_2 and Z_3.;

wherein any R_1, R_2 or R_3 in the 4-indolinone position is not a heterocycle or heteroaryl group;

wherein the Cy is optionally substituted cycloalkyl;

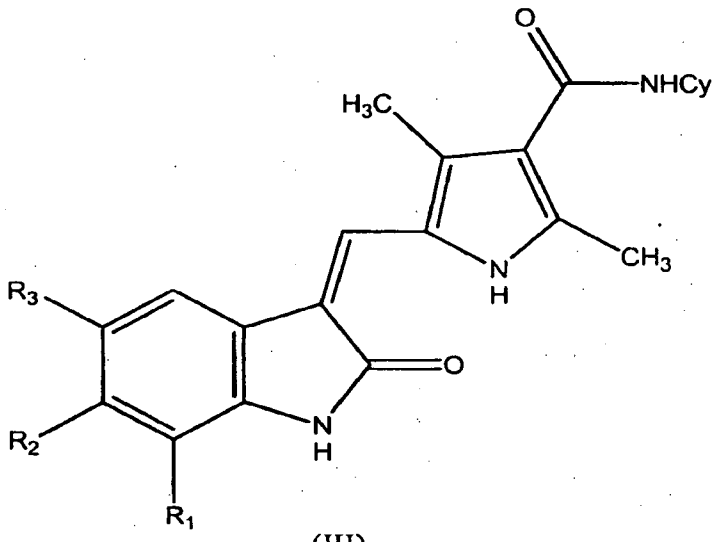
wherein the Cy is optionally substituted 5-membered ring heterocyclic;

wherein the Cy is optionally substituted 6-membered ring heterocyclic;

wherein the Cy is optionally substituted heteroaryl; and

wherein the compound of formula I is a compound delineated in any of the tables herein, or pharmaceutical salt, solvate or hydrate thereof.

Another aspect is a compound (or pharmaceutical salt, solvate or hydrate thereof) having the structure of formula III:



(III)

wherein R_1, R_2, R_3, and Cy are as defined herein, including in formula (I).

Other aspects of formula (III) are those: wherein R_3 is halo; wherein R_3 is fluoro; and wherein R_1 and R_2 are H, and R_3 is fluoro.

In another aspect, the invention relates to a method of treating a disease or disease symptom in a subject in need thereof including administering to the subject an effective amount of a compound of any formulae herein, or pharmaceutical salt, solvate or hydrate thereof (or composition thereof). The disease or disease symptom can be any of those modulated by a kinase enzyme (e.g., VEGFR, PDGFR, KIT, Flt-3, RET). The disease or disease symptom can be cancer, including for example renal cell carcinoma and GI stroma tumor, tumor or proliferative disorder.

In another aspect, the invention relates to a method of modulating (e.g., inhibiting, antagonism, agonism) kinase activity including contacting a kinase with a compound of any of the formulae herein or pharmaceutical salt, solvate or hydrate thereof (or composition thereof).

In another aspect, the invention relates to a method of making a compound of formula I herein, including reacting an intermediate delineated herein with a reagent to provide a compound of formula I as defined herein.

In another aspect, the invention relates to a composition including a compound of any of the formulae herein, or pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier. The composition can further include an additional therapeutic agent.

In another aspect, the invention relates to a method of modulating a growth factor receptor (e.g. VEGFR, PDGFR, KIT, Flt-3, RET) activity in a subject in need thereof including administering to the subject an effective amount of a compound of any of the formulae herein, or pharmaceutical salt thereof (or composition thereof).

In other aspects, the invention relates to a composition comprising a compound of any of the formulae herein, an additional therapeutic agent, and a pharmaceutically acceptable carrier. The additional therapeutic agent can be an anticancer agent, antitumor agent, antiproliferative agent, or any other agent typically administered as a primary or adjuvant agent in cancer treatment protocols (e.g., antinausea, antianemia, etc.).

Yet another aspect of this invention relates to a method of treating a subject (e.g., mammal, human, horse, dog, cat) having a disease or disease symptom (including, but not limited to) that is or is associated with cancer, tumor(s), proliferative disorders, etc. The method includes administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

Yet another aspect of this invention relates to a method of treating a subject (e.g., mammal, human, horse, dog, cat) having a kinase-mediated disease or disease symptom (including, but not limited to cancer, tumor, proliferative disorder, etc). The

method includes administering to the subject (including a subject identified as in need of such treatment) an effective amount of a compound described herein, or a composition described herein to produce such effect. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

The methods of treatment include aspects where adverse side effects are minimized or non-existent. In one aspect the compound selectively inhibits a kinase target preferentially over inhibition of AMPK; in another aspect the compound selectively inhibits a kinase target preferentially over inhibition of AMPK with greater selectivity than Sunitinib; in another aspect the subject experiences little or no fatigue side effect.

Another aspect is a method of identifying a kinase inhibitor that selectively inhibits a kinase target preferentially over inhibition of AMPK comprising: (i) assaying a test compound for inhibition of a kinase enzyme; (ii) assaying the test compound for inhibition of AMPK; (iii) assessing whether the test compound inhibits a kinase target preferentially over inhibition of AMPK. Other aspects are the method wherein the test compound inhibits a kinase target preferentially over inhibition of AMPK with greater selectivity than Sunitinib.

Another aspect is a method of treating a disease or disease symptom in a subject in need thereof comprising administering to the subject an effective amount of a compound identified by the method above, or pharmaceutical salt, solvate or hydrate thereof.

The invention also relates to a method of making a compound described herein, the method including any reactions or reagents as delineated in the schemes or examples herein. Alternatively, the method includes taking any one of the intermediate compounds described herein and reacting it with one or more chemical reagents in one or more steps to produce a compound described herein.

Also within the scope of this invention is a packaged product. The packaged product includes a container, one of the aforementioned compounds in the container,

and a legend (e.g., a label or an insert) associated with the container and indicating administration of the compound for treating a disorder associated with kinase modulation (e.g., cancer, tumor, proliferative disorder, etc.).

Another aspect of the invention is a compound of the invention for use in the treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein.

Another aspect of the invention is the use of a compound of the invention in the manufacture of a medicament for treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein.

In other embodiments, the compounds, compositions, and methods delineated herein are any of the compounds of the tables herein or methods including them.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

As used herein, the term "halo" or "halogen" refers to any radical of fluorine, chlorine, bromine or iodine.

The terms "alk" or "alkyl" refer to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. The expression "lower alkyl" refers to alkyl groups of 1 to 4 carbon atoms (inclusive). The term "arylalkyl" refers to a moiety in which an alkyl hydrogen atom is replaced by an aryl group. The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one double bond. Where an alkenyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a double bond.

The term "alkoxy" refers to an -O-alkyl radical. The term "alkylenedioxo" refers to a divalent species of the structure -O-R-O-, in which R represents an alkylene.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one triple bond. Where an

alkynyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a triple bond.

The term "alkylene" refers to a divalent straight chain bridge of 1 to 5 carbon atoms connected by single bonds (e.g., $-(CH_2)_x-$, wherein x is 1 to 5), which may be substituted with 1 to 3 lower alkyl groups.

The term "alkenylene" refers to a straight chain bridge of 2 to 5 carbon atoms having one or two double bonds that is connected by single bonds and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkenylene groups are -CH=CH-CH=CH-, $-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-C(CH_3)_2CH=CH-$ and $-CH(C_2H_5)-CH=CH-$.

The term "alkynylene" refers to a straight chain bridge of 2 to 5 carbon atoms that has a triple bond therein, is connected by single bonds, and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkynylene groups are –CC-, $-CH_2-CC-$, $-CH(CH_3)-CC-$ and $-CC-CH(C_2H_5)CH_2-$.

The terms "cycloalkyl" and "cycloalkenyl" as employed herein includes saturated and partially unsaturated cyclic, respectively, hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbon.

The terms "Ar" or "aryl" refer to aromatic cyclic groups (for example 6 membered monocyclic, 10 membered bicyclic or 14 membered tricyclic ring systems) which contain 6 to 14 carbon atoms. Exemplary aryl groups include phenyl, naphthyl, biphenyl and anthracene.

The terms "heterocycle", "heterocyclic" or "heterocyclo" refer to fully saturated or partially unsaturated cyclic groups, for example, 3 to 7 membered monocyclic, 7 to 12 membered bicyclic, or 10 to 15 membered tricyclic ring systems, which have at least one heteroatom in at least one ring, wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system.

"Heteroaryl" refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group of 5 to 12 ring atoms containing one, two, three or four

ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, and, in addition, having a completely conjugated pi-electron system, wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent.. Examples, without limitation, of heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, quinazoline, isoquinoline, purine and carbazole.

The term "oxo" refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

The term "acyl" refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted by substituents.

The term "substituents" refers to a group "substituted" on any functional group delineated herein, e.g., alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, or heteroaryl group at any atom of that group. Suitable substituents include, without limitation halogen, CN, NO_2, OR^{15}, SR^{15}, $S(O)_2OR^{15}$, $NR^{15}R^{16}$, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^{15}$, $C(O)NR^{15}R^{16}$, $OC(O)NR^{15}R^{16}$, $NR^{15}C(O)NR^{15}R^{16}$, $C(NR^{16})NR^{15}R^{16}$, $NR^{15}C(NR^{16})NR^{15}R^{16}$, $S(O)_2NR^{15}R^{16}$, R^{17}, $C(O)R^{17}$, $NR^{15}C(O)R^{17}$, $S(O)R^{17}$, $S(O)_2R^{17}$, R^{16}, oxo, $C(O)R^{16}$, $C(O)(CH_2)nOH$, $(CH_2)nOR^{15}$, $(CH_2)nC(O)NR^{15}R^{16}$, $NR^{15}S(O)_2R^{17}$, where n is independently 0-6 inclusive. Each R^{15} is independently hydrogen, C_1-C_4 alkyl or C_3-C_6 cycloalkyl. Each R^{16} is independently hydrogen, C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each R^{17} is independently C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl and C_1-C_4 alkyl in each R^{15}, R^{16} and R^{17} can optionally be substituted with halogen, CN, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, or 1,2-methylenedioxy.

In one aspect, the substituents on a group are independently, hydrogen, hydroxyl, halogen, nitro, SO_3H, trifluoromethyl, trifluoromethoxy, alkyl (C1-C6

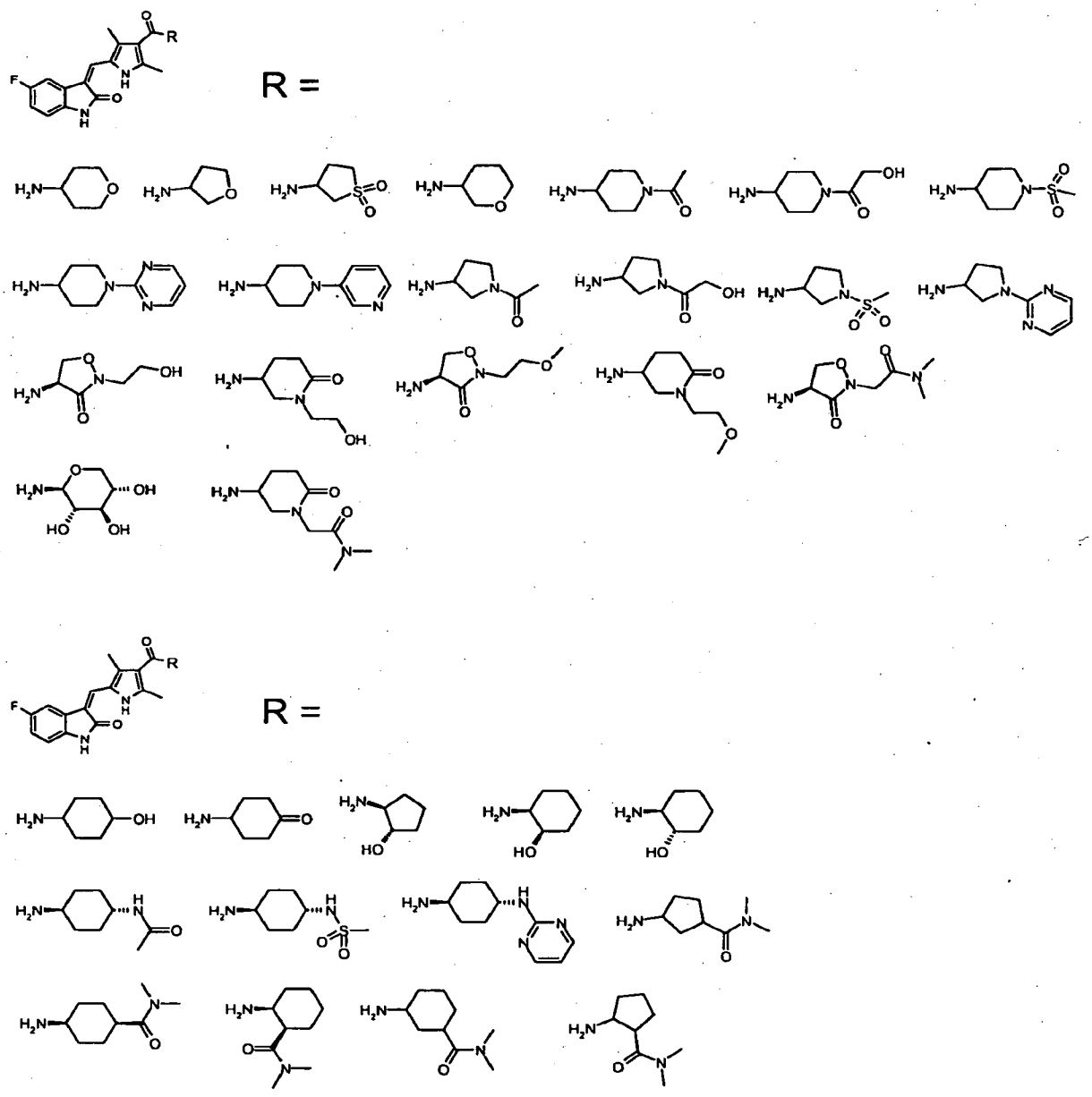
straight or branched), alkoxy (C1-C6 straight or branched), O-benzyl, O-phenyl, phenyl, 1,2-methylenedioxy, carboxyl, morpholinyl, piperidinyl, amino or $OC(O)NR^{15}R^{16}$. Each R^{15} and R^{16} is as described above.

The term "treating" or "treated" refers to administering a compound described herein to a subject with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect a disease, the symptoms of the disease or the predisposition toward the disease.

"An effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

Representative compounds useful in the compositions and methods are delineated herein:

TABLE 1



The Table 1 compounds also include the following:

5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-acetyl-piperidin-4-yl)-amide,

5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-methanesulfonyl-piperidin-4-yl)-amide,

N-(2H-3,4,5,6-tetrahydropyran-4-yl){5-[(5-fluoro-2-oxo(1H-benzo [d]azolin-3- ylidene)) methyl]-2,4-dimethylpyrrol-3-yl}carboxamide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid piperidin-4-ylamide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-acetyl-pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-methanesulfonyl-pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1,1-dioxo-tetrahydro-thiophen-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-pyrimidin-2-yl-piperidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-hydroxy- 1,1-dioxo-tetrahydro-thiophen-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1,1-dioxo- hexahydro-thiopyran-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-6-oxo- piperidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((2S,3S,4R,5S,6S)- 3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-hydroxy-acetyl)- piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-hydroxy- acetyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-hydroxy-tetrahydro- furan-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-2-oxo- pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-benzyl-4-hydroxy- pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-acetyl-4-hydroxy- pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-dimethylaminooxalyl- piperidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-dimethylaminooxalyl- pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((2S,3S,4R,5S)-3,4- dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1- carbamoylmethyl-2-oxo-pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-hydroxy- ethyl)-2-oxo-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-hydroxy- ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-dimethylcarbamoylmethyl-3-oxo-isoxazolidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-ethyl-3-oxo- isoxazolidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-carbamoylmethyl- 3-oxo-isoxazolidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-methoxy- ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-3-oxo-2-pyridin- 3-ylmethyl-isoxazolidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2- (tetrahydro-pyran-4-yl)-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2- (tetrahydro-furan-3-yl)-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(morpholine-4- carbonyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(morpholine- 4-carbonyl)-pyrrolidin-3-yl]-amide,

4-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-piperidine- 1-carboxylic acid dimethylamide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1- dimethylcarbamoyl-pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-methoxy- acetyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy-acetyl)-pyrrolidin-3-yl]-amide,

N-((3R)oxolan-3-yl){5-[(5-fluoro-2-oxo(1H-benzo[d] azolin-3-ylidene))methyl]-2,4-dimethylpyrrol-3-yl}carboxamide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-morpholin- 4-yl-ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy- ethyl)-2-oxo-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-2-oxo-1-pyridin- 4-ylmethyl-pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2- (tetrahydro-pyran-4-ylmethyl)-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy- ethyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-methoxy- ethyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-dimethylamino- acetyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-dimethylamino-acetyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-hydroxy- ethyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-hydroxy- ethyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (6'-methyl-3,4,5,6- tetrahydro-2H-[1,3']bipyridinyl-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(6-methyl- pyridin-3-yl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2-oxo-1- (tetrahydro-pyran-4-ylmethyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2- methanesulfonyl-ethyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methanesulfonyl-ethyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-methanesulfonyl-ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2-(2-methoxy- ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-ethoxy- ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy- ethyl)-2,5-dioxo-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2- (tetrahydro-furan-3-ylmethyl)-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2- (tetrahydro-furan-2-ylmethyl)-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2,5-dioxo- 1-(tetrahydro-pyran-4-ylmethyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2,5-dioxo-1- (tetrahydro-pyran-4-yl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-dimethylcarbamoyl-2-oxo-pyrrolidin-3-yl)-amide.

The Table 1 compounds also include the following:

5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-hydroxy-cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-amino-cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-oxo-cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclopentyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((1S,2R)-2-hydroxy-cyclopentyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-acetylamino-cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-methanesulfonylamino-cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((1S,2S)-2-hydroxy- cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [4-(morpholine-4- carbonyl)-cyclohexyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [4-(pyrrolidine-1- carbonyl)-cyclohexyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [4-(aziridine-1- carbonyl)-cyclohexyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,3S)-3-(pyrrolidine-1- carbonyl)-cyclopentyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,3S)-3- (morpholine-4- carbonyl)-cyclopentyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,3S)-3- (aziridine-1-carbonyl)-cyclopentyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,2S)-2- (pyrrolidine-1-carbonyl)-cyclopentyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,2S)-2- (morpholine-4-carbonyl)-cyclopentyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,2S)-2- (aziridine-1-carbonyl)-cyclopentyl]-amide.

In the structures in the table above, the attachment of the R group is via the amino nitrogen atom depicted as "NH_2" and thus is meant that moiety attached to the depicted carbonyl group as an "-N-cyclic group" where the cyclic group is cycloalkyl, cycloalkenyl, heterocyclo (any of which may be substituted).

Kinase-modulating compounds can be identified through both *in vitro* (e.g., cell and non-cell based) and *in vivo* methods. Representative examples of these methods are described in the Examples herein.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

The compounds delineated herein can be synthesized using conventional methods, as illustrated in the schemes herein. In the schemes herein, unless expressly to the contrary, variables in chemical formulae correspond to similar positions as defined in other formulae herein.

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, 2nd. Ed., Wiley-VCH Publishers (1999); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd. Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1999); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of these compounds are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein. All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

As used herein, the compounds of this invention, including the compounds of formulae described herein, and are in embodiments intended to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of

the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species. Preferred prodrugs include derivatives where a group which enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein. See, e.g., Alexander, J. et al. *Journal of Medicinal Chemistry* **1988**, *31*, 318-322; Bundgaard, H. *Design of Prodrugs*; Elsevier: Amsterdam, 1985; pp 1-92; Bundgaard, H.; Nielsen, N. M. *Journal of Medicinal Chemistry* **1987**, *30*, 451-454; Bundgaard, H. *A Textbook of Drug Design and Development*; Harwood Academic Publ.: Switzerland, 1991; pp 113-191; Digenis, G. A. et al. *Handbook of Experimental Pharmacology* **1975**, *28*, 86-112; Friis, G. J.; Bundgaard, H. *A Textbook of Drug Design and Development*; 2 ed.; Overseas Publ.: Amsterdam, 1996; pp 351-385; Pitman, I. H. *Medicinal Research Reviews* **1981**, *1*, 189-214; Sinkula, A. A.; Yalkowsky. *Journal of Pharmaceutical Sciences* **1975**, *64*, 181-210; Verbiscar, A. J.; Abood, L. G *Journal of Medicinal Chemistry* **1970**, *13*, 1176-1179; Stella, V. J.; Himmelstein, K. J. *Journal of Medicinal Chemistry* **1980**, *23*, 1275-1282; Bodor, N.; Kaminski, J. J. *Annual Reports in Medicinal Chemistry* **1987**, *22*, 303-313.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the

invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(alkyl)$_4^+$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The compounds of the formulae described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is

retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

The compositions delineated herein include the compounds of the formulae delineated herein, as well as additional therapeutic agents if present, in amounts effective for achieving a modulation of disease or disease symptoms, including kinase-mediated disorders or symptoms thereof. References which include examples of additional therapeutic agents are: 1) *Burger's Medicinal Chemistry & Drug Discovery* 6th edition, by Alfred Burger, Donald J. Abraham, ed., Volumes 1 to 6, Wiley Interscience Publication, NY, 2003. Additional therapeutic agents include but are not limited to agents for treatment of diseases, disorders or symptoms thereof including for example, anticancer agents, antiproliferative agents, antineoplastic agents, antitumor agents, antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents, alkylating-type antineoplastic agents, antibiotic-type antineoplastic agents, or, any other agent typically administered as a primary or adjuvant agent in cancer treatment protocols (e.g., antinausea, antianemia, etc.), including for example, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, tamoxifen, toremifen, raloxifene, droloxifene, iodoxyfene, megestrol acetate, anastrozole, letrazole, borazole, exemestane, flutamide, nilutamide, bicalutamide, cyproterone acetate, goserelin acetate, luprolide, finasteride, herceptin, methotrexate, 5-fluorouracil, cytosine arabinoside, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, cisplatin, carboplatin, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotephan, vincristine, taxol, taxotere, etoposide, teniposide, amsacrine, irinotecan, topotecan, an epothilone, Iressa, Avastin, OSI-774, angiogenesis inhibitors, EGF inhibitors, MEK inhibitors, VEGF inhibitors, CDK inhibitors, Her1 and Her2 inhibitors and monoclonal antibodies.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to,

ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. 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-butanediol. Among the acceptable vehicles and solvents

that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, 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. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active

components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

A composition having the compound of the formulae herein and an additional agent (e.g., a therapeutic agent) can be administered using an implantable device. Implantable devices and related technology are known in the art and are useful as delivery systems where a continuous, or timed-release delivery of compounds or compositions delineated herein is desired. Additionally, the implantable device delivery system is useful for targeting specific points of compound or composition delivery (e.g., localized sites, organs). Negrin et al., Biomaterials, 22(6):563 (2001). Timed-release technology involving alternate delivery methods can also be used in this invention. For example, timed-release formulations based on polymer technologies, sustained-release techniques and encapsulation techniques (e.g., polymeric, liposomal) can also be used for delivery of the compounds and compositions delineated herein.

Also within the invention is a patch to deliver active chemotherapeutic combinations herein. A patch includes a material layer (e.g., polymeric, cloth, gauze, bandage) and the compound of the formulae herein as delineated herein. One side of the material layer can have a protective layer adhered to it to resist passage of the compounds or compositions. The patch can additionally include an adhesive to hold

the patch in place on a subject. An adhesive is a composition, including those of either natural or synthetic origin, that when contacted with the skin of a subject, temporarily adheres to the skin. It can be water resistant. The adhesive can be placed on the patch to hold it in contact with the skin of the subject for an extended period of time. The adhesive can be made of a tackiness, or adhesive strength, such that it holds the device in place subject to incidental contact, however, upon an affirmative act (e.g., ripping, peeling, or other intentional removal) the adhesive gives way to the external pressure placed on the device or the adhesive itself, and allows for breaking of the adhesion contact. The adhesive can be pressure sensitive, that is, it can allow for positioning of the adhesive (and the device to be adhered to the skin) against the skin by the application of pressure (e.g., pushing, rubbing,) on the adhesive or device.

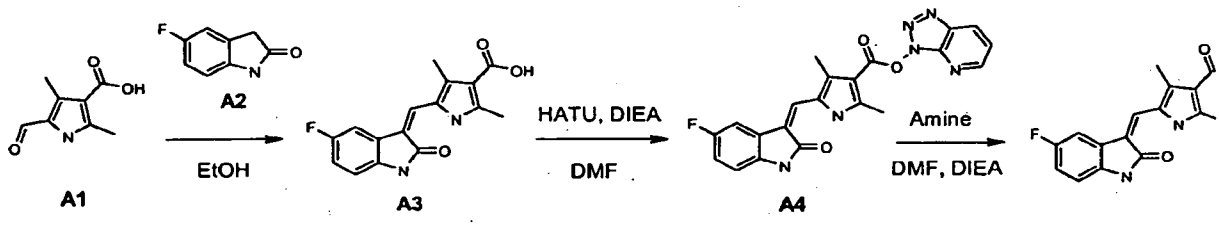
When the compositions of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

The invention will be further described in the following examples. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

Examples

The general procedure for the preparation of many examples is shown below:



Step 1: A mixture of 5-fluoro-1,3-dihydroindol-2-one (**A2**) (20g, 132mmol), 5-formyl-2,4-dimethylpyrrole-3-carboxylic acid (**A1**) (21.1g, 126mmol), pyrrolidine (5ml) and absolute ethanol (400mL) were heated to reflux for 3 hours. Then the mixture was cooled to room temperature and the solid was collected by filtration, washed with ethanol (100mL). The solid was stirred in ethanol (350ml) at reflux for 0.5h again. The mixture was cooled to room temperature and the solid was collected by filtration, washed with ethanol (100ml) and dried under vacuum overnight to give (Z)-5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (**A3**) (35.3g, 93%) as orange solid. LC-MS observed $[M-H]^+$: 299.2.

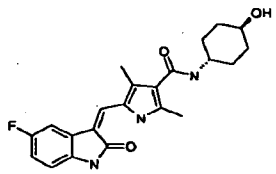
Step 2: (Z)-5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-

carboxylic acid (**A3**) (5g, 16.7mmol) was suspended in DMF (25mL) with stirring for 5 min. DIEA (4.4mL, 25mmol) was then added and the mixture was stirred for 10 min. HATU (6.32g, 16.6mmol) was added and the reaction mixture was stirred at room temperature for several hours. LC/MS was used to detect the completion of the reaction. Most DMF was evaporated under vacuum and the residue was suspended in ACN and stirred for another 30 min. The solid was collected via filtration and washed with ACN, dried under vacuum to provide (Z)-3H-[1,2,3] triazolo[4,5-b]pyridin-3-yl-5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (**A4**) (5.36g, 77%). LC-ESIMS observed $[M-H]^+$: 417.3.

Step 3: To the solution of (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-((5-fluoro-2-oxoindolin -3-ylidene) methyl)-2,4- dimethyl-1H-pyrrole-3-carboxylate (**A4**) (1.0 eq) in DMF solution was added the appropriate amine (1.2 eq) and DIEA (2.0 eq). The reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. After removal of most

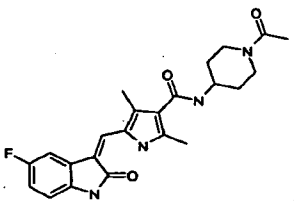
DMF under vacuum the mixture was precipitated with 5% diethylamine/methanol (25mL) with stirring. The solid was collected by filtration and washed with methanol (5mL) for several times, dried under high vacuum to provide the final compound (40-85% yields).

Example 1: Preparation of 5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-hydroxy-cyclohexyl)-amide



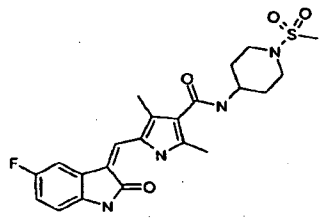
Following the general procedure, an orange solid was obtained (162mg, 86% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.64(s, 1H), 10.86(s, 1H), 7.72-7.77(dd, 1H), 7.70(s, 1H), 7.45-7.47(d, 1H), 6.81-6.95(m, 2H), 4.52-4.53(d, 1H), 3.66-3.68(m, 1H), 3.36-3.39(m, 1H), 2.38-2.40(ds, 6H), 1.82-1.86(d, 4H), 1.23-1.34(m, 4H). LC/MS: 398.3 $[M+H]^+$.

Example 2: Preparation of 5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-acetyl-piperidin-4-yl)-amide



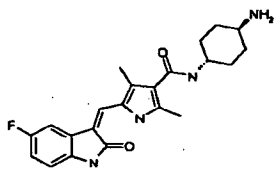
Following the general procedure, an orange solid was obtained (174mg, 83% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.88(s, 1H), 7.74-7.78(dd, 1H), 7.71(s, 1H), 7.59-7.62(d, 1H), 6.81-6.96(m, 2H), 4.23-4.27(d, 1H), 3.96-3.99(m, 1H), 3.76-3.81(m, 1H), 3.11-3.19(m, 1H), 2.70-2.74(m, 1H), 2.39-2.41(ds, 6H), 2.00(s, 3H), 1.77-1.89(m, 2H), 1.31-1.47(m, 2H). LC/MS: 423.4 $[M-H]^+$.

Example 3: Preparation of 5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-methanesulfonyl-piperidin-4-yl)-amide



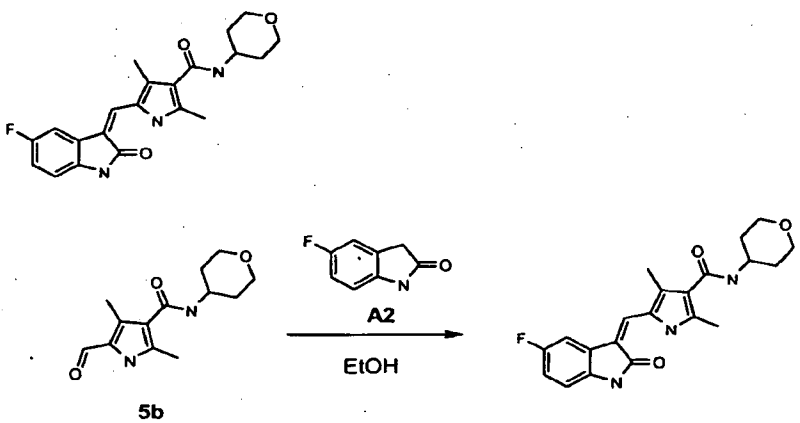
Following the general procedure, an orange solid was obtained (171mg, 77% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.90(s, 1H), 7.67-7.79(m, 3H), 6.83-6.93(m, 2H), 3.89-3.91(m, 1H), 3.51-3.55(d, 2H), 2.85-2.91(m, 5H), 2.27-2.41(ds, 6H), 1.90-1.95(d, 2H), 1.58-1.61(m, 2H). LC/MS: 459.4 $[M-H]^+$.

Example 4: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-amino-cyclohexyl)-amide



Following the general procedure, an orange solid was obtained (121mg, 63% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ = 13.65(s, 1H), 7.70-7.77(m, 2H), 7.44-7.47(d, 1H), 6.81-6.92(m, 2H), 3.62-3.71(m, 1H), 2.38-2.40(ds, 6H), 1.76-1.84(m, 4H), 1.10-1.32(m, 5H). LC/MS: 397.2 $[M+H]^+$.

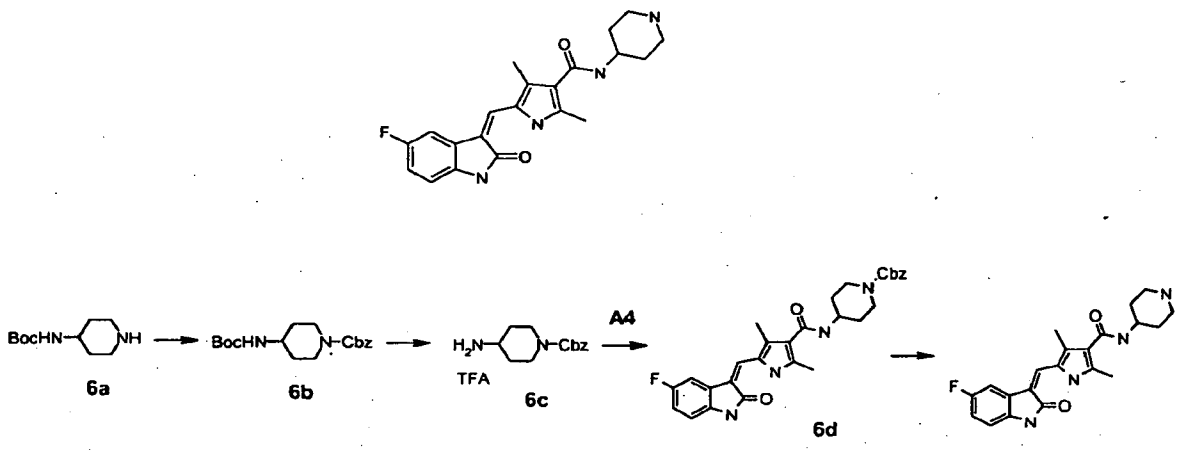
Example 5: Preparation of N-(2H-3,4,5,6-tetrahydropyran-4-yl){5-[(5-fluoro-2-oxo(1H-benzo [d]azolin-3- ylidene)) methyl]-2,4-dimethylpyrrol-3-yl}carboxamide



Step 1: A mixture of 5-formyl-2,4-dimethylpyrrole-3-carboxylic acid (**A1**) (1g, 6.0mmol) in 25 mL of anhydrous DMF was stirred at room temperature while HOBt (1.216g, 9.0mmmol), EDCI (1.726g, 9.0mmol), TEA (3.4mL, 24mmol) and 2H-3,4,5,6-tetrahydropyran-4- ylamine (**5a**) (0.99g, 7.2mmol) were added. The resulting mixture was stirred for 20h at room temperature. Then the reaction mixture was diluted with 3 mL each of H_2O, brine and saturated sodium bicarbonate solution. The pH was adjusted to greater than 10 with 10N aqueous NaOH solution. The mixture was extracted three times with 10 mL of DCM containing 10% methanol. The extracts were combined, dried over anhydrous $MgSO_4$ and evaporated under vacuum. The residue was triturated with mixed solvent of EA:MeOH (5:1, 10 mL). The resulting solid was filtered and dried to provide compound N-(2H-3,4,5,6-tetrahydropyran-4-yl) (5-formyl- 2,4-dimethylpyrrol-3-yl)carboxamide (**5b**) as white solid. (475mg, 32%). LC-MS: 249.3 $[M-H]^+$.

Step 2: A mixture of 2N-(2H-3,4,5,6-tetrahydropyran-4-yl)(5-formyl- 2,4-dimethylpyrrol-3-yl)-carboxamide (**5b**) (200mg, 0.8mmol), 5-fluoroindolin-2-one (**A2**) (126mg, 0.84mmol) and pyrrolidine (two drops) in 10 mL of ethanol were heated to reflux for 3h. The mixture was cooled to room temperature and the solid was collected by filtration and washed with ethanol. The obtained solid was stirred in ethanol (10ml) at reflux for 0.5h again. The mixture was cooled to room temperature and the solid was collected by filtration, washed with ethanol and dried under vacuum to give the title compound (80mg, 26% yield) as orange solid. ^1H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.87(s, 1H), 7.74-7.78(dd, 1H), 7.71(s, 1H), 7.60-6.63 (d, 1H), 6.82-6.96 (m, 2H), 3.83-3.98(m, 3H), 3.38-3.42(m, 2H), 2.40-2.42(ds, 6H), 1.76-1.81(dd, 1H), 1.56-1.59 (m, 2H). LC/MS: 382.4 $[M-H]^+$.

Example 6: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid piperidin-4-ylamide



Step 1: Cbz-Cl (0.938g, 5.5mmol) was added to the solution of compound **6a** (1g, 5mmol) and TEA (0.823mL, 6mmol) in 30mL of DMF. The resulting mixture was stirred at room temperature for 45min., then 30mL of H_2O was added. The mixture was extracted by EA (50mL*3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the filtrate was evaporated under reduced pressure to give a residue, which was purified by column chromatography (EA:PE=1:10) to provide compound **6b** (1.46g, 87%) as white solid, which was used directly to the next step.

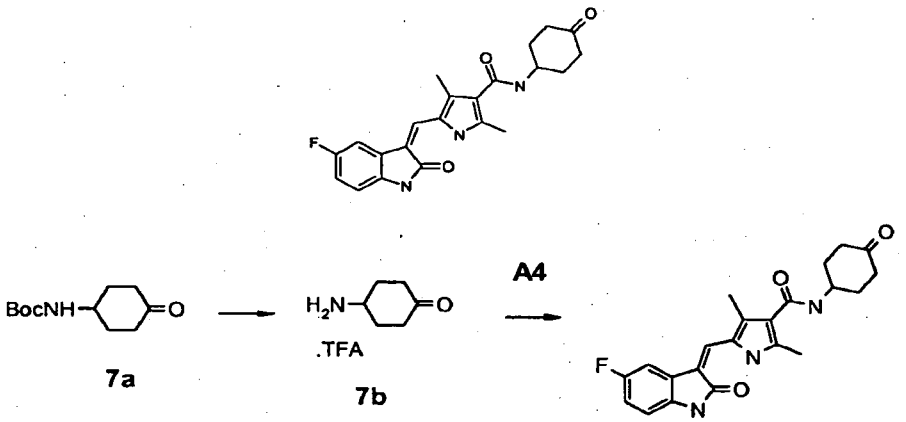
Step 2: Compound **6b** (1.46g, 0.44mmol) was dissolved in 50mL of DCM and 5.76mL of TFA was added. The resulting solution was stirred at room temperature for 2h, evaporated to dryness to provide compound **6c** (1.84g, 99%) which was used directly in the next step.

Steps 3 & 4: To the solution of (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-[(5-fluoro-

2-oxoindolin-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxylate (**A4**) (0.2g, 0.48mmol) in 25 mL of DMF solution was added compound **6c** (0.268g, 0.58mmol). The reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. 200mg of 5% Pd/C was added to the mixture, followed by 25mL of MeOH. The mixture was stirred under H_2 atmosphere for 30min and filtered. The filtrate was evaporated under reduced pressure and the residue was triturated with 5% diethylamine/methanol

(25mL) under sonication. The solid was collected by filtration and washed with methanol (5mL*2), dried under vacuum to provide the title compound (80mg, 43.7% yield) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.89(s, 1H), 7.67-7.78(m, 3H), 6.82-6.96(m, 2H), 3.87-3.92(m,1H), 3.06-3.09(d,2H), 2.72-2.79(t,2H), 2.39-2.41(ds, 6H), 1.84-1.89 (d,6H), 1.46-1.57(m, 2H). LC/MS: 383.1 $[M+H]^+$.

Example 7: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-oxo-cyclohexyl)-amide

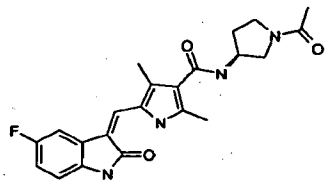


Step 1: Compound **7a** (2.5g, 11.74mmol) was dissolved in 40mL of DCM. 15.3mL of TFA was added slowly. The resulting mixture was stirred at room temperature for 2h, then evaporated to dryness under vacuum to provide crude compound **7b** (2.60g, 98%), which was used directly for the next step.

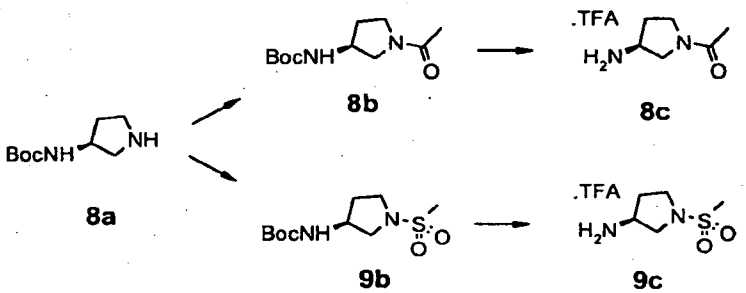
Step 2: To the solution of (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl-5-[(5-fluoro -2-oxoindolin-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3- carboxylate (**A4**) (0.2g, 0.48mmol) in 25mL of DMF solution was added compound **7b** (0.13g, 0.58mmol), the reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (25mL) under sonication. The solid was collected by filtration and washed with methanol (5mL*2), dried under vacuum to provide the title compound (50mg, 26% yield) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.89(s, 1H), 7.70-7.78(m, 3H), 6.82-6.93(m, 2H), 4.21-4.28(m,1H),

2.41-2.49(m, 8H), 2.28-2.31(m,2H), 2.07-2.13(m,2H), 1.76-1.80(m, 2H). LC/MS: 394.3 $[M-H]^+$.

Example 8: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-acetyl-pyrrolidin-3-yl)-amide



Preparation of amines for examples **8** and **9**:



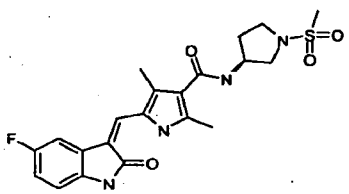
Step 1a: Compound **8a** (0.5g, 2.7mmol) and TEA (0.326g, 3.2mmol) were combined in 5mL of DCM. Acetyl chloride (0.253g, 3.2mmol) was added drop-wise. The resulting mixture was stirred at room temperature for 4h and evaporated under reduced pressure. The residue was dissolved in EA and washed with aqueous 5% $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to provide crude compound **8b** (0.548g, 90%), which was used directly for the next step.

Step 1b: To an ice-bath cooled solution of crude compound **8a** (0.5g, 2.7mmol) and DIEA (1.6g, 12.3mmol) in 20mL of THF was added mesyl chloride (0.54g, 4.7mmol) drop-wise. The mixture was then stirred at room temperature for about 1h, poured into water and extracted with DCM. The combined organic phase was washed with 5% aq. $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, filtered and the filtrate was evaporated under reduced pressure to give the crude compound **9b** (0.654g, 92%), which was used directly for the next step.

Step 2: Compound **8b** or **9b** (1.0 eq.) was dissolved in DCM. TFA (10 eq.) was added slowly. The resulting mixture was stirred at room temperature for 2h, evaporated to dryness under vacuum to provide compound **8c** or **9c**.

Step 3: To the solution of (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (**A4**) (1.0 eq.) and DIEA (2.0eq.) in DMF solution was added compound **8c** (1.2 eq), the reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol under sonication. The solid was collected by filtration and washed with methanol twice, dried under high vacuum to provide the title compound (136mg, 66% yield) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.89(s, 1H), 7.72-7.92(m, 3H), 6.82-6.96(m, 2H), 4.34-4.48(m,1H), 3.25-3.75(m, 4H), 2.39-2.42(ds,6H), 1.86-2.20(m, 6H). LC/MS: 409.3 $[M-H]^+$.

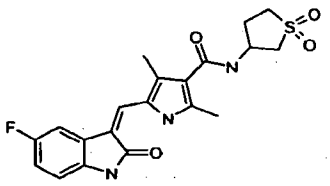
Example 9: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-methanesulfonyl-pyrrolidin-3-yl)-amide



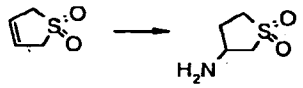
To the solution of (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (**A4**) (1.0 eq.) and DIEA (2.0eq.) in DMF solution was added compound **9c** (1.2 eq), the reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol under sonication. The solid was collected by filtration and washed with methanol twice, dried under high vacuum to provide the title compound (129mg, 61% yield) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.70(s, 1H), 10.90(s, 1H), 7.72-7.90(m,

3H), 6.82-6.96(m, 2H), 4.42-4.48(m,1H), 3.53-3.58(m, 1H), 3.36-3.42(m, 1H), 3.13-3.18(m, 1H), 2.93(s, 3H), 2.41-2.43(ds, 6H), 1.90-2.18(m,3H). LC/MS: 445.4 $[M-H]^+$.

Example 10: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1,1-dioxo-tetrahydro-thiophen-3-yl)-amide



Preparation of 1,1-Dioxo-tetrahydro-thiophen-3-ylamine:

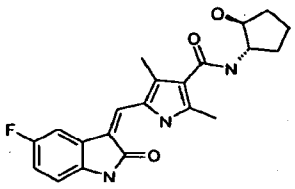


10a **10b**

A solution of compound **10a** (0.5g, 4.2mmol) in 10mL of 26% NH_4OH was heated in a sealed tube at 80°C for 4h. The mixture was concentrated under reduced pressure to yellow oil which was dissolved in 3mL of EtOH and treated with 1mL of concentrated HCl. The mixture was stirred for 0.5h and ethyl ether was added to precipitate the crystalline hydrochloride. The solid was collected by filtration, washed with ether and dried in vacuum to provide compound **10b** (0.533g, 74%).

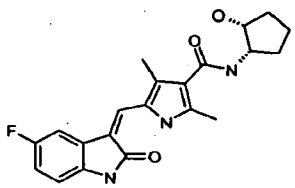
To the solution of (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-[(5-fluoro-2-oxoindolin-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxylate (**A4**) (0.207g, 0.5mmol) and DIEA (0.296g, 2.0 eq.) in 25mL of DMF solution was added compound **10b** (0.162g, 0.94mmol), the reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (10mL) under sonication. The solid was collected by filtration and washed with methanol (5mL) twice, dried under vacuum to provide the title compound as orange solid (181mg, 88% yeild). ^1H NMR (300 MHz, DMSO-d6): δ=13.72(s, 1H), 10.91(s, 1H), 7.97-7.80(d, 1H), 7.73-7.70(m, 2H), 6.82-6.97(m, 2H),4.63-4.65(m, 1H), 3.44-3.51(m, 1H), 3.18-3.29(m, 1H), 3.03-3.10(m, 1H), 2.42-2.50(m, 8H), 2.16-2.23(d,6H). LC/MS: 416.2 $[M-H]^+$.

Example 11: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclopentyl)-amide



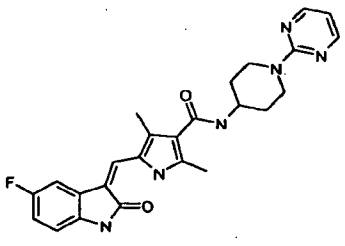
Following the general procedure, an orange solid was obtained (85mg, 93% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.88(s, 1H), 7.52-7.78(m, 3H), 6.82-6.96(m, 2H), 4.76-4.77(d, 1H), 3.92-3.97(m, 2H), 2.39-2.42(ds,6H), 1.96-2.01(m, 1H), 1.80-1.84(m,1H), 1.60-1.69(m, 1H). LC/MS: 384.2 $[M+H]^+$.

Example 12: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((1S,2R)-2-hydroxy-cyclopentyl)-amide

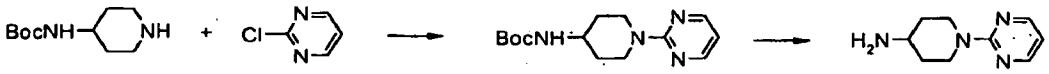


Following the general procedure, an orange solid was obtained (75mg, 82% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.72(s, 1H), 10.90(s, 1H), 7.72-7.79(m, 2H), 6.82-7.01(m, 3H), 4.81-4.83(d, 1H), 4.02-4.04(d, 2H),2.44-2.47(ds,6H), 1.47-1.90(m, 6H). LC/MS: 384.1 $[M+H]^+$.

Example 13: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-pyrimidin-2-yl-piperidin-4-yl)-amide



Preparation of amine:



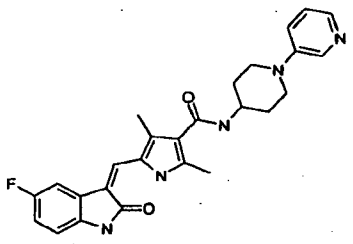
6a 13a 13b

Step 1: A mixture of compound **6a** (0.5g, 2.5mmol), 2-chloropyrimidine(0.86g, 7.5mmol) and K_2CO_3 (1.725g, 12.5mmol) in 10mL of 1,4-dioxane was refluxed for 48h, cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (EA:PE=1:4) to provide compound **13a** (0.61g, 88%).

Step 2: Compound **13a** (0.61g, 2.2mmol) was dissolved in 10mL DCM, 3mL TFA was added. The mixture was stirred at room temperature for 2h and evaporated to dryness under reduced pressure to give the crude compound **13b** (0.87g, 98%).

To the solution of (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (**A4**) (0.207g, 0.5mmol) and DIEA (0.15g, 2.0 eq.) in 25mL of DMF solution was added compound **13b** (0.235g, 0.58mmol), the reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (10mL) under sonication. The solid was collected by filtration and washed with methanol (5mL*2), dried under vacuum to provide title compound (189mg, 82%) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H), 10.87(s, 1H), 8.34-8.36(d, 2H), 7.71-7.77(m, 2H), 7.56-7.59(d, 1H), 6.82-6.95(m, 2H), 6.58-6.61(t,1H), 4.56-4.60(d, 2H), 4.04-4.10(m, 1H), 3.06-3.13(m, 2H), 2.40-2.42(ds, 6H), 1.86-1.91(d, 2H), 1.40-1.52(m, 2H). LC/MS: 459.4 $[M-H]^+$.

Example 14: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-amide



Preparation of amine:



6a 14a 14b

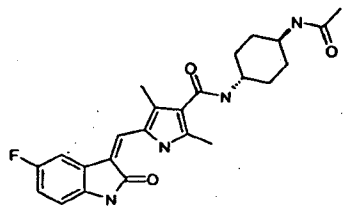
Step 1: Pd(dba)3 (0.046g, 0.05mmol), Xantphos (0.087g, 0.15mmol) and Cs_2CO_3 (1.1g, 3.37mmol) were added to 20mL of 1,4-dioxane under N_2, compound **6a** (0.5g, 2.5mmol) and 3-bromopyridine (0.513g, 3.2mmol) were added to this mixture. The resulting mixture was heated to 100°C for 24h and cooled to room temperature which was taken up in EA (50mL), washed with brine and water. The organic phase was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give a residue which was purified by column chromatography (PE:EA=1:2) to provide compound **14a** (0.51g, 73.6%).

Step 2: Compound **14a** (0.51g, 1.84mmol) was dissolved in 10mL of DCM and 3mL of TFA was added. The mixture was stirred at room temperature for 2h and evaporated to dryness under reduced pressure to give the crude compound **14b** (0.74g, 99%).

To the solution of (Z)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl 5-((5-fluoro-2-oxoindolin-3-ylidene) methyl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (**A4**) (0.1g, 0.24mmol) and DIEA (0.074g, 2.4eq.) in 10mL of DMF solution was added crude **14b** (0.12g, 0.29mmol). The reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (10mL) under sonication. The solid was collected by filtration and washed with methanol (5mL) twice, dried under vacuum to provide title compound (90mg, 82% yield) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.89(s, 1H), 8.32-8.33(d, 1H), 7.95-7.97(dd, 1H), 7.74-7.78(dd, 1H),

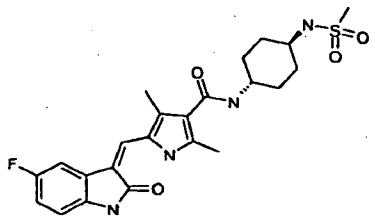
7.62-7.64(d, 1H), 7.32-7.36(m, 1H), 7.18-7.22(m,1H), 6.82-6.96(m, 2H), 3.95-3.97(m, 1H), 3.74-3.78(m, 2H), 2.86-2.90(t, 2H), 2.40-2.42(ds, 6H), 1.89-1.93(d, 2H), 1.59-1.68(m, 2H). LC/MS: 460.1 $[M+H]^+$.

Example 15: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-acetylamino-cyclohexyl)-amide



To the solution of Example 4 (1.0 eq.) and DIEA (2.0 eq.) in DMF solution was added compound acetyl chloride (1.2 eq), the reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol under sonication. The solid was collected by filtration and washed with methanol twice, dried under high vacuum to provide title compound (10mg, 27% yield) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H), 10.90(s, 1H), 7.71-7.78(m, 2H), 7.54-7.60(m, 1H), 6.84-6.95(m, 2H),3.67-3.71(m, 1H), 3.45-3.51(m, 2H),3.31(s, 3H), 2.38-2.40(ds, 6H), 1.84-2.00(m,4H), 1.29-1.44(t, 6H). LC/MS: 437.4 $[M-H]^+$.

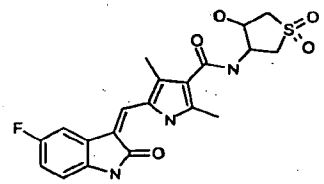
Example 16: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-methanesulfonylamino-cyclohexyl)-amide



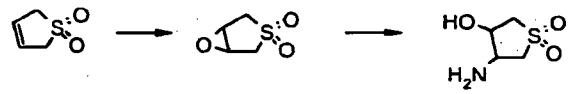
Follow the procedure of Example 15, the title compound was obtained (21mg, 84% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H), 10.87(s, 1H), 7.71-7.77(m, 2H), 7.52-7.56(m, 1H), 6.82-7.02(m, 3H), 3.63-3.66(m, 1H), 3.07-

3.12(m,1H), 2.92(s, 3H), 2.36-2.38(ds, 6H), 1.87-2.01(m,4H), 1.24-1.44(m, 4H). LC/MS: 473.3 $[M-H]^+$.

Example 17: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-hydroxy- 1,1-dioxo-tetrahydro-thiophen-3-yl)-amide



Preparation of 4-Amino-1,1-dioxo-tetrahydro-thiophen-3-ol



10a **17a** **17b**

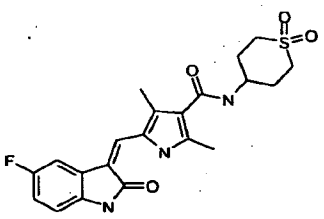
Step 1: To a cooled solution of compound **10a** (2g, 16.9mmol) in 11mL of 88% formic acid was added 30% hydrogen peroxide (3mL) dropwise. After addition, the mixture was stirred for two days at r.t. Excess iron (II) sulfate heptahydrate (10g) was added to consume the remaining hydrogen peroxide. The mixture was then evaporated under reduced pressure to remove most of the solvent. The resulting solid was collected by filtration, rinsed with water and dried in reduced pressure to provide compound **17a** (0.6g, 26%) as needles.

Step 2: Compound **17a** (0.60g, 4.48mmol) was added to 26% aqueous ammonia hydroxide (15mL) and the resulting mixture was allowed to stir overnight at r.t. A small amount of solid was filtered off and the filtrate was evaporated to dryness. The residue was triturated with ether, acetone and ethyl acetate, dried to provide compound **17b** as white solid (205mg, 30%).

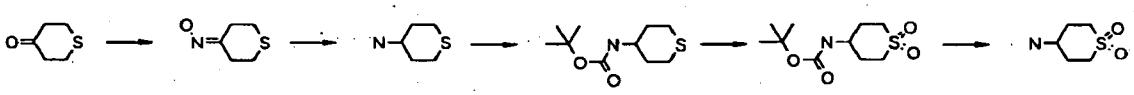
Step 3: To the solution of **A4** (150mg, 0.36mmol) in 20mL of DMF, were added compound **17b** (110mmg, 0.73mmol) and DIEA (96mg, 0.73mmol), the reaction mixture was stirred at r.t. for several hours. LC/MS was applied to determine completion of the reaction. The reaction mixture was evaporated under reduced pressure and the residue was triturated with 5% diethylamine/methanol (25mL) under

sonication. The solid was collected by filtration and washed with methanol, dried under vacuum to provide title compound (110mg, 71%) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.74(s, 1H), 10.92(s, 1H), 7.76-7.79(m, 2H), 7.57-7.59(d, 1H), 6.82-6.97(m, 2H), 5.99-6.00(d, 1H), 4.67-4.72(m, 1H), 4.55(s, 1H),3.42-3.52(m, 2H), 3.25-3.33(m, 2H), 2.45-2.48(ds, 6H). LC/MS: 432.0 $[M-H]^+$.

Example 18: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1,1-dioxo-hexahydro-thiopyran-4-yl)-amide



Preparation of 1,1-Dioxo-hexahydro-thiopyran-4-ylamine



18a 18b 18c 18d 18e 18f

Step 1: To a solution of **18a** (2.96g, 25.5mmol) in 23mL of ethanol was added NH2OH.HCl (3.64g, 51mmol). The mixture was cooled to 0 °C in ice bath and was added a solution of NaOH (2.08g) in 8mL of H2O. With the addition of NaOH solution, precipitate was formed. The reaction mixture was warmed to r.t. and stirred for an additional 2h, evaporated to remove ethanol. The aqueous solution was extracted with ether. The ether layer was washed with water and brine, dried over anhydrous Na2SO4. The organic layer was evaporated to dryness and the residue was recrystallized from hexane/ether to give compound **18b** (1.81g, 54%).

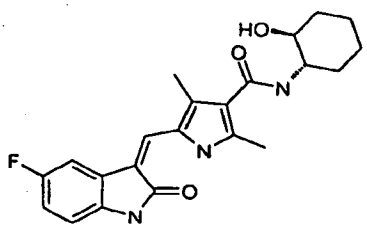
Step 2: To a mixture of LAH (2.84g, 75mmol) in 215mL of THF was added a solution of compound **18b** (1.81g, 13.8mmol) in 15mL of THF with stirring under ice cooling. The resulting mixture was heated to reflux overnight. After cooling, the reaction mixture was added 9mL of 2N aq.NaOH. The precipitate was filtered off and rinsed with THF for several times. The filtrate was concentrated to half volume and (Boc)2O (3.8g, 17.4mmol) was added drop-wise with stirring under ice cooling. The mixture was stirred at r.t. for 2h, concentrated, diluted with ethyl acetate and washed

with water. The organic layer was dried over anhydrous MgSO4 and evaporated to dryness. The solid residue was re-crystallized from hexane/ether to give compound **18d** as white solid (2.45g, 81%).

Step 3: To a solution of compound **18d** (509mg, 2.34mmol) in 5mL of THF was added 85% mCPBA (1.25g, 6.15mmol) with stirring under ice cooling. The resulting mixture was diluted with ethyl acetate and washed successively with saturated aq. NaHCO3, water and brine. The organic layer was dried over anhydrous MgSO4 and evaporated to dryness. The residue was re-crystallized from EA/hexane to give compound **18e** as white solid (0.551g, 94%). To a solution of **18e** in DCM (15mL) was added TFA (2.5mL). The mixture was stirred for 0.5h at r.t. and evaporated to give crude compound **18f** (1.12g) as yellow oil which was used in the next step without further purification.

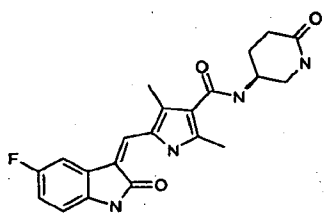
Step 4: To the solution of **A4** (107mg, 0.256mmol) in 10mL of DMF solution, was added compound **18f** (238mg) and DIEA(133mg, 1.03mmol), the reaction mixture was stirred at r.t. for several hours. LC/MS was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (25mL) under sonication. The solid was collected by filtration and washed with methanol, dried under vacuum to provide title compound (102mg, 92%) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.89(s, 1H), 7.72-7.78(m, 3H), 6.82-6.96(m, 2H), 4.13-4.15(m, 1H), 3.08-3.12(d, 2H), 2.40-2.42(ds, 6H),1.97-2.16(m, 4H). LC/MS: 430.3 $[M-H]^+$.

Example 19: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclohexyl)-amide



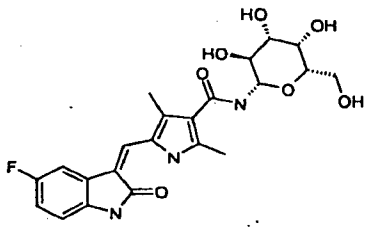
To the solution of **A4** (100mg, 0.24mmol) and DIEA (140mg, 0.96mmol) in 10mL of DMF, was added (1S,2S)-2-Amino-cyclohexanol (45mg, 0.29mmol). The reaction mixture was stirred at room temperature for several hours. LC/MS was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (25mL) under sonication. The solid was collected by filtration and washed with methanol), dried under vacuum to provide to provide title compound (70mg, 74%yield) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.62(s, 1H), 10.88(s, 1H), 7.71-7.77(m, 2H), 7.36-7.39(d, 1H), 6.81-6.95(m, 2H), 4.58-4.60(d, 1H), 3.48-3.60(m, 1H),3.30-3.35(m, 1H), 2.41-2.44(ds, 6H),1.88-1.90(t, 2H), 1.62(S, 2h), 1.23(s, 4H). LC/MS: 398.1 $[M+H]^+$.

Example 20: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-6-oxo- piperidin-3-yl)-amide



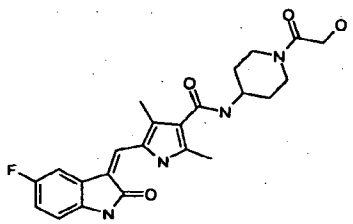
The synthesis of the title compound is similar to that of Example 19 (19.1% yield): ^{1}H NMR (300 MHz, DMSO-d6): δ=13.71(s, 1H), 10.92(s, 1H), 7.95-7.98(d, 1H),7.72-7.79(m, 2H),6.82-6.96(m, 2H), 4.92-4.96(q, 1H), 4.53-4.89(t, 1H), 3.96-4.02(q, 1H), 2.39-2.43(ds, 6H),1.88-1.90(t, 2H), 1.62(S, 2h), 1.23(s, 4H). LC/MS: 383.2 $[M-H]^+$.

Example 21: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((2S,3S,4R,5S,6S)-3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)-amide

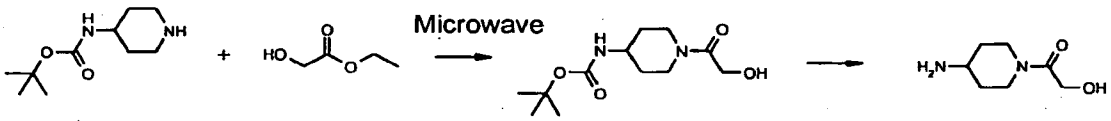


The synthesis of the title compound is similar to that of Example 19 (36.7% yield): ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H),10.88(s,1H), 7.95-7.97(d, 1H), 7.71-7.78(m, 2H), 6.82-6.96(m, 2H), 4.84-4.90(t, 1H), 4.70-4.75(m, 2H), 4.56-4.57(m, 1H), 4.38-4.39(d, 1H), 3.71-3.73(t, 1H), 3.29-3.55(m, 5H), 2.44-2.47(ds, 6H). LC/MS: 462.1 $[M+H]^+$.

Example 22: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-hydroxy-acetyl)-piperidin-4-yl]-amide



Preparation of 1-(4-Amino-piperidin-1-yl)-2-hydroxy-ethanone



6a **22a** **22b** **22c**

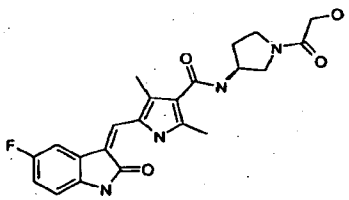
Step 1: Compound **6a** (2.12g, 10.6mmol) and compound **22a** (1.0g) were placed into a microwave reactor. The resulting mixture was reacted at 160°C for 30min. The mixture was evaporated and purified by column chromatography (EA:PE=1:1) to provide compound **22b** (1.3g).

Step 2: To a solution of compound **22b** (1.3g, 5mmol) in DCM (20mL), was added TFA (6mL). The resulting mixture was stirred at r.t. for about 1h and evaporated which was used for the next step without further purification.

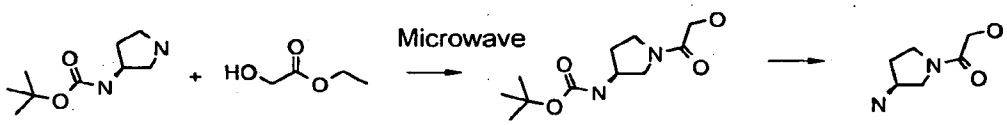
Step 3: To the solution of **A4** (200mg, 0.478mmol) and DIEA (0.2mL, 1.15mmol) in 25mL of DMF, was added compound **22c** (91mg, 0.57mmol). The reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (10mL) under sonication. The solid was collected by filtration and washed with

methanol, dried under vacuum to provide title compound (180mg, 86.9%). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.88(s, 1H), 7.62-7.78(m, 3H),6.82-6.96(m, 2H), 4.48-4.52(t, 1H), 4.22-4.23(d, 1H), 3.97-4.10(m, 3H), 3.65-3.69(d, 1H), 3.03-3.12(t, 1H), 2.49-2.51(t, 1H), 2.37-2.40(ds, 6H), 1.80-1.83 (t, 2h), 1.36-1.46(m, 2H). LC/MS: 439.3 $[M-H]^+$.

Example 23: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-hydroxy-acetyl)-pyrrolidin-3-yl]-amide



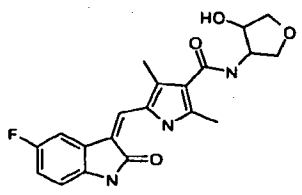
Preparation of 1-((S)-3-Amino-pyrrolidin-1-yl)-2-hydroxy-ethanone



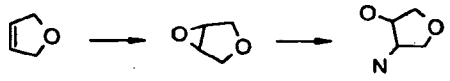
8a **22b** **23b** **23c**

Follow the preparation of Compound **22c**, Compound **23c** was prepared. The title compound was prepared following Example **22** (85.4%yield): ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H), 10.86(s, 1H), 7.70-7.89(m, 3H), 6.80-6.94(m, 2H), 4.37-4.54(m, 2H), 3.95-4.00(t, 2H), 3.57-3.63(m, 1H), 3.35-3.50(m, 1H), 2.13-2.14(ds, 6H), 1.86-1.93(m, 4H). LC/MS: 425.4 $[M-H]^+$.

Example 24: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-hydroxy-tetrahydro- furan-3-yl)-amide



Preparation of 4-Amino-tetrahydro-furan-3-ol



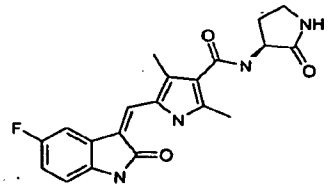
24a 24b 24c

Step 1: To the solution of **24a** (5.04g, 0.072mol) in 150mL of DCM was added 85% mCPBA(18.86g, 0.093mol) at 0°C using ice-water bath. The mixture was stirred over weekend at r.t. and the precipitate was filtered off. The filtrated was washed successfully with saturated aqueous NaHCO3, water and brine. The organic layer was dried over anhydrous Na2SO4 and concentrated to give a mixture of white solid and yellow oil (5.24g, 84.6%).

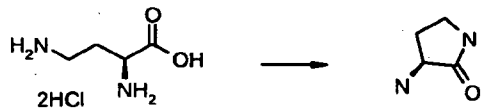
Step 2: A mixture of crude **24b** (300mg, 3.49mmol) obtained from last step, i-PrOH (3mL) and 26% NH4OH (10mL) was heated at a sealed tube at 80 °C for 18hs. A small amount of solid was filtered off and the filtrate was evaporated to give the crude **24c** (0.348g, 96.8%).

Step 3: To the solution of **A4** (199mg, 0.476mmol) in 20mL of DMF was added compound **24c** (0.348g, 3.378mmol), the reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (10mL). The slurry was then placed in a refrigerator overnight and concentrated to remove most of the solvents. The resulting yellow slurry was added ethanol and concentrated to remove most of the solvent. The resulting yellow slurry was then placed into a refrigerator for an hour and the precipitate was collected by filtration, washed with ethanol and dried in vacuum to give title compound as an orange solid (170mg, 93% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H),10.88(s, 1H), 7.71-7.78(m, 3H),6.82-6.96(m, 2H), 5.25-5.27(d, 1H), 4.14-4.19(m, 2H), 3.96-4.00(q, 1H),3.86-3.90(q, 1H), 3.52-3.63(m, 2H), 2.39-2.41(ds,6H). LC/MS: 384.3 $[M+H]^+$.

Example 25: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-2-oxo- pyrrolidin-3-yl)-amide



Preparation of (S)-3-Amino-pyrrolidin-2-one

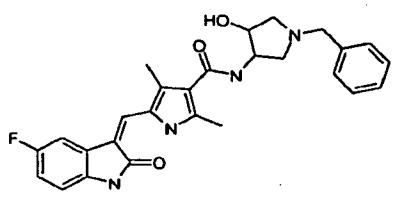


25a **25b**

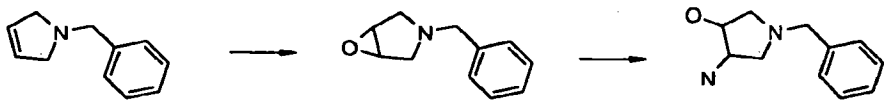
Step 1: HMDS (67mL, 0.32mol) in ACN (50mL) was added dropwise to a solution of **25a** (5g, 32mmol) in ACN (50mL) at room temperature. The resulting mixture was heated to reflux for 48h under the protection of N2. When the reaction was complete, the mixture was cooled, poured into cold methanol (50mL) and stirred for 30min. The obtained mixture was evaporated to dryness and the residue was extracted with chloroform (150mL*3) under reflux. The combined chloroform solution was evaporated to provide crude **25b** (3.1g, 96%).

Step 2: To the solution of **A4** (334mg, 0.8mmol) and DIEA (1mL) in 20mL of DMF was added **25b** (120mg, 1.28mmol). The reaction mixture was stirred at room temperature for several hours. LC/MS was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (10mL). The precipitate was collected by filtration, washed with ethanol and dried in vacuum to give title compound as an orange solid (83mg, 27% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H),10.89(s,1H), 7.71-7.82(m, 4H),6.82-6.96(m, 2H), 4.47-4.56(q, 1H),3.18-3.25(m, 2H), 2.42-2.45(ds, 6H), 2.27-2.39(m, 1H), 1.92-2.00(q,1H). LC/MS: 383.0 $[M+H]^+$.

Example 26: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-benzyl-4-hydroxy-pyrrolidin-3-yl)-amide



Preparation of 4-Amino-1-benzyl-pyrrolidin-3-ol



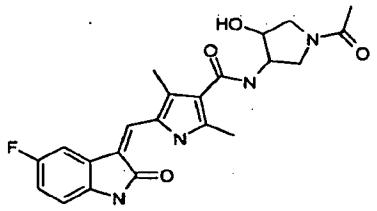
26a **26b** **26c**

Step 1: To an ice-cooled solution of **26a** (4.77g, 30mmol), 98% H2SO4 (1.95mL), H2O (4.5mL) and acetone (30mL) was added 85% mCPBA (7.91g, 39mmol) with stirring. The mixture was allowed to react for 48hrs at r.t. Acetone was evaporated and the mixture was neutralized with 1N aq. NaOH and extracted with toluene. The organic phase was dried over anhy. MgSO4 and evaporated. The residue was purified by column chromatography (EA:PE=1:4) to provide **26b** (2.0g, 38%).

Step 2: A mixture of **26b** (618mg, 3.53mmol) in 10mL of 26% ammonium hydroxide was heated in a sealed tube at 110°C for 24hrs. A small amount of solid was filtered off and the filtrate was evaporated to give the crude **26c** (630mg, 93% yield).

Step3: To the solution of **A4** (493mg, 1.18mmol) in 50mL of DMF was added compound **26c** (0.455mg, 2.37mmol), the reaction mixture was stirred at room temperature for several hours. LC/MS was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol. The precipitate was collected by filtration, washed with ethanol and dried in vacuo to give title compound (517mg, 92.5% yield) an orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H),10.87(s, 1H), 7.71-7.77(m, 3H),7.22-7.32(m, 5H), 6.82-6.95(m, 2H), 5.03-5.05(d, 1H), 4.06-4.15(m, 2H), 3.50-3.64(q, 2H), 2.82-2.89(m, 2H), 2.35-2.41(m,8H). LC/MS: 475.2 $[M+H]^+$.

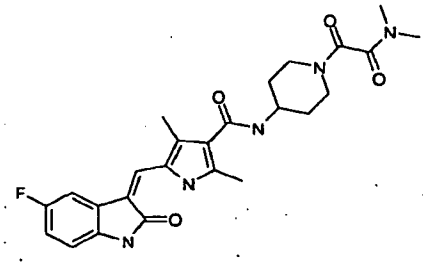
Example 27: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-acetyl-4-hydroxy-pyrrolidin-3-yl)-amide



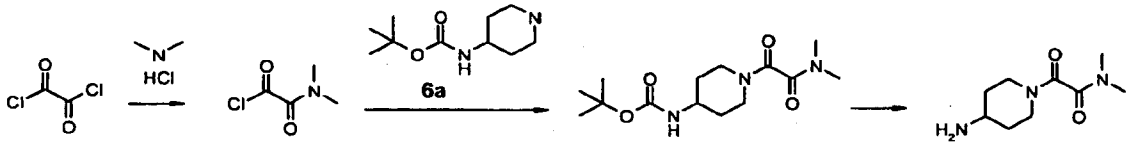
A mixture of Example **26** (283.7mg, 0.59mmol), 10% Pd/C (282mg) and acetic acid (3drops) in 30mL of [DMF:MeOH=1:1] was stirred at r.t. under H2 atmosphere. After the reaction was complete as detected by LC/MS, the catalyst was filtered off and the filtrate was evaporated to dryness. The residue was triturated with ethanol to provide 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole- 3-carboxylic acid (4-hydroxy-pyrrolidin-3-yl)-amide (178mg, 67%).

To the solution of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole- 3-carboxylic acid (4-hydroxy-pyrrolidin-3-yl)-amide (150mg, 0.39mmol) and DIEA (89mg, 0.69mmol) was added CH3COCl (33.7mg, 0.43mmol) on an ice bath. The mixture was stirred at r.t. for 3hrs. After the reaction was complete, DMF was evaporated under reduced pressure and the residue was triturated with methanol and the solid was collected by filtration, washed with ethanol and dried in vacuum to give title compound (82mg, 57% yield) as an orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H),10.87(s, 1H), 8.07-8.10(d, 1H),7.71-7.85(m, 3H), 6.82-6.92(m, 2H), 5.34-5.44(dd, 1H), 4.13-4.18(d, 2H), 3.67-3.81(m, 4H), 2.38-2.40(ds, 6H), 1.92-1.93(d,3H). LC/MS: 427.0 $[M+H]^+$.

Example 28: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-dimethylaminooxalyl- piperidin-4-yl)-amide



Preparation of 2-(4-Amino-piperidin-1-yl)-N,N-dimethyl-2-oxo-acetamide



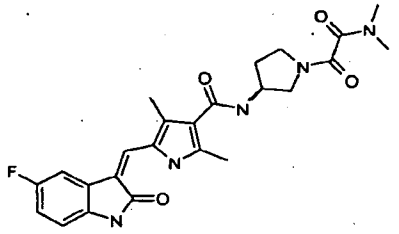
28a 28b 28c

Step 1: DIEA (0.87mL, 5mmol) was added to an ice-cooled solution of oxalyl chloride (0.22mL, 2.5mmol) and dimethylamine (0.204g, 2.5mmol) in 30mL of THF. The mixture was stirred at r.t. for 1h which was used for the next step directly.

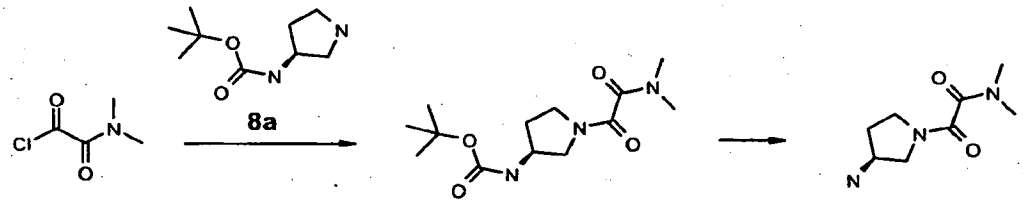
Step 2: Compound **6a** (0.5g, 2.5mmol) was added to the above solution, followed by DIEA (0.87ml, 5mmol). The resulting mixture was stirred at r.t. overnight and evaporated. The residue was purified by column chromatography to provide **28b** (307mg, 41%).

Step 3: To a solution of compound **28b** (172mg, 0.57mmol) in 5mL of DCM was added TFA (0.66mL, 8.6mmol). The resulting mixture was stirred at r.t. for ca. 1h and evaporated. The residue was added to a solution of **A4** (159mg, 0.38mmol) and DIEA (1mL) in 20mL of DMF. The reaction mixture was stirred at room temperature for several hours. LC/MS was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (10mL). The precipitate was collected by filtration, washed with methanol and dried in vacuum to give an orange solid (169mg, 92.5% yield): ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H),10.89(s, 1H), 7.64-7.78(m, 3H),6.82-6.96(m, 2H), 4.03-4.23(m, 2H), 3.38-3.49(m, 1H), 3.16-3.29(m, 1H), 2.87-2.99(m, 7H), 2.39-2.42(ds, 6H), 1.87-1.90(m,2H), 1.40-1.49(m, 2H). LC/MS: 482.1 $[M+H]^+$.

Example 29: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-dimethylaminooxalyl- pyrrolidin-3-yl)-amide



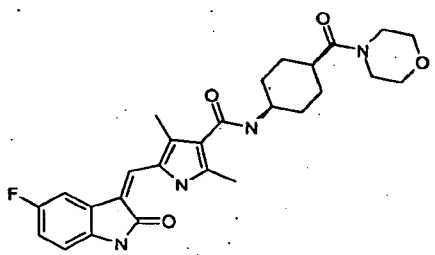
Preparation of 2-((S)-3-Amino-pyrrolidin-1-yl)-N,N-dimethyl-2-oxo-acetamide (**29b**) is similar to that of **28c**:



28a **29a** **29b**

The synthesis of the title compound is similar to that of Example **28** (32mg, 53.9% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67-13.68(d, 1H),10.87(s, 1H), 7.71-7.92(m, 3H),6.82-6.93(m, 2H), 4.40-4.47(m, 1H), 3.39-3.62(m, 4H), 2.86-2.92(dd, 6H), 2.39-2.41(dd, 6H), 2.15-2.18(m, 1H), 1.94-2.13(m, 1H). LC/MS: 466.4 $[M-H]^+$.

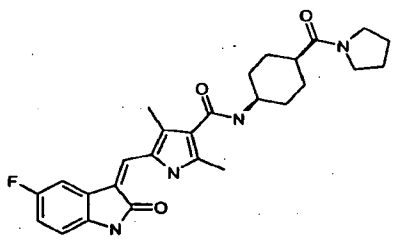
Example 30: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [4-(morpholine-4-carbonyl)-cyclohexyl]-amide



Step 1: 4-Amino-cyclohexanecarboxylic acid (84mg, 0.573mmol) was added to a solution of **A4** (200mg, 0.478mmol) and DIEA (0.125mL, 0.717mmol) in 15mL of DMF. The mixture was stirred at r.t. LC-MS was used to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was triturated with ACN for several times to provide 4-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-cyclohexanecarboxylic acid (180mg, 88.5%).

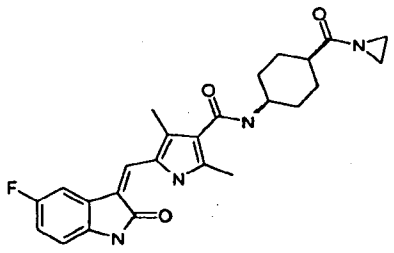
Step 2: To the solution of 4-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-cyclohexanecarboxylic acid in 20mL of DMF were added HATU (0.161g, 0.424mmol), DIEA(0.072mL, 0.424mmol) and morpholine (0.0737g, 0.847mmol). The reaction mixture was stirred at r.t. overnight. LC-MS was used to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (5mL). The precipitate was collected by filtration, washed with methanol and dried in vacuum to give title compound (69mg, 32.9% yield) as an orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H),10.87(s,1H), 7.71-7.77(m, 2H),7.53-7.55(d, 1H), 6.81-6.92(m, 2H),3.95-3.96(m, 1H), 3.29-3.54(m, 8H),2.64-2.67(m, 1H), 2.39-2.41(ds,6H), 1.47-1.88(m, 8H). LC/MS: 495.1 $[M+H]^+$.

Example 31: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [4-(pyrrolidine-1-carbonyl)-cyclohexyl]-amide



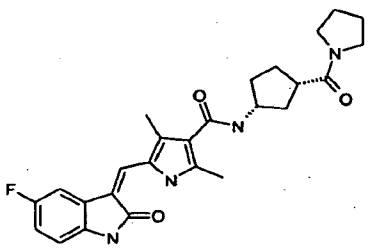
The synthesis of the title compound is similar to that of Example **30** (92mg, 67.8% yield): ^{1}H NMR (300 MHz, DMSO-d6): δ=13.64(s, 1H), 10.86(s, 1H), 7.70-7.76(m, 2H), 7.52-7.55(d, 1H), 6.80-6.94(m, 2H), 3.93-3.95(m, 1H), 3.41-3.46(m, 2H), 3.22-3.28(m, 3H), 2.40-2.42(ds, 6H), 1.68-1.90(m, 8H), 1.45-1.60(m, 4H). LC/MS: 479.1 $[M+H]^+$.

Example 32: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [4-(aziridine-1-carbonyl)-cyclohexyl]-amide



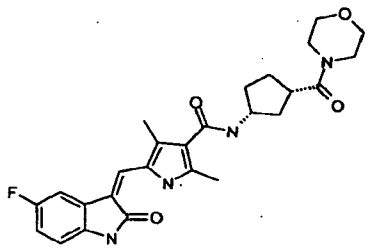
The synthesis of the title compound is similar to that of Example **30**: LC/MS: 449.3 $[M-H]^+$.

Example 33: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,3S)-3-(pyrrolidine-1- carbonyl)-cyclopentyl]-amide



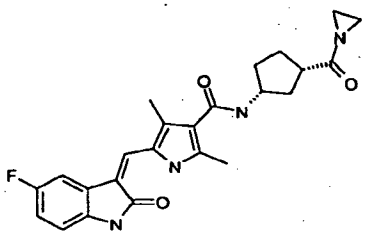
The synthesis of the title compound is similar to that of Example **30**: ^1H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.88(s, 1H), 7.71-7.80(m, 3H), 6.81-6.95(m, 2H), 4.29-4.31(m, 1H), 3.38-3.0(m, 2H), 3.17-3.30(m, 2H), 3.01-3.06(m, 1H), 2.42-2.43(ds, 6H), 1.65-2.08(m, 10H). LC/MS: 465.2 $[M+H]^+$.

Example 34: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,3S)-3-(morpholine-4- carbonyl)-cyclopentyl]-amide



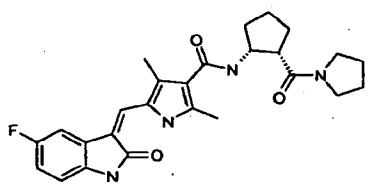
The synthesis of the title compound is similar to that of Example **30**: ^1H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.88(s, 1H), 7.64-7.78(m, 3H), 6.81-6.95(m, 2H), 4.25-4.31(m, 1H), 3.38-3.55(m, 8H), 3.14-3.19(m, 1H), 2.41-2.42(ds, 6H), 1.62-2.08(m, 10H). LC/MS: 481.2 $[M+H]^+$.

Example 35: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,3S)-3- (aziridine-1-carbonyl)-cyclopentyl]-amide



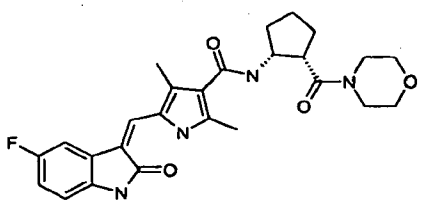
The synthesis of the title compound is similar to that of Example **30**: LC/MS: 435.2 $[M-H]^+$.

Example 36: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,2S)-2-(pyrrolidine-1-carbonyl)-cyclopentyl]-amide



The synthesis of the title compound is similar to that of Example **30**: ^1H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.88(s, 1H), 7.70-7.77(m, 2H), 7.40-7.42(d, 2H), 6.82-6.93(m, 2H), 4.52-4.61(m, 1H), 3.62-3.70(m, 2H), 3.42-3.51(m, 1H), 3.09-3.30(m, 3H), 2.38-2.41(ds, 6H), 1.49-1.98(m, 10H). LC/MS: 465.1 $[M+H]^+$.

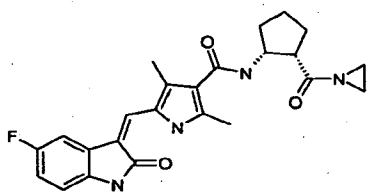
Example 37: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,2S)-2-(morpholine-4-carbonyl)-cyclopentyl]-amide



The synthesis of the title compound is similar to that of Example **30**: ^1H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.88(s, 1H), 7.70-7.77(m, 2H), 7.30-7.33(d,

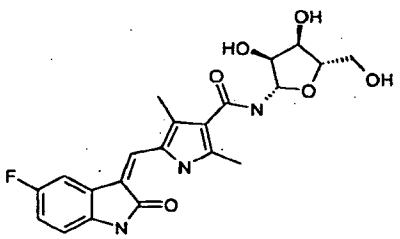
1H), 6.81-6.93(m, 2H), 4.56-4.63(m, 1H), 3.37-3.60(m, 8H), 3.21-3.27(m, 1H), 2.38-2.42(ds, 6H), 1.45-2.06(m, 6H). LC/MS: 481.1 $[M+H]^+$.

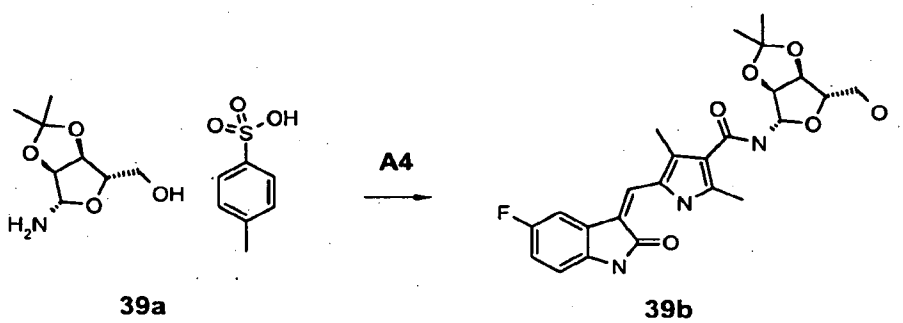
Example 38: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,2S)-2- (aziridine-1-carbonyl)-cyclopentyl]-amide



The synthesis of the title compound is similar to that of Example **30**: LC/MS: 435.3$[M-H]^+$.

Example 39: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((2S,3S,4R,5S)-3,4-dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl)-amide



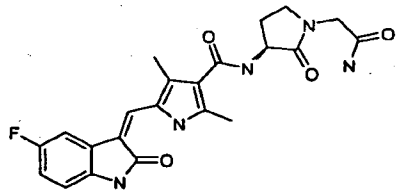


39a **39b**

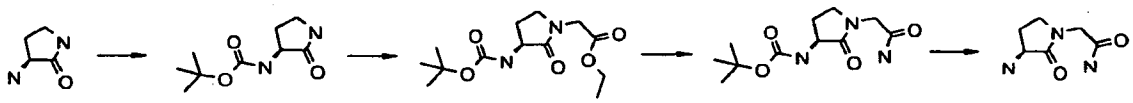
To the solution of **A4** (200mg, 0.478mmol) and DIEA (1mL) in 20mL of DMF was added compound **39a** (225mg, 0.623mmol), the reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (10mL). The precipitate was collected by filtration, washed with Methanol and dried in vacuum to

give crude **39b** which was dissolved in 5ml 95% TFA at r.t. for 0.5h. The mixture was then evaporated to dryness and the residue was triturated with methanol for several times to provide title compound (89mg, 43% yield). LC/MS: 432.2$[M+H]^+$.

Example 40: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-carbamoylmethyl-2-oxo-pyrrolidin-3-yl)-amide



Preparation of 2-((S)-3-Amino-2-oxo-pyrrolidin-1-yl)-acetamide



25b **40a** **40b** **40c** **40d**

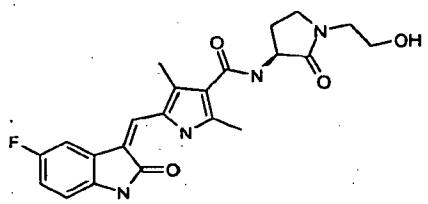
Step 1: To a solution of **25b** (3.1g, 32mmol) in methanol (130mL) was added TEA (16mL) and (Boc)2O (7.7g, 35.2mmol) at room temperature. The mixture was stirred overnight at room temperature, followed by refluxing for 2h. Solvent was removed and the residue was purified by column chromatography (EA) to provide **40a** (5.0g, 78%) as white solid.

Step 2: To a solution of **40a** (700mg, 3.5mmol) in THF (50mL) was added 60% NaH (560mg, 14mmol) at 0°C. After stirring for 1h at 0°C, ethyl bromoacetate (700mg, 4.2mmol) was added and the mixture was stirred at room temperature overnight. After the reaction was complete, the mixture was diluted by EA (50mL) and quenched by brine (50mL). The organic and aqueous layers were separated. The aqueous layer was extracted by EA (50mL*3). The combined EA phase was dried by anhydrous Na2SO4 and evaporated to provide the crude **40b** (1.0g, 99%).

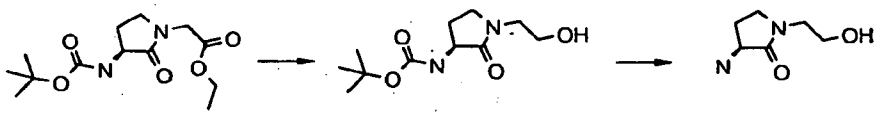
Step 3: Gas NH3 was bubbled for 1h into a solution of **40b** (0.27g, 0.94mmol) in MeOH (20mL). The solution was kept under stirring at r.t. for 24hs. The solvent was evaporated and the residue was purified by column chromatography to provide **40c** (170mg, 70.3%). To a solution of compound **40c** (160mg, 0.62mmol) in 5mL of

DCM, was added TFA (0.66mL, 8.6mmol). The resulting mixture was stirred at r.t. for about 1h and evaporated. The residue was added to a solution of **A4** (172mg, 0.41mmol) and DIEA (0.22mL, 1.23mmol) in 20mL of DMF. The reaction mixture was stirred at room temperature for several hours. LC/MS was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (10mL). The precipitate was collected by filtration, washed with ethanol and dried in vacuum to give title compound as an orange solid (136mg, 75.3% yield). ^{1}H NMR (300 MHz, DMSO-d6): δ=13.71(s, 1H), 10.92(s, 1H), 7.95-8.00(t, 1H), 7.73-7.79(m, 2H), 7.22-7.42(ds, 2H), 6.82-6.97(m, 2H), 4.53-4.62(q, 1H), 3.73-3.87(q,2H), 3.37-3.46(m, 2H), 2.39-2.40(ds,6H), 1.95-2.02(m, 1H). LC/MS: 440.0 $[M+H]^+$.

Example 41: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-hydroxy-ethyl)-2-oxo-pyrrolidin-3-yl]-amide



Preparation of (S)-3-Amino-1-(2-hydroxy-ethyl)-pyrrolidin-2-one

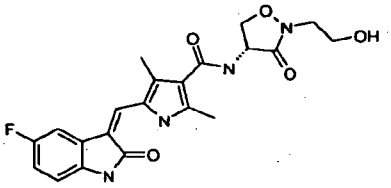


40b **41a** **41b**

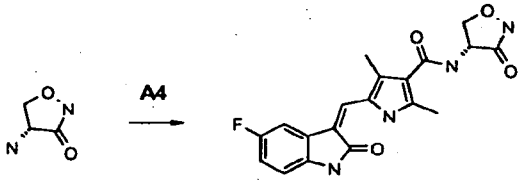
NaBH4 (85mg, 2.24mmol) was added to a solution of **40b** (160mg, 0.56mmol) in ter-butyl alcohol (5mL). The temperature was brought to 80 °C, and MeOH (0.6mL) was added slowly. The resulting mixture was kept under reflux for 2h. After cooling under an ice bath, H2O (20mL) was added and the alcohols were evaporated under vacuum. The aqueous phase was extracted with EA for several times. The organic layer was dried over anhydrous MgSO4 and concentrated. The residue was purified by Prep TLC to provide **41a** (38mg). To a solution of compound **41a** (38mg, 0.156mmol) in 5mL of DCM, was added TFA (0.18mL, 2.34mmol). The resulting mixture was stirred at r.t. for about 1h and evaporated. The residue was added to a solution of **A4** (36mg, 0.086mmol) and DIEA (0.08mL, 0.43mmol) in

20mL of DMF. The reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (5mL). The precipitate was collected by filtration, washed with ethanol and dried in vacuo to give an orange solid (29mg, 79.2% yield): ^{1}H NMR (300 MHz, DMSO-d6): δ=13.69(s, 1H), 10.91(s, 1H), 7.72-7.85(m, 3H), 6.82-6.96(m, 2H), 4.58-4.74(m,2H), 3.37-3.54(m, 4H), 3.12-3.20(m, 1H), 1.87-2.45(m, 8H), 1.23-1.97(m, 1H). LC/MS: 427.0 $[M+H]^+$.

Example 42: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-hydroxy-ethyl)-3-oxo-isoxazolidin-4-yl]-amide



Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-3-oxo-isoxazolidin-4-yl)-amide (**42b**)

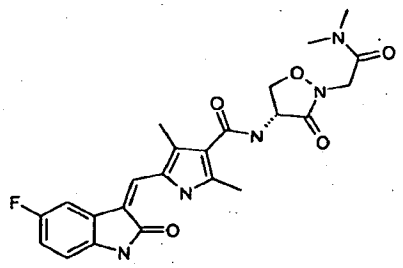


42a **42b**

To the solution of **A4** (1.75g, 4.2mmol) and DIEA (2.5g, 17mmol) in 150mL of DMF, was added compound **42a** (800mg, 5.1mmol). The reaction mixture was stirred at room temperature for several hours. LC/MS was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (500mL) under sonication. The solid was collected by filtration and washed with methanol, dried under vacuum to provide to provide **42b** (1.41g, 87.6% yield): ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H),10.88(s,1H), 7.71-7.77(m, 3H), 7.41(s, 1H), 6.82-6.96(m, 2H), 4.08-4.13(m, 1H), 3.06-3.13(m, 1H), 2.41-2.45(ds, 6H), 2.25-2.31(m, 2H), 1.79-1.98(m, 3H). LC/MS: 395.3 $[M-H]^+$.

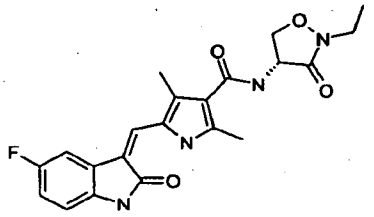
To the solution of **42b** (1.0eq.) cooled on ice bath was added NaH (4.0 or 1.5eq.). The resulting mixture was stirred for an hour and was then added 2-bromoethanol (3eq.), the reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol under sonication. The solid was collected by filtration, washed with methanol twice, and further purified by Prep-LC to obtain the title compound (18mg, 11%yield) as orange solids: ^{1}H NMR (300 MHz, DMSO-d6): δ=13.70(s, 1H), 10.91(s, 1H), 8.08-8.10(d, 1H), 7.72-7.79(m, 2H), 6.82-6.97(m, 2H), 5.01-5.10(q, 1H), 4.79-4.81(t, 1H), 4.56-4.62(t, 1H), 4.02-4.08(q, 1H), 3.49-3.63(m, 4H), 2.41-2.43(ds, 6H). LC/MS: 428.9 $[M+H]^+$.

Example 43: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-dimethylcarbamoylmethyl-3-oxo-isoxazolidin-4-yl)-amide

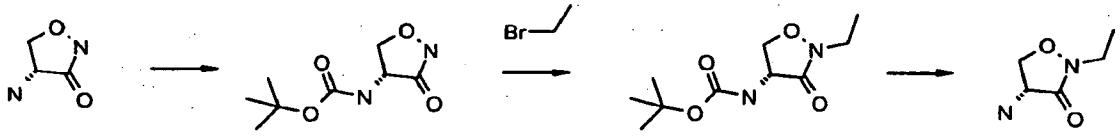


To the solution of **42b** (1.0eq.) cooled on ice bath was added NaH (4.0 or 1.5eq.). The resulting mixture was stirred for an hour and was then added 2-bromo-N,N-dimethylacetamide (1.0eq.), the reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol under sonication. The solid was collected by filtration, washed with methanol twice, and further purified by column chromatography to obtain title compound (30mg, 13.6% yield) as orange solids: ^{1}H NMR (300 MHz, DMSO-d6): δ=13.73(s, 1H), 10.93(s, 1H), 8.05-8.08(d, 1H), 7.74-7.80(m, 2H), 6.82-6.97(m, 2H), 5.06-5.15(q, 1H), 4.39-4.58(m, 3H), 4.05-4.11(q, 1H), 2.97(s, 3H), 2.84(s, 3H), 2.44-2.47(ds, 6H). LC/MS: 468.2 $[M-H]^+$.

Example 44: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-ethyl-3-oxo-isoxazolidin-4-yl)-amide



Preparation of (R)-4-Amino-2-ethyl-isoxazolidin-3-one



42a **44a** **44b** **44c**

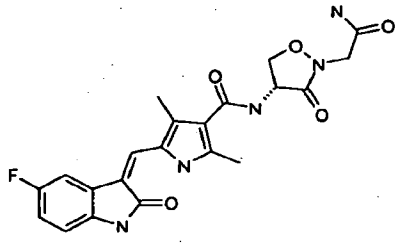
Step 1: Compound **42a** (500mg, 4.9mmol) and TEA (976mg, 9.64mmol) were dissolved in a mixture of THF/water (85mL, V/V 10:7). (Boc)2O (1.17g, 5.4mmol) was added dropwise under ice cooling. After the addition was complete, the mixture was warmed to r.t. and stirred for 5h. The mixture was evaporated to dryness and the residue was purified by column chromatography (EA:PE=3:1) to provide compound **44a** (600mg, 61%) as white solid.

Step 2: To the solution of compound **44a** (100mg, 0.5mmol), was added 60%NaH (24mg, 0.6mmol) under ice cooling. The resulting mixture was stirred for 1h and was added bromoethane (60mg, 0.55mmol). The mixture was warmed to r.t. and stirred overnight and evaporated to dryness. The residue was purified by column chromatography (EA:PE=10:1) to provide compound **44b** (109mg, 94.7%).

Step 3: To a solution of compound **44b** (109mg, 0.47mmol) in 5mL of DCM, was added TFA (810mg, 7.1mmol). The resulting mixture was stirred at r.t. for about 1h and evaporated which was then added to the solution of **A4** (160mg, 0.38mmol) and DIEA (196mg, 1.52mmol) in 18mL of DMF. The reaction mixture was stirred at room temperature for several hours. LC/MS detection was applied to determine completion of the reaction. DMF was evaporated under reduced pressure and the residue was precipitated with 5% diethylamine/methanol (10mL) under sonication.

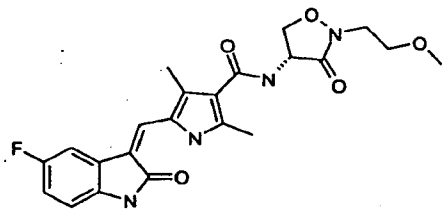
The solid was collected by filtration and washed with methanol, dried under vacuum to provide title compound (123mg, 77.8% yield). ^{1}HNMR (300 MHz, DMSO-d6): δ=13.71(s, 1H),10.39(s, 1H), 8.07-8.10(d, 1H),7.72-7.78(m, 2H), 6.82-6.96(m, 2H), 4.97-5.06(q, 1H), 4.57-4.62(t, 1H), 4.02-4.08(q, 1H), 3.50-3.58(m, 2H), 2.43-2.45(ds,6H), 1.13-1.18(t,3H). LC/MS: 412.9 $[M+H]^+$.

Example 45: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-carbamoylmethyl- 3-oxo-isoxazolidin-4-yl)-amide



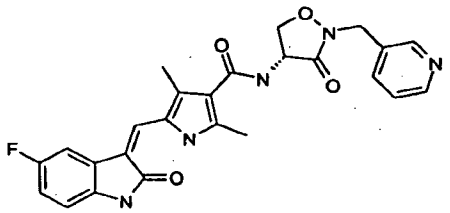
The synthesis of the title compound is similar to that of Example **44** (71%yield): ^{1}H NMR (300 MHz, DMSO-d6): δ=13.73(s, 1H),10.91(s, 1H), 8.09-8.11(d, 1H),7.73-7.79(m, 2H), 7.33-7.53(ds, 2H), 6.82-6.97(m, 2H), 5.02-5.07(q, 1H), 4.55-4.60(t, 1H), 4.01-4.17(m, 3H), 2.44-2.46(ds,6H). LC/MS: 441.9 $[M+H]^+$.

Example 46: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-methoxy-ethyl)-3-oxo-isoxazolidin-4-yl]-amide



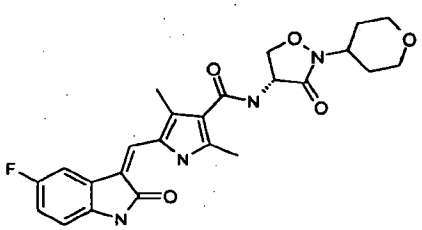
The synthesis of the title compound is similar to that of Example **44** (89.3%yield): ^{1}H NMR (300 MHz, DMSO-d6): δ=13.75(s, 1H),10.91(s,1H), 8.09-8.12(d, 1H), 7.72-7.79(m, 2H), 6.82-6.97(m, 2H), 4.99-5.08(q, 1H), 4.57-4.63(t, 1H), 4.01-4.07(q, 1H), 3.37-3.74(m, 4H),3.22(s, 3H), 2.35-2.37(ds, 6H). LC/MS: 443.0 $[M+H]^+$.

Example 47: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-3-oxo-2-pyridin-3-ylmethyl-isoxazolidin-4-yl)-amide

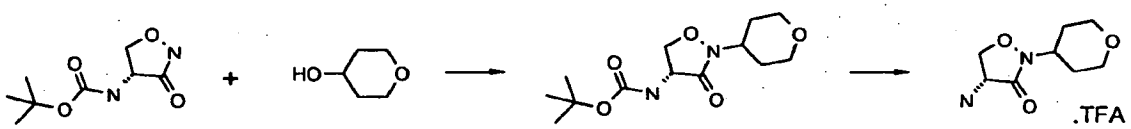


The synthesis of the title compound is similar to that of Example **44** (73.8%yield): ^{1}H NMR (300 MHz, DMSO-d6): δ=13.73(s, 1H),10.91(s,1H), 8.52-8.57(m, 2H), 8.17-8.19(d, 1H), 7.73-7.79(m, 3H), 7.39-7.43(m, 1H), 6.82-6.97(m, 2H), 5.05-5.14(q, 1H), 4.63-4.85(q, 2H), 4.57-4.63(t, 1H), 4.06-4.13(q, 1H), 2.43-2.46(ds, 6H). LC/MS: 476.1 $[M+H]^+$.

Example 48: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2-(tetrahydro-pyran-4-yl)-isoxazolidin-4-yl]-amide



Preparation of (R)-4-Amino-2-(tetrahydro-pyran-4-yl)-isoxazolidin-3-one **(48c)**



44a **48a** **48b** **48c**

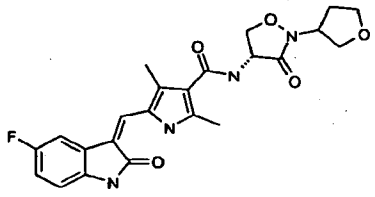
Step 1: To a solution of **44a** (150mg, 0.74mmol), **48a** (83mg, 0.82mmol) and PPh3 (290mg, 1.1mmol) in THF (20mL) was added DEAD (206mg, 1.2mmol) in THF (2mL) dropwise at -60°C. After the addition was complete, the reaction mixture was warmed to room temperature gradually and stirred for 2 days. The mixture was then evaporated and the residue was purified by column chromatography (EA:PE=4:1) to provide a clear oil which still contained small amount of **44a**. The

obtained oil was purified again by Prep-TLC to provide a mixture of **48b** and POPh3 (131mg).

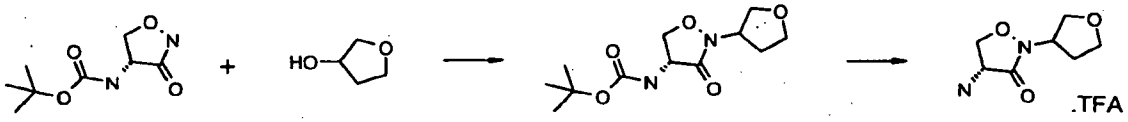
Step 2: To a solution of the obtained mixture of **48b** and POPh3 (131mg) in DCM (4mL) was added TFA (1mL) at room temperature. The mixture was stirred for 3h and evaporated to provide crude **48c** which was used for the next step directly.

Step 3: To a solution of **A4** (84mg, 2mmol) in 10mL of DMF, were added the crude **48c** from last step and DIEA (2mL), the reaction mixture was stirred at room temperature overnight. LC/MS was applied to determine completion of the reaction. The reaction mixture was evaporated under reduced pressure and the residue was triturated with 5% diethylamine/methanol (25mL). The solid was collected by filtration and washed with methanol, dried under vacuum to provide the title compound (58mg, 62%) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.73(s, 1H), 10.94(s, 1H), 8.12-8.15(d, 1H), 7.73-7.80(m, 2H), 6.82-6.87(m, 2H), 5.02-5.05(q, 1H), 4.58-4.64(t, 1H), 3.86-4.14(m, 4H),3.38-3.44(m, 2H), 2.42-2.50(ds, 6H), 1.65-1.88(m, 4H). LC/MS: 469.0 $[M+H]^+$.

Example 49: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2-(tetrahydro-furan-3-yl)-isoxazolidin-4-yl]-amide



Preparation of (R)-4-Amino-2-(tetrahydro-furan-3-yl)-isoxazolidin-3-one (**49c**)

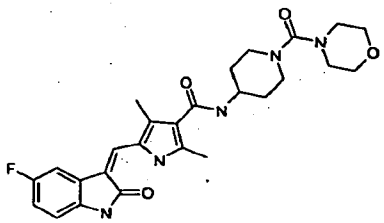


44a **49a** **49b** **49c**

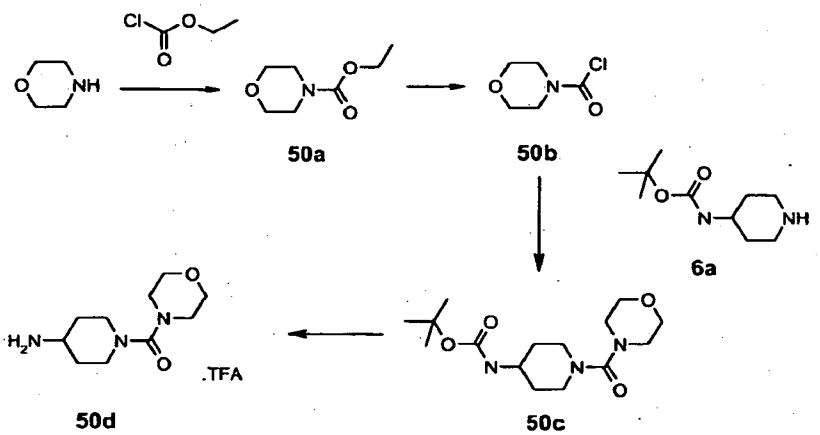
The synthesis was similar to that of Example **48** except that compound **49a** was used. The title compound (59mg, 65%) was obtained as orange solid. ^{1}H NMR

(300 MHz, DMSO-d6): δ=13.72(s, 1H), 10.94(s, 1H), 8.12-8.15(d, 1H), 7.73-7.80(m, 2H), 6.82-6.97(m, 2H), 4.99-5.05(q, 1H), 4.58-4.78(m, 2H), 4.03-4.10(m, 1H), 3.69-3.88(m, 4H), 2.13-2.40(ds, 6H), 2.03-2.13(m, 4H). LC/MS: 454.9 $[M+H]^+$.

Example 50: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(morpholine-4-carbonyl)-piperidin-4-yl]-amide



Preparation of (4-Amino-piperidin-1-yl)-morpholin-4-yl-methanone (**50d**):



Step 1: To a solution of morpholine (20g, 0.23mol), pyridine (31mL, 0.38mol) in DCM (100mL), was added ethyl chlorooate (27.4g, 0.253mol) drop-wise at 0°C. The obtained mixture was stirred at room temperature overnight and washed with saturated aqueous NaHCO3 and brine. The organic phase was dried over anhydrous Na2SO4 and evaporated to provide crude **50a** (36g, 96%) as yellow solid.

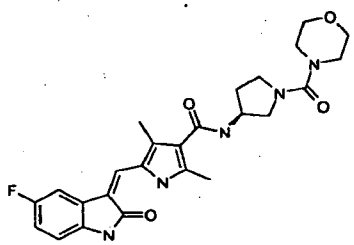
Step 2: A mixture of **50a** (20g, 0.126mol) and POCl3 (97g, 0.63mol) in dry ACN (200mL) was refluxed for 18h with stirring. After being cooled, the reaction mixture was diluted by DCM (80mL) and poured into crushed ice. The organic layer was separated and the aqueous layer was extracted by DCM (200mL*3). The combined DCM phase was washed with saturated aqueous NaHCO3 and brine, dried over anhydrous Na2SO4 and evaporated. The residue was purified by distillation.

Compound **50b** was obtained by collecting the distillate of 82-84 °C (1mmHg) (13g, 69%).

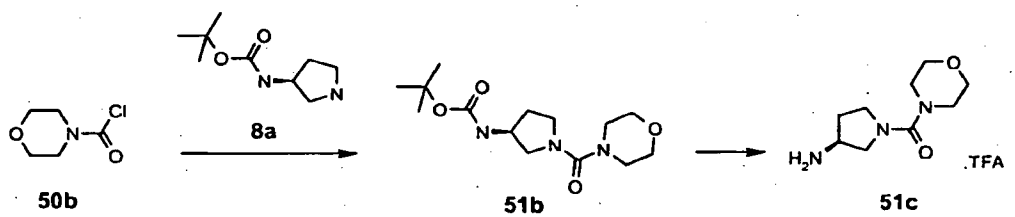
Step 3: To a solution of **6a** (20g, 0.23mol), TEA (31mL, 0.38mol) in DCM (100mL), was added **50b** (27.4g, 0.253mol) in DCM drop-wise at 0°C. The obtained mixture was stirred at room temperature overnight and washed with saturated aqueous NaHCO3 and brine. The organic phase was dried over anhydrous Na2SO4 and evaporated to provide crude **50c** (77mg, 95%) as yellow solid.

The de-Boc step and final coupling to **A4** were similar to that of example **48** to obtain the title compound (45mg, 60%) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.90(s, 1H), 7.59-7.78(m, 3H), 6.81-6.93(m, 2H), 3.91-3.94(m, 1H), 3.56-3.60(m, 6H), 3.11-3.13(m, 4H), 2.83-2.91(t, 2H), 2.39-2.41(ds, 6H), 1.79-1.1.83(m, 2H), 1.44-1.51(m, 2H). LC/MS: 496.0 $[M+H]^+$.

Example 51: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(morpholine- 4-carbonyl)-pyrrolidin-3-yl]-amide



Preparation of ((R)-3-Amino-pyrrolidin-1-yl)-morpholin-4-yl-methanone **(51c)**:

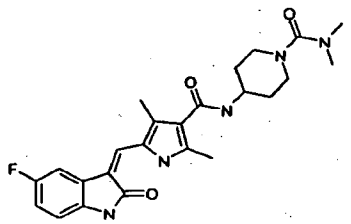


50b **51b** **51c**

The synthesis was similar to that of Example **50** except compound **51a** was used. The title compound (83mg, 79%) was finally obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.90(s, 1H), 7.72-7.84(m, 3H), 6.82-6.93(m,

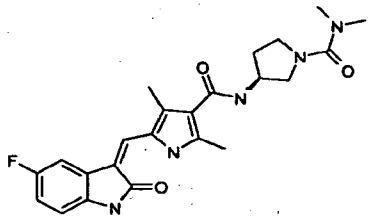
2H), 4.31-4.33(m, 1H), 3.48-3.58(m, 6H), 3.24-3.34(m, 2H), 3.13-3.16(m, 4H), 2.38-2.40(ds, 6H), 1.87-2.03(m, 2H). LC/MS: 480.3 $[M-H]^+$.

Example 52: Preparation of 4-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-piperidine- 1-carboxylic acid dimethylamide



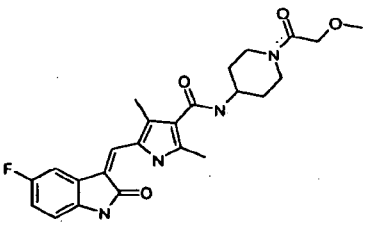
The title compound (35mg, 56%) was obtained as orange solid following the procedure for Example **50**. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.91(s, 1H), 7.60-7.79(m, 3H), 6.81-6.96(m, 2H), 3.90-3.92(m, 1H), 3.50-3.54(d, 2H), 2.77-2.84(t, 2H), 3.13-3.16(m, 4H), 2.73(s, 6H), 2.39-2.41(ds, 6H), 1.78-1.82(m, 2H), 1.45-1.52(m, 2H). LC/MS: 452.3 $[M-H]^+$.

Example 53: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-dimethylcarbamoyl-pyrrolidin-3-yl)-amide

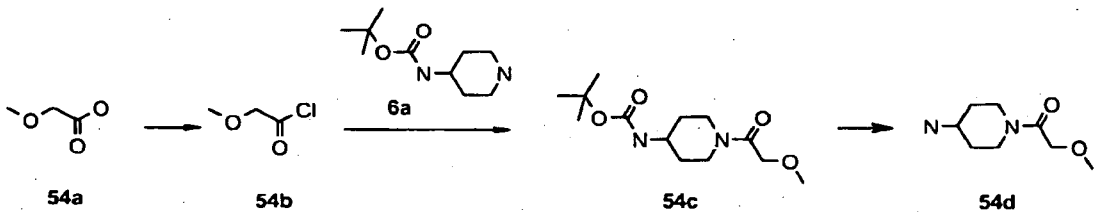


The title compound (20mg, 55%) was obtained as orange solid following the procedure for Example **51**. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.91(s, 1H), 7.72-7.83(m, 3H), 6.82-6.96(m, 2H), 4.28-4.36(m, 1H), 3.21-3.53(m, 4H), 2.73(s, 6H), 2.38-2.40(ds, 6H), 1.85-2.04(m, 2H). LC/MS: 438.3 $[M-H]^+$.

Example 54: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-methoxy-acetyl)-piperidin-4-yl]-amide



Preparation of 1-(4-Amino-piperidin-1-yl)-2-methoxy-ethanone (**54d**):

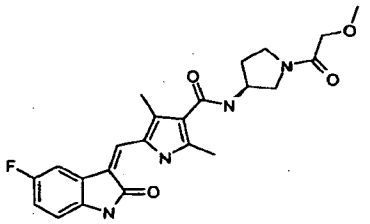


Step 1: To a solution of compound **54a** (20mL, 0.26mol) in DCM (170mL) at 0°C, was added oxalyl chloride (30mL, 0.34mol) drop-wise and a few drops of DMF. The mixture was stirred at room temperature overnight and evaporated. The residue was distilled to provide **54b** (25.4g, 90%).

Step 2: To a solution of **6a** (100mg, 0.5mmol) and TEA (0.16mL, 2mmol) in DCM (10mL) was added **54b** (60mg, 0.55mmol) in DCM (2mL) drop-wise at 0°C. The obtained mixture was stirred at room temperature overnight and washed with saturated aqueous NaHCO3 and brine. The organic phase was dried over anhydrous Na2SO4 and evaporated to provide crude **54c** (129mg, 95%) as yellow solid.

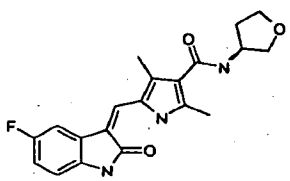
The de-Boc step and final coupling to **A4** were similar to that of Example **48**. The title compound (65mg, 41%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.65(s, 1H), 10.87(s, 1H), 7.59-7.76(m, 3H), 6.80-7.94(m, 2H), 3.96-4.23(m, 4H), 3.70-3.76(m, 2H), 3.26(s, 3H), 3.08-3.16(m, 1H), 2.71-2.87(m, 1H), 2.37-2.40(ds, 6H), 1.83-1.85(m, 2H), 1.33-1.45(m, 2H). LC/MS: 454.9 $[M+H]^+$.

Example 55: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy-acetyl)-pyrrolidin-3-yl]-amide



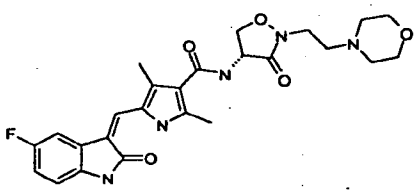
The title compound (51mg, 31%) was obtained as orange solid following the procedure for Example **54**. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.88(s, 1H), 7.70-7.89(m, 3H), 6.80-6.94(m, 2H), 4.35-4.43(m, 1H), 3.97-3.99(d, 2H), 3.33-3.67(m, 4H), 3.23(s, 3H), 2.37-2.39(ds, 6H), 1.85-2.15(m, 2H). LC/MS: 440.9 $[M+H]^+$.

Example 56: Preparation of N-((3R)oxolan-3-yl){5-[(5-fluoro-2-oxo(1H-benzo[d] azolin-3-ylidene))methyl]-2,4-dimethylpyrrol-3-yl}carboxamide



The synthesis was similar to the final step of Example **48** using (S)-(Tetrahydro- furan-3-yl)amine as starting material. The title compound (82mg, 93%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.91(s, 1H), 7.72-7.88(m, 3H), 6.83-6.93(m, 2H), 4.21-4.25(m, 1H), 3.53-3.87(m, 4H), 2.39-2.41(ds, 6H), 2.39-2.41(m, 1H), 2.09-2.12(m, 1H). LC/MS: 370.1 $[M+H]^+$.

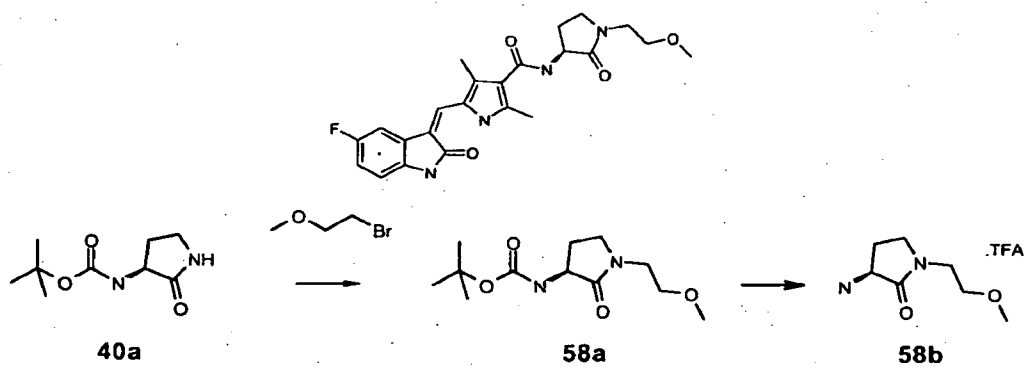
Example 57: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-morpholin-4-yl-ethyl)-3-oxo-isoxazolidin-4-yl]-amide



To a solution of **42b** (200mg, 0.52mmol), NaI (78mg, 0.52mmol) and DIEA (134mg, 1.04mmol) in DMF (25mL) was added 60% NaH (125mg, 3.13mmol) at 0°C. After stirring at room temperature for 1h, the mixture was added 4-(2-Chloro-ethyl)- morpholine chloride (194mg, 1.05mmol). The obtained mixture was stirred

48h at room temperature. LC-MS was used to detect completion of the reaction. The mixture was evaporated under reduced pressure and the residue was triturated with 5% diethylamine/methanol (25mL). The solid was collected by filtration which was purified again by column chromatography (CH2Cl2:MeOH=20:1) to provide the title compound (60mg, 23%) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.59(s, 1H), 11.53(s, 1H), 7.79-8.13(m, 3H), 7.04-7.12(m, 2H), 5.00-5.06(q, 1H), 4.57-4.62(t, 1H), 3.97-4.10(m, 3H), 3.44-3.58(m, 4H), 2.78-2.94(m, 1H), 2.47-2.50(ds, 6H). LC/MS: 498.2 $[M+H]^+$.

Example 58: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy-ethyl)-2-oxo-pyrrolidin-3-yl]-amide

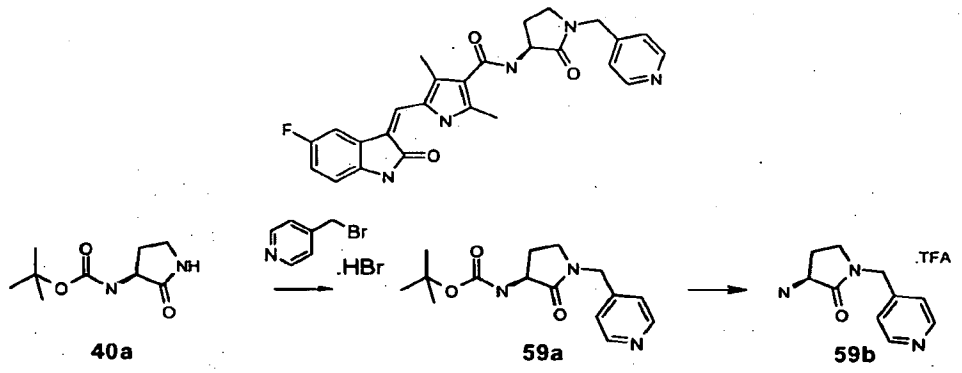


40a **58a** **58b**

Step1: To a solution of **40a** (100mg, 0.5mmol) in DMF (5mL) was added 60% NaH (21mg, 0.53mmol) at 0°C. After stirring at room temperature for 1h, the mixture was added compound 1-Bromo-2-methoxy-ethane (67.5mg, 0.49mmol). The obtained mixture was stirred overnight at room temperature, evaporated. The residue was purified by column chromatography (EA:PE=1:1) to provide **58a** (68mg, 54%).

Step2: The de-Boc step and final coupling to **A4** were similar to that of Example **48**. The title compound (54mg, 77%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.68(s, 1H), 10.91(s, 1H), 7.72-7.87(m, 3H), 6.82-6.93(m, 2H), 4.59-4.62(q, 2H), 3.38-3.49(m, 6H), 3.30(s, 3H), 2.42-2.45(ds, 6H), 2.15-2.20(m, 1H), 1.90-2.00(m, 1H). LC/MS: 439.3 $[M-H]^+$.

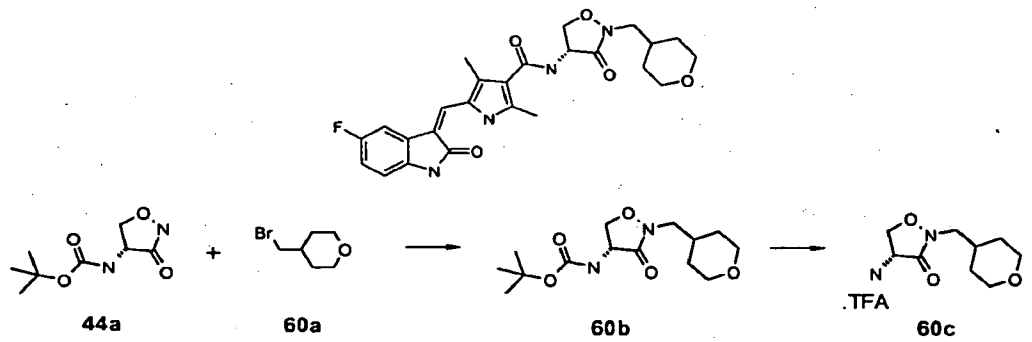
Example 59: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-yl)-amide



40a 59a 59b

The synthesis was similar to that of Example **58**. The title compound (24mg, 66%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.71(s, 1H), 10.93(s, 1H), 8.53-8.55(m, 1H), 8.00-8.02(d, 1H), 7.73-7.80(m, 2H), 7.30-7.32(d, 2H), 6.82-6.95(m, 2H), 4.40-4.69(m, 3H), 3.28-3.34(m, 2H), 2.44-2.47(ds, 6H). LC/MS: 472.2 $[M-H]^+$.

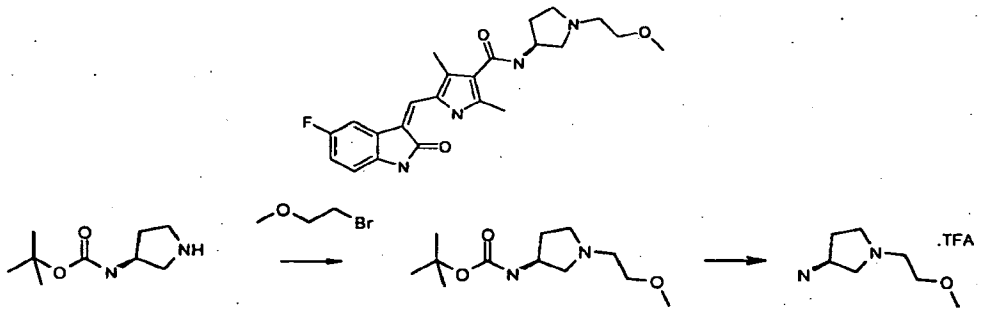
Example 60: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2-(tetrahydro-pyran-4-ylmethyl)-isoxazolidin-4-yl]-amide



44a 60a 60b 60c

The synthesis was similar to that of Example **58**. The title compound (51mg, 79%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.72(s, 1H), 10.94(s, 1H), 8.14-8.16(d, 1H), 7.73-7.80(m, 2H), 6.82-6.94(m, 2H), 5.06-5.10(q, 1H), 4.57-4.63(t, 1H), 4.03-4.12(m, 2H), 3.82-3.87(m, 2H), 3.40-3.42(m, 1H), 3.15-3.42(m, 4H), 2.42-2.45(ds, 6H), 1.80-1.95(m, 1H), 1.53-1.64(m, 2H), 1.18-1.26(m, 2H). LC/MS: 481.2 $[M-H]^+$.

Example 61: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy-ethyl)-pyrrolidin-3-yl]-amide

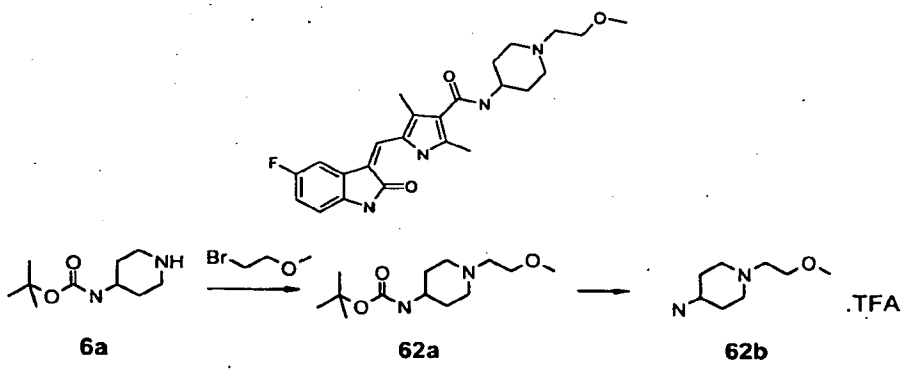


8a 61a 61b

Step 1: A solution of **8a** (100mg, 0.54mmol), 1-bromo-2-methoxy-ethane (89.5mg, 0.64mmol), KI (94mg, 0.56mmol) and K2CO3 (370mg, 2.69mmol) in 15mL of acetonitrile were stirred under reflux for 48h. After being cooled, the mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by column chromatography (EA:MeOH=10:1) to give **61a** (102mg, 78%) as yellow oil.

Step 2: The de-Boc step and final coupling to **A4** were similar to that of Example **48**. The title compound (73mg, 84%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.65(s, 1H), 10.91(s, 1H), 7.71-7.79(m, 3H), 6.82-6.96(m, 2H), 4.31-4.33(m, 1H), 3.40-3.44(t, 2H), 3.24(s, 3H), 2.82-2.88(m, 1H), 2.53-2.60(m, 5H), 3.39-3.41(ds, 6H), 2.09-2.12(m, 1H), 1.67-1.71(m, 1H). LC/MS: 427.1 $[M+H]^+$.

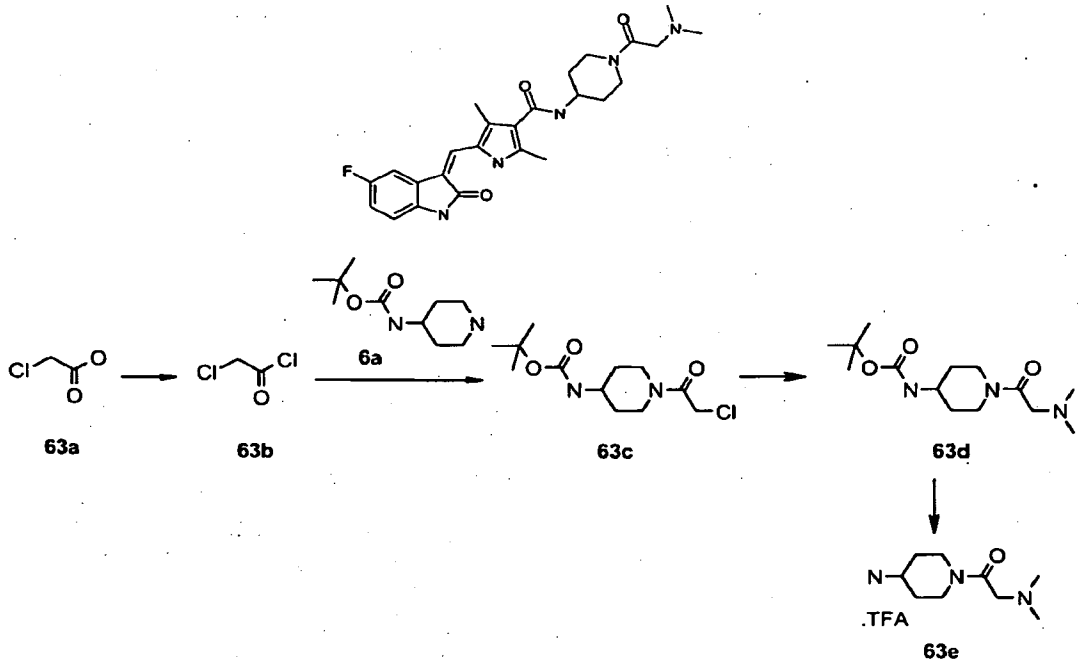
Example 62: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-methoxy- ethyl)-piperidin-4-yl]-amide



6a 62a 62b

The synthesis was similar to that of Example **61**. The title compound (71mg, 76%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H), 10.90(s, 1H), 7.54-7.78(m, 3H), 6.81-6.96(m, 2H), 3.68-3.72(m, 1H), 3.40-3.44(t, 2H), 3.23(s, 3H), 2.83-2.92(m, 2H), 2.45-2.50(m, 2H), 2.39-2.41(ds, 6H), 2.04-2.11(t, 2H), 1.76-1.79(m, 2H), 1.46-1.57(m, 2H). LC/MS: 441.1 $[M+H]^+$.

Example 63: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-dimethylamino-acetyl)-piperidin-4-yl]-amide

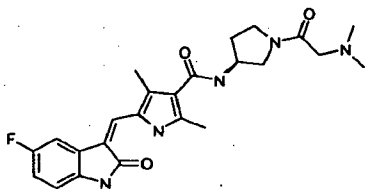


Step 1: Compound **63c** (125mg, 60%) was synthesized following procedure in making **54c** in Example **54**.

Step 2: To a solution of **63c** (125mg, 0.45mmol) in 15mL of acetonitile were added NH(CH3)2.HCl (110mg, 1.36mmol) and DIEA (232mg, 1.8mmol) at room temperature. The obtained mixture was stirred overnight and evaporated. The residue was re-dissolved in DCM and washed with brine. The DCM phase was separated, dried over anhydrous Na2SO4 and evaporated to provide crude **63d** which was directly used for the next step synthesis (118mg, 92%).

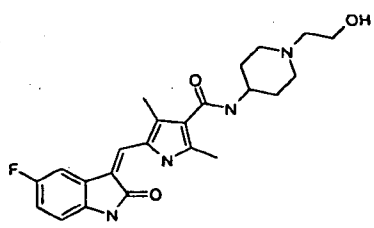
Step 3: The de-Boc step and final coupling to **A4** were similar to that of Example **48**. The title compound (49mg, 51%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H), 10.89(s, 1H), 7.61-7.77(m, 3H), 6.80-6.91(m, 2H), 4.21-4.25(d, 1H), 3.95-3.99(d, 2H), 3.07-3.18(m, 4H), 2.70-2.79(m, 2H), 2.38-2.40(ds, 6H), 2.15(s, 6H), 1.79-1.83(m, 2H). LC/MS: 466.3 $[M-H]^+$.

Example 64: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-dimethylamino-acetyl)-pyrrolidin-3-yl]-amide



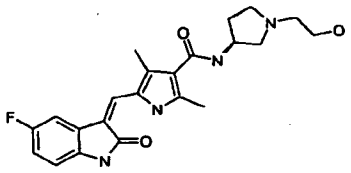
The title compound (44mg, 47%) was synthesized as orange solid following the procedure of Example **63**. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.72(s, 1H), 10.91(s, 1H), 7.71-7.89(m, 3H), 6.81-6.95(m, 2H), 4.35-4.44(m, 1H), 3.57-3.78(m, 4H), 2.99-3.01(d, 2H), 2.38-2.40(ds, 6H), 2.08-2.13(ds, 6H), 1.85-2.04(m, 2H). LC/MS: 452.3 $[M-H]^+$.

Example 65: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-hydroxy- ethyl)-piperidin-4-yl]-amide



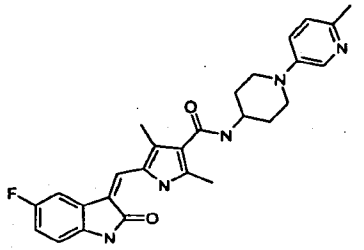
The title compound (31mg, 39%) was synthesized as orange solid following the procedure of Example **62**. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H), 10.90(s, 1H), 7.56-7.78(m, 3H), 6.81-6.95(m, 2H), 4.40-4.46(m, 1H), 3.69-3.73(m, 1H), 3.45-3.50(m, 2H), 2.72-2.84(d, 2H), 2.38-2.40(m, 8H), 1.90-2.20(m, 2H), 1.76-1.80(m, 2H), 1.24-1.44(m, 2H). LC/MS: 427.2 $[M+H]^+$.

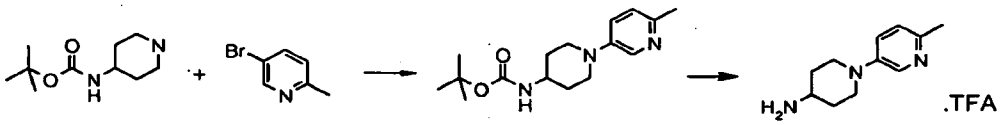
Example 66: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-hydroxy-ethyl)-pyrrolidin-3-yl]-amide



The title compound (29mg, 35%) was synthesized as orange solid following the procedure of Example **61**. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H), 10.87(s, 1H), 7.70-7.77(m, 3H), 6.81-6.95(m, 2H), 4.32-4.40(m, 2H), 3.44-3.50(q, 2H), 2.77-2.83(t, 1H), 2.52-2.66(m, 2H), 2.39-2.46(m, 8H), 2.07-2.13(m, 1H), 1.62-1.69(m, 2H), 0.88-0.97-1.44(m, 1H). LC/MS: 413.2 $[M+H]^+$.

Example 67: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (6'-methyl-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-amide



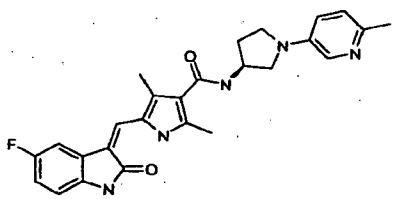


6a **66a** **66b** **66c** .TFA

Step 1: Pd(dba)3 (18.3mg, 0.02mmol), Xantphos (35mg, 0.06mmol) and Cs_2CO_3 (456g, 1.4mmol) were added to 10mL of 1,4-dioxane under the protection of N_2, compounds **6a** (200mg, 1mmol) and **66a** (224mg, 1.3mmol) were added to this mixture. The resulting mixture was heated to 100°C for 24h, cooled to room temperature which was taken up in EA (50mL), washed with brine and water. The organic phase was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give a residue which was purified by column chromatography (PE:EA=1:1) to provide compound **66b** (159mg, 55%).

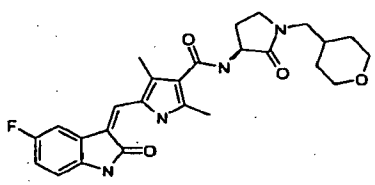
Step 2: The following de-Boc and final coupling steps were similar to that of Example **48**. The title compound (61mg, 71%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.89(s, 1H), 8.16-8.17(d, 1H), 7.62-7.78(m, 3H), 7.24-7.28(dd, 1H), 7.05-7.07(d, 1H), 6.81-6.95(m, 2H), 3.88-3.93(m, 1H), 3.65-3.69(d, 2H), 3.17-3.26(m, 2H), 2.79-2.88(m, 2H), 2.40-2.42(ds, 6H), 2.34(s, 3H), 1.84-1.92(m, 2H), 1.56-1.67(m, 2H). LC/MS: 474.2 $[M+H]^+$.

Example 68: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(6-methyl-pyridin-3-yl)-pyrrolidin-3-yl]-amide



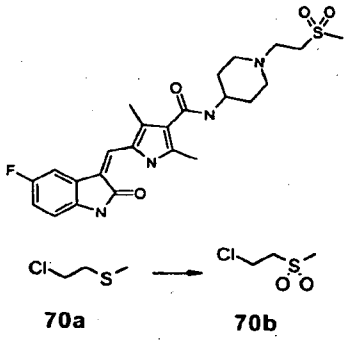
The title compound (64mg, 65%) was synthesized as orange solid following the procedure of Example **67**. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.89(s, 1H), 7.92-7.95(d, 1H), 7.71-7.82(m, 3H), 7.00-7.03(d, 1H), 6.81-6.95(m, 3H), 4.54-4.58(m, 1H), 3.54-3.59(m, 1H), 3.37-3.42(m, 1H), 3.28-3.30(m, 3H), 3.15-3.20(q, 1H), 2.38-2.40(ds, 6H), 2.29(s, 3H), 2.22-2.27(m, 1H), 1.99-2.05(m, 1H). LC/MS: 460.2 $[M+H]^+$.

Example 69: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2-oxo-1-(tetrahydro-pyran-4-ylmethyl)-pyrrolidin-3-yl]-amide



The title compound (30mg, 50%) was synthesized as orange solid following the procedure of Example **60**. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.91(s, 1H), 7.71-7.88(m, 3H), 6.82-6.96(m, 2H), 4.60-4.62(q, 1H), 3.82-3.85(d, 2H), 2.29-3.31(m, 6H), 2.42-2.44(ds, 6H), 2.31-2.35(m, 1H), 1.84-1.98(m, 2H), 1.49-1.58(m, 2H), 1.05-1.19(m, 2H). LC/MS: 481.0 $[M+H]^+$.

Example 70: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-methanesulfonyl-ethyl)-piperidin-4-yl]-amide

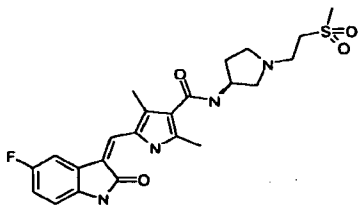


70a **70b**

Step 1: 30% H2O2 aqueous solution (5mL) was added to a solution of **70a** (900mg, 8.2mmol) in acetic acid (5mL) at room temperature. During the addition, heat was giving off. The resulting mixture was stirred overnight at room temperature and evaporated. The residue was purified by column chromatography (EA:PE=1:4) to provide **70b** (538mg, 46%) as colorless oil.

Subsequent steps are similar to that in Example **62**. The title compound (97mg, 84%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.66(s, 1H), 10.90(s, 1H), 7.55-7.79(m, 3H), 6.81-6.96(m, 2H), 3.71-3.74(m, 1H), 3.26-3.31(m, 2H), 3.04(s, 3H), 2.85-2.89(m, 2H), 2.68-2.72(t, 2H), 2.39-2.41(ds, 6H), 2.04-2.12(t, 2H), 1.76-1.82(m, 2H), 1.49-1.56(m, 2H). LC/MS: 487.2 $[M-H]^+$.

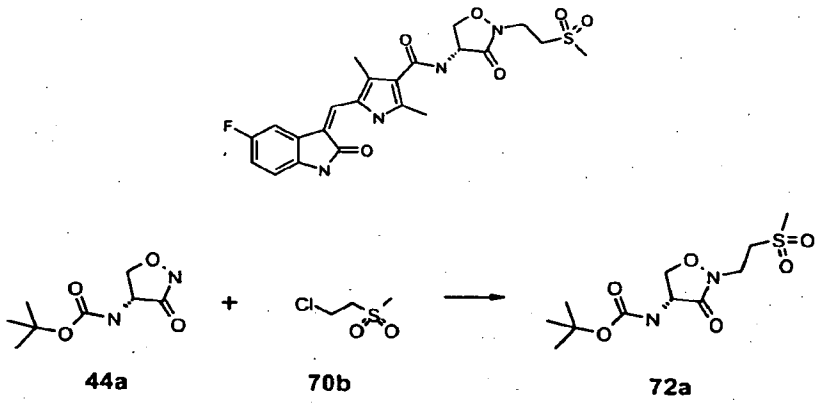
Example 71: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methanesulfonyl-ethyl)-pyrrolidin-3-yl]-amide



The title compound (96mg, 84%) was synthesized as orange solid following the procedure of Example **70**. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.67(s, 1H), 10.90(s, 1H), 7.71-7.80(m, 3H), 6.81-6.96(m, 2H), 4.35-4.37(m, 1H), 3.27-3.34(m,

4H), 3.04(s, 3H), 2.68-2.81(m, 4H), 2.39-2.41(ds, 6H), 2.11-2.18(m, 1H), 1.68-1.74(m, 1H). LC/MS: 473.2 $[M-H]^+$.

Example 72: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-methanesulfonyl-ethyl)-3-oxo-isoxazolidin-4-yl]-amide

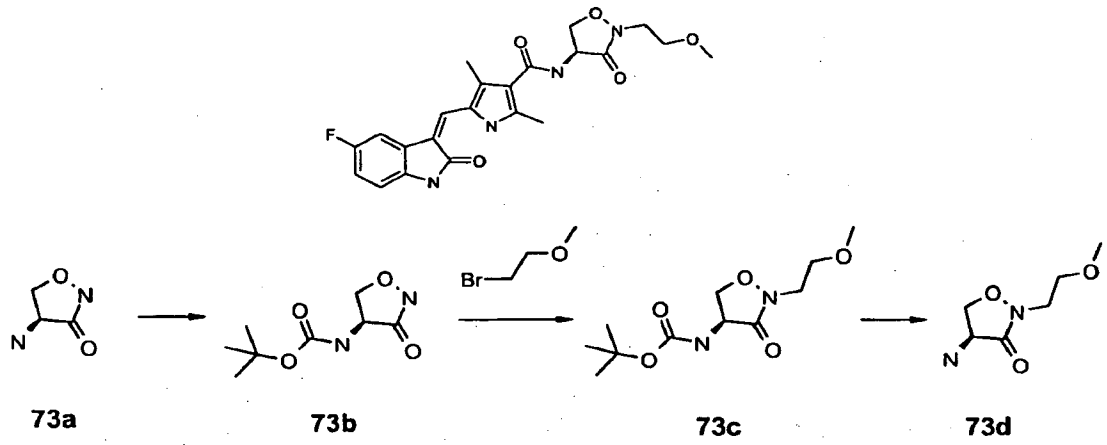


44a 70b 72a

Step 1: Compound **44a** (100mg, 0.5mmol), **70b** (86mg, 0.61mmol), KI (86mg, 0.52mmol), K2CO3 (342mg, 2.48mmol) and acetonitrile (20mL) were mixed in a microwave vial. The resulting mixture was reacted under microwave condition at 140°C for 1h. After being cooled, the mixture was filtered. The filtrate was evaporated and the residue was purified by column chromatography (EA) to provide **72a** (82mg, 49%).

Subsequent steps are similar to that of Example **48**. The title compound (71mg, 81%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.73(s, 1H), 10.93(s, 1H), 8.13-8.16(d, 1H), 7.73-7.80(m, 2H), 6.82-6.97(m, 2H), 4.96-5.05(q, 1H), 4.59-4.64(t, 1H), 4.08-4.14(t, 1H), 3.91-3.96(t, 2H), 3.44-3.49(t, 2H), 3.06(s, 3H), 2.43-2.45(ds, 6H). LC/MS: 491.0 $[M+H]^+$.

Example 73: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2-(2-methoxy-ethyl)-3-oxo-isoxazolidin-4-yl]-amide

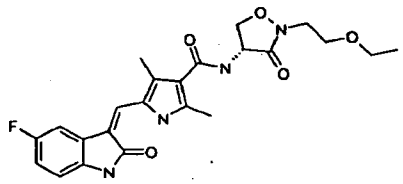


Step1: Compound **73a** (500mg, 4.9mmol) and TEA (990mg, 9.8mmol) were dissolved in a mixture of THF/water (75mL, V/V 2:1). (Boc)2O (1.18g, 5.4mmol) was added drop-wise under ice cooling. After the addition was complete, the mixture was warmed to room temperature and stirred overnight. The mixture was evaporated to dryness and the residue was purified by column chromatography (EA:PE=1:3) to provide compound **73b** (406mg, 41%) as white solid.

Step 2: Compound **73b** (200mg, 0.935mmol), 1-bromo-2-methoxy-ethane (156mg, 1.12mmol), KI (163mg, 0.98mmol), K2CO3 (645mg, 4.68mmol) and acetonitrile (20mL) were mixed in a microwave vial. The resulting mixture was reacted under microwave condition at 140°C for 1h. After being cooled, the mixture was filtered. The filtrate was evaporated and the residue was purified by column chromatography (EA::PE=1:3) to provide **73c** (138mg, 54%).

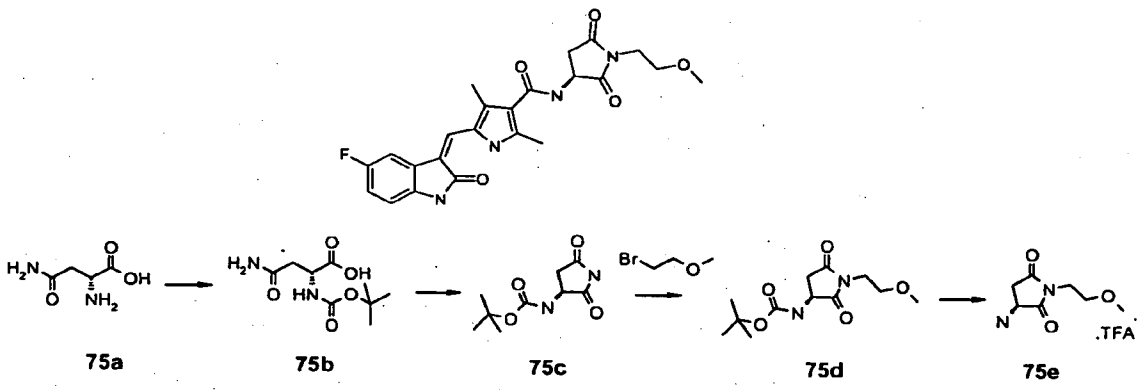
Step 3: The following de-Boc and final coupling steps were similar to that of Example **48**. The title compound (83mg, 83%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.72(s, 1H), 10.94(s, 1H), 8.12-8.15(d, 1H), 7.73-7.80(m, 2H), 6.82-6.97(m, 2H), 5.00-5.06(q, 1H), 4.57-4.63(t, 1H), 4.01-4.07(m, 1H), 3.45-3.71(m, 4H), 3.27(s, 3H), 2.43-2.45(ds, 6H). LC/MS: 442.9 $[M+H]^+$.

Example 74: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-ethoxy-ethyl)-3-oxo-isoxazolidin-4-yl]-amide



Following the procedure of Example **44**, the title compound (42mg, 91%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.73(s, 1H), 10.94(s, 1H), 8.11-8.14(d, 1H), 7.73-7.80(m, 2H), 6.82-6.97(m, 2H), 5.02-5.05(q, 1H), 4.37-4.63(t, 1H), 4.01-4.07(m, 1H), 3.40-3.70(m, 6H), 2.43-2.45(ds, 6H), 1.03-1.17(m, 3H). LC/MS: 457.2 $[M+H]^+$.

Example 75: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy-ethyl)-2,5-dioxo-pyrrolidin-3-yl]-amide



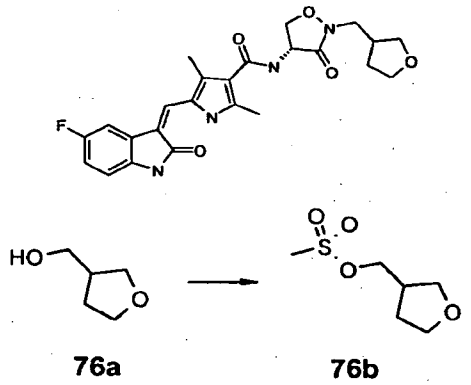
Step1: To a solution of **75a** (2.0g 15mmol), Na2CO3 (1.6g, 15mmol) in H2O/1,4-dioxane (30mL/30mL) was added (Boc)2O (3.96g, 18.2mmol) dropwise at room temperature. The mixture was stirred overnight and evaporated to remove 1,4-dioxane. The obtained aqueous solution was adjusted to pH=2 with 37% HCl. The formed precipitate was filtered, washed with water and dried to provide **75b** (2.97g, 84%) as white solid.

Step 2: To a stirred solution of **75b** (2.0g, 8.62mmol) in DMF (15mL) was added DCC (1.775g, 8.62mmol) and HOSu (0.99g, 8.62mmol). The mixture was heated to 80°C with stirring for 6h. DMF was evaporated and the residue was dissolved in EA (25mL) and filtered. The filtrate was washed with water, brine and dried by Na2SO4. After evaporation, the residue was purified by column

chromatography (EA:PE=1:1) to provide a pale yellow solid which was re-crystallized from EA to give **75c** (0.83g, 45%) as white solid.

Step 3: Subsequent steps are similar to that in Example **73** to obtain the title compound (83mg, 90%) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.73(s, 1H), 10.92(s, 1H), 8.17-8.19(d, 1H), 7.72-7.79(m, 2H), 6.82-6.97(m, 2H), 4.63-4.71(m, 1H), 3.58-3.63(q, 2H), 3.43-3.47(t, 2H), 3.30(s, 3H), 3.00-3.09(q, 1H), 2.63-2.70(dd, 1H), 2.43-2.44(ds, 6H). LC/MS: 455.0 $[M+H]^+$.

Example 76: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2-(tetrahydro-furan-3-ylmethyl)-isoxazolidin-4-yl]-amide

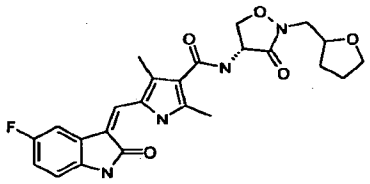


76a **76b**

Step1: To a solution of **76a** (250mg 2.45mmol), TEA (273mg, 2.7mmol) in DCM (20mL) was added methane sulfonyl chloride (298mg, 2.6mmol) drop-wise at 0°C. The mixture was stirred overnight at room temperature. After the reaction was complete, the mixture was washed with Na2CO3 solution. The organic phase was separated and the aqueous phase was extracted by DCM (20mL*3). The organic phase was combined, dried over anhydrous Na2SO4 and evaporated to provide **76b** (387mg, 88%) as an oil.

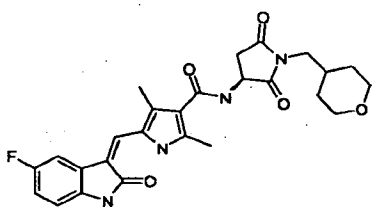
Subsequent steps are similar to that in Example **72** to obtain the title compound (33mg, 78%) obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.72(s, 1H), 10.92(s, 1H), 8.13-8.16(d, 1H), 7.73-7.79(m, 2H), 6.82-6.97(m, 2H), 5.01-5.10(q, 1H), 4.58-4.63(t, 2H), 4.04-4.11(m, 1H), 3.40-3.76(m, 6H), 2.72-2.88(m, 1H), 2.43-2.45(ds, 6H), 1.95-2.01(m, 1H), 1.59-1.63(m, 1H). LC/MS: 469.2 $[M+H]^+$.

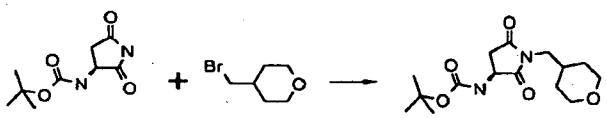
Example 77: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2-(tetrahydro-furan-2-ylmethyl)-isoxazolidin-4-yl]-amide



Following the procedure of Example **76**, the title compound (20mg, 72%) was obtained as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.72(s, 1H), 10.92(s, 1H), 8.10-8.14(m, 1H), 7.73-7.79(m, 2H), 6.82-6.94(m, 2H), 5.00-5.10(m, 1H), 4.57-4.62(t, 1H), 4.02-4.08(m, 2H), 3.57-3.77(m, 3H), 2.42-2.48(m, 1H), 2.40-2.49(ds, 6H), 1.60-1.93(m, 4H). LC/MS: 468.9 $[M+H]^+$.

Example 78: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2,5-dioxo- 1-(tetrahydro-pyran-4-ylmethyl)-pyrrolidin-3-yl]-amide





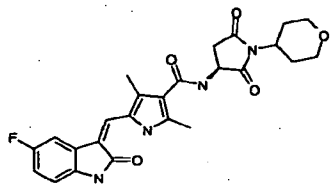
75c **60a** **78a**

Step1: Compound **75c** (200mg, 0.93mmol), **60a** (201mg, 1.12mmol), KI (163mg, 0.98mmol), K2CO3 (644mg, 4.67mmol) and acetonitrile (20mL) were mixed in a microwave vial. The resulting mixture was reacted under microwave condition at 140°C for 1h. After being cooled, the mixture was filtered. The filtrate was evaporated and the residue was purified by column chromatography (EA::PE=1:3) to provide **78a** (224mg, 77%).

Subsequent steps are similar to that in Example **48** to obtain the title compound (60mg, 72%) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.72(s, 1H), 10.93(s, 1H), 8.22-8.24(d, 1H), 7.72-7.79(m, 2H), 6.82-6.97(m, 2H), 4.58-

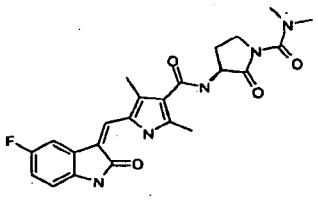
4.65(m, 1H), 3.81-3.85(m, 1H), 3.20-3.32(m, 4H), 2.97-3.06(q, 1H), 2.65-2.72(dd, 1H), 2.42-2.43(ds, 6H), 1.84-1.89(m, 1H), 1.58-1.64(m, 2H), 1.15-1.23(m, 2H). LC/MS: 495.2 $[M+H]^+$.

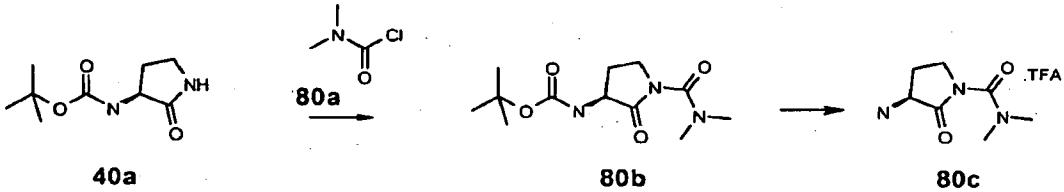
Example 79: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2,5-dioxo-1-(tetrahydro-pyran-4-yl)-pyrrolidin-3-yl]-amide



Following the procedure of Example **48**, the title compound (71mg, 62%) was obtained as orange solid. ^1H NMR (300 MHz, DMSO-d6): δ=13.73(s, 1H), 10.92(s, 1H), 8.17-8.20(d, 1H), 7.73-7.79(m, 2H), 6.82-6.97(m, 2H), 4.55-4.62(m, 1H), 4.10-4.18(m, 1H), 3.90-3.95(dd, 2H), 3.32-3.39(m, 2H), 2.93-3.02(q, 1H), 2.59-2.67(dd, 1H), 2.38-2.43(ds, 6H), 2.26-2.37(m, 2H), 1.48-1.51(d, 2H). LC/MS: 481.2 $[M+H]^+$.

Example 80: Preparation of 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-dimethylcarbamoyl-2-oxo-pyrrolidin-3-yl)-amide





40a **80b** **80c**

To a solution of **40a** (200mg, 1.0mmol) in DMF (10mL) was added 60% NaH (80mg, 2.0mmol) at 0°C. After stirring for another 1h at room temperature, the mixture was added compound **80a** (118mg, 1.1mmol). The resulted mixture was stirred at room temperature overnight and evaporated. The residue was purified by column chromatography (EA:PE=1:1) to provide **80b** (98mg, 36%).

Subsequent steps are similar to that in Example **48** to obtain the title compound (83mg, 76%) as orange solid. ^{1}H NMR (300 MHz, DMSO-d6): δ=13.70(s, 1H), 10.90(s, 1H), 8.04-8.07(m, 1H), 7.72-7.78(m, 2H), 6.82-6.96(m, 2H), 4.36-4.53(m, 1H), 3.57-3.62(m, 2H), 2.92(s,6H), 2.42-2.45(ds, 6H), 2.30-2.34(m,2H),2.12-2.19(m, 2H). LC/MS: 453.8 $[M+H]^+$.

Compounds in the tables herein are prepared in a manner similar as described above and in the general schemes.

Example 81: Biological Activity Assessment

VEGFR2 (KDR) Biochemical Assay

The compounds are assayed for biochemical activity essentially according to the following procedure. In a final reaction volume of 25 µl, KDR (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.33 mg/ml myelin basic protein, 10 mM MgAcetate and [(γ-33P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 µl of a 3% phosphoric acid solution. 10 µl of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

PDGFRβ Biochemical Assay

The compounds are assayed for biochemical activity essentially according to the following procedure. In a final reaction volume of 25 µl, PDGFRβ (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.1 mg/ml poly(Glu, Tyr) 4:1, 10 mM MgCl2, 10 mM MgAcetate and [(γ-33P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 µl of a 3% phosphoric acid solution. 10 µl of the reaction

is then spotted onto a filtermat A and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

AMPK Biochemical Assay

The compounds are assayed for biochemical activity essentially according to the following procedure. In a final reaction volume of 25 µl, AMPK (r) (5-10 mU) is incubated with 32 mM HEPES pH7.4, 0.65mM DTT, 0.012% Brij-35, 200 µM AMP, 200 µM AMARAASAAALARRR, 10 mM MgAcetate and [(γ-33P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 µl of a 3% phosphoric acid solution. 10 µl of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

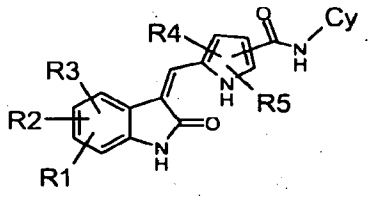
Some compounds exhibited significantly less AMPK inhibitory activities than sunitinib. They include, but are not limited to Examples 17, 22, 25, 29, 30, 31, 36, and 48.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited to, abstracts, articles, journals, publications, texts, treatises, internet web sites, databases, patents, and patent publications.

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed:

1. A compound of formula (I) or pharmaceutical salt, solvate or hydrate thereof:



I

wherein Cy is a cyclic structure that can be cycloalkyl, heterocyclic, aryl, or heteroaryl, each optionally substituted with Z_1, Z_2 and Z_3;

R_1, R_2, R_3, R_4, and R_5 are each independently:

(1) hydrogen or R_6, where R_6, is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with Z_1, Z_2 and one or more (preferably, one or two) groups Z_3;

(2) –OH or $-OR_6$;

(3) –SH or $-SR_6$;

(4) $-C(O)_2H$, $-C(O)_qR_6$, $-C(O)NR_7R_8$, $-C(O)C(O)NR_7R_8$, or $-O-C(O)_qR_6$, where q is 1 or 2;

(5) $-SO_3H$, $-S(O)_qR_6$, or $-S(O)_qNR_7R_8$;

(6) halo;

(7) cyano;

(8) nitro;

(9) $-Z_4$-NR_7R_8;

(10) $-Z_4-N(R_9)-Z_5-NR_{10}R_{11}$;

(11) $-Z_4-N(R_{12})-Z_5-R_6$;

(12) $-P(O)(OR_6)_2$;

R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are each independently:

(1) hydrogen or R_6;

(2) R_7 and R_8 together with the nitrogen atom to which they are attached may be a heterocycle which is unsubstituted or substituted with Z_1, Z_2 and Z_3; or

(3) any two of R_9, R_{10} and R_{11} together with the nitrogen atoms to which they are attached may be a 3- to 12-membered saturated or unsaturated mono-, bi-, or tri- heterocyclic ring which is unsubstituted or substituted with Z_1, Z_2 and Z_3;

Z_1, Z_2 and Z_3 are each independently:

(1) hydrogen or Z_6, where Z_6 is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (13);

(2) –OH or $-OZ_{16}$;

(3) –SH or $-SZ_{16}$;

(4) $-C(O)_2H$, $C(O)_qZ_{16}$, $-C(O)NZ_{17}Z_{18}$, $-C(O)C(O)NZ_{17}Z_{18}$, or $-O-C(O)_qZ_{16}$, where q is 1 or 2;

(5) $-SO_3H$, $-S(O)_qZ_{16}$, or $-S(O)_qNZ_{17}Z_{18}$;

(6) halo;

(7) cyano;

(8) nitro;

(9) $-Z_4-NZ_{17}Z_{18}$;

(10) $-Z_4-N(Z_{18})-Z_5-NZ_{19}Z_{20}$;

(11) oxo;

(12) $-O-C(O)-Z_{16}$;

(13) any two of Z_1, Z_2, and Z_3 may together be alkylene, alkenylene, aryl, heteroaryl, or heterocyclo completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z_4 and Z_5 are each independently

(1) a single bond;

(2) $-Z_{11}-S(O)_q-Z_{12}-$;

(3) $-Z_{11}-C(O)-Z_{12}-$;

(4) $-Z_{11}-O-Z_{12}-$;

(5) $-Z_{11}$-S-Z_{12}-;

(6) $-Z_{11}$-O-C(O)-Z_{12}-; or

(7) $-Z_{11}$-C(O)-O-Z_{12};

Z_{11} and Z_{12} are each independently

(1) a single bond;

(2) alkylene;

(3) alkenylene; or

(4) alkynylene;

each Z_{16} is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl, each optionally substituted with one or more of the following groups:

(2) –OH or $-OZ_{21}$;

(3) –SH or $-SZ_{21}$;

(4) $-C(O)_2H$, $C(O)_qZ_{21}$, $-C(O)NZ_{17}Z_{18}$, $-C(O)C(O)NZ_{17}Z_{18}$, or $-O-C(O)_qZ_{21}$, where q is 1 or 2;

(5) $-SO_3H$, $-S(O)_qZ_{21}$, or $-S(O)_qNZ_{17}Z_{18}$;

(6) halo;

(7) cyano;

(8) nitro;

(9) $-Z_4$-$NZ_{17}Z_{18}$;

(10) $-Z_4-N(Z_{18})-Z_5-NZ_{19}Z_{20}$;

(11) oxo;

(12) –O-C(O)-Z_{21};

each Z_{17} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl;

each Z_{18} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl;

each Z_{19} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl;

each Z_{20} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl;

each Z_{21} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; each Z_{22} is independently is,

(2) –OH or $-OZ_{21}$;

(3) –SH or $-SZ_{21}$;

(4) $-C(O)_2H$, $C(O)_qZ_{21}$, $-C(O)NZ_{21}Z_{21}$, $-C(O)C(O)NZ_{21}Z_{21}$, or $-O-C(O)_qZ_{21}$, where q is 1 or 2;

(5) $-SO_3H$, $-S(O)_qZ_{21}$, or $-S(O)_qNZ_{21}Z_{21}$;

(6) halo;

(7) cyano;

(8) nitro;

(9) $-Z_4-NZ_{21}Z_{21}$;

(10) $-Z_4-N(Z_{21})-Z_5-NZ_{21}Z_{21}$;

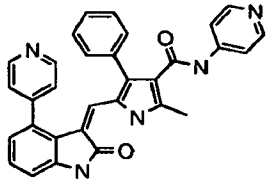
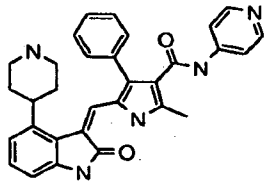
(11) oxo;

(12) $-O-C(O)-Z_{21}$;

where Z_{17} and Z_{18}, or Z_{19} and Z_{20}, together with the nitrogen atom to which they are attached may be a heterocycle which is unsubstituted or substituted with 1, 2, or 3 independent Z_{22}; and

where any two of Z_{18}, Z_{19} or Z_{20} together with the nitrogen atoms to which they are attached may be a 3- to 12-membered saturated or unsaturatedmono-, bi-, or tri- heterocyclic ring which is unsubstituted or substituted with 1, 2, or 3 independent Z_{22};

provided said compound is other than a compound of formula IIa or IIb.

IIa  IIb 

2. The compound of claim 1 wherein Cy is a non-aromatic cycloalkyl or heterocyclic structure that is optionally substituted with Z_1, Z_2 and Z_3.

3. The compound of claim 1 wherein Cy is a heterocyclic structure that is optionally substituted with Z_1, Z_2 and Z_3.

4. A molecule of claim 1 wherein any R_1, R_2 or R_3 in the 4-indolinone position is not a heterocycle or heteroaryl group.

5. The compound of claim 1 that is selected from:

5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-acetyl-piperidin-4-yl)-amide,

5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-methanesulfonyl-piperidin-4-yl)-amide,

N-(2H-3,4,5,6-tetrahydropyran-4-yl){5-[(5-fluoro-2-oxo(1H-benzo [d]azolin-3- ylidene)) methyl]-2,4-dimethylpyrrol-3-yl}carboxamide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid piperidin-4-ylamide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-acetyl-pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-methanesulfonyl-pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1,1-dioxo-tetrahydro-thiophen-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-pyrimidin-2-yl-piperidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-hydroxy- 1,1-dioxo-tetrahydro-thiophen-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1,1-dioxo- hexahydro-thiopyran-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-6-oxo- piperidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((2S,3S,4R,5S,6S)- 3,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-hydroxy-acetyl)- piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-hydroxy- acetyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-hydroxy-tetrahydro- furan-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-2-oxo- pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-benzyl-4-hydroxy- pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-acetyl-4-hydroxy- pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1-dimethylaminooxalyl- piperidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-dimethylaminooxalyl- pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((2S,3S,4R,5S)-3,4- dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1- carbamoylmethyl-2-oxo-pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-hydroxy- ethyl)-2-oxo-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-hydroxy- ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-dimethylcarbamoylmethyl-3-oxo-isoxazolidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-ethyl-3-oxo- isoxazolidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-2-carbamoylmethyl- 3-oxo-isoxazolidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-methoxy- ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((R)-3-oxo-2-pyridin- 3-ylmethyl-isoxazolidin-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2- (tetrahydro-pyran-4-yl)-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2- (tetrahydro-furan-3-yl)-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(morpholine-4- carbonyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(morpholine- 4-carbonyl)-pyrrolidin-3-yl]-amide,

4-({5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carbonyl}-amino)-piperidine- 1-carboxylic acid dimethylamide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1- dimethylcarbamoyl-pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-methoxy- acetyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy-acetyl)-pyrrolidin-3-yl]-amide,

N-((3R)oxolan-3-yl){5-[(5-fluoro-2-oxo(1H-benzo[d] azolin-3-ylidene))methyl]-2,4-dimethylpyrrol-3-yl}carboxamide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-morpholin- 4-yl-ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy- ethyl)-2-oxo-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-2-oxo-1-pyridin- 4-ylmethyl-pyrrolidin-3-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2- (tetrahydro-pyran-4-ylmethyl)-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy- ethyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-methoxy- ethyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-dimethylamino- acetyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-dimethylamino-acetyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2-hydroxy- ethyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-hydroxy- ethyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (6'-methyl-3,4,5,6- tetrahydro-2H-[1,3']bipyridinyl-4-yl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(6-methyl- pyridin-3-yl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2-oxo-1- (tetrahydro-pyran-4-ylmethyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [1-(2- methanesulfonyl-ethyl)-piperidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methanesulfonyl-ethyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-methanesulfonyl-ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2-(2-methoxy- ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-2-(2-ethoxy- ethyl)-3-oxo-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-1-(2-methoxy- ethyl)-2,5-dioxo-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2- (tetrahydro-furan-3-ylmethyl)-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(R)-3-oxo-2- (tetrahydro-furan-2-ylmethyl)-isoxazolidin-4-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2,5-dioxo- 1-(tetrahydro-pyran-4-ylmethyl)-pyrrolidin-3-yl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(S)-2,5-dioxo-1- (tetrahydro-pyran-4-yl)-pyrrolidin-3-yl]-amide, and

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((S)-1-dimethylcarbamoyl-2-oxo-pyrrolidin-3-yl)-amide.

6. The compound of claim 1 that is selected from:

5-[5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-hydroxy-cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-amino-cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-oxo-cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclopentyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((1S,2R)-2-hydroxy-cyclopentyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-acetylamino-cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (4-methanesulfonylamino-cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ((1S,2S)-2-hydroxy- cyclohexyl)-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [4-(morpholine-4- carbonyl)-cyclohexyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [4-(pyrrolidine-1- carbonyl)-cyclohexyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [4-(aziridine-1- carbonyl)-cyclohexyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,3S)-3-(pyrrolidine-1- carbonyl)-cyclopentyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,3S)-3- (morpholine-4- carbonyl)-cyclopentyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,3S)-3- (aziridine-1-carbonyl)-cyclopentyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,2S)-2- (pyrrolidine-1-carbonyl)-cyclopentyl]-amide,

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,2S)-2- (morpholine-4-carbonyl)-cyclopentyl]-amide, and

5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)- ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid [(1R,2S)-2- (aziridine-1-carbonyl)-cyclopentyl]-amide.

7. The compound of claim 1, wherein the Cy is optionally substituted cycloalkyl.

8. The compound of claim 1, wherein the compound of formula I is a compound delineated in Table 1, or pharmaceutical salt, solvate or hydrate thereof.

9. A method of treating a disease or disease symptom in a subject in need thereof comprising administering to the subject an effective amount of a compound of formula (I) in claim 1, or pharmaceutical salt, solvate or hydrate thereof.

10. The method of claim 9, wherein the disease or disease symptom is modulated by a kinase enzyme.

11. The method of claim 10, wherein the disease or disease symptom is modulated by any one or any combination of the kinases selected from VEGFR, PDEGFR, KIT, Flt-1, Flt-3, Flt-4, and RET.

12. The method of claim 9, wherein the disease or disease symptom is cancer, tumor, or a proliferative disorder.

13. A method of modulating the activity of a kinase enzyme comprising contacting a kinase enzyme with a compound of formula I in claim 1.

14. A method of making a compound of formula I in claim 1, comprising reacting an intermediate delineated herein with a reagent to provide a compound of formula I as defined herein.

15. A composition comprising a compound of formula I, or pharmaceutically acceptable salt thereof, according to any of claims 1-8 and a pharmaceutically acceptable carrier.

16. The composition of claim 15, further comprising an additional therapeutic agent.

17. The composition of claim 16, wherein the additional therapeutic agent is an anticancer agent.

18. A method of modulating kinase activity in a subject in need thereof comprising administering to the subject an effective amount of a compound of formula (I) in claim 1, or pharmaceutical salt, solvate or hydrate thereof.

19. The method of claim 18, wherein the compound selectively inhibits a kinase target preferentially over inhibition of AMPK.

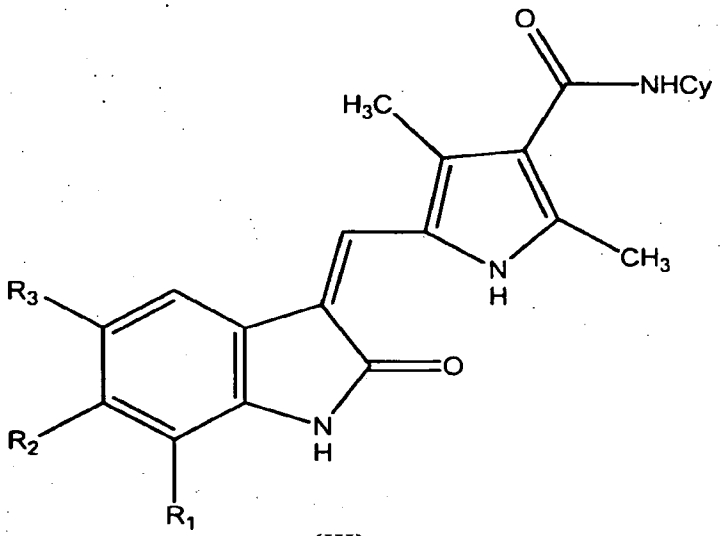
20. The method of claim 19, wherein the compound selectively inhibits a kinase target preferentially over inhibition of AMPK with greater selectivity than Sunitinib.

21. The method of claim 18, wherein the subject experiences little or no fatigue side effect.

22. The compound of claim 1, wherein the Cy is optionally substituted 5-membered ring heterocyclic.

23. The compound of claim 1, wherein the Cy is optionally substituted 6-membered ring heterocyclic.

24. The compound of claim 1, having the structure of formula III:



(III)

25. The compound of claim 24, wherein R_3 is halo.

26. The compound of claim 25, wherein R_3 is fluoro.

27. The compound of claim 24, wherein R_1 and R_2 are H, and R_3 is fluoro.

28. A method of identifying a kinase inhibitor that selectively inhibits a kinase target preferentially over inhibition of AMPK comprising: (i) assaying a test compound for inhibition of a kinase enzyme; (ii) assaying the test compound for inhibition of AMPK; (iii) assessing whether the test compound inhibits a kinase target preferentially over inhibition of AMPK.

29. The method of claim 28, wherein the test compound inhibits a kinase target preferentially over inhibition of AMPK with greater selectivity than Sunitinib.

30. A method of treating a disease or disease symptom in a subject in need thereof comprising administering to the subject an effective amount of a compound identified by the method of claim 28, or pharmaceutical salt, solvate or hydrate thereof.