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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
07 March 2019 (07.03.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/046186 A1

(51) International Patent Classification:
A61K 31/165 (2006.01) *C07D 209/46* (2006.01)

(21) International Application Number:
PCT/US2018/048131

(22) International Filing Date:
27 August 2018 (27.08.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/550,951 28 August 2017 (28.08.2017) US

(71) Applicant: **ENANTA PHARMACEUTICALS, INC.** [US/US]; 500 Arsenal Street, Watertown, MA 02472 (US).

(72) Inventors: **WANG, Guoqiang**; 65 Becket Road, Belmont, MA 02478 (US). **HE, Jing**; 21 Cedar Ave, Somerville, MA 02143 (US). **WANG, Bin**; 1925 Commonwealth Ave., Apt. 1416, Brighton, MA 02135 (US). **SHEN, Ruichao**; 72 Pond Street, Belmont, MA 02478 (US). **GRANGER, Brett**; 1 Lillian Avenue, Sudbury, MA 01776 (US). **OR, Yat, Sun**; 169 Fayette Street, Watertown, MA 02472 (US).

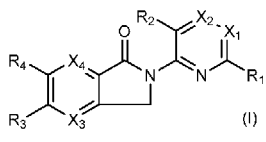
(74) Agent: **HARLAN, Edgar, W.** et al.; Elmore Patent Law Group, P.C., 484 Groton Road, Westford, MA 01886 (US).

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

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

Published:
— *with international search report (Art. 21(3))*

(54) **Title:** TETRAZOLE CONTAINING APOPTOSIS SIGNAL-REGULATING KINASE 1 INHIBITORS AND METHODS OF USE THEREOF



(I)

(57) **Abstract:** The present invention discloses compounds of Formula (I), or pharmaceutically acceptable salts, ester, stereoisomer, tautomer, solvate, hydrate, or combination thereof: (I) which inhibit the Apoptosis signal-regulating kinase 1 (ASK-1), which associated with autoimmune disorders, neurodegenerative disorders, inflammatory diseases, chronic kidney disease, cardiovascular disease. The present invention further relates to pharmaceutical compositions comprising the aforementioned compounds for administration to a subject suffering from ASK-1 related disease. The invention also relates to methods of treating an ASK-1 related disease in a subject by administering a pharmaceutical composition comprising the compounds of the present invention. The present invention specifically relates to methods of treating ASK-1 associated with hepatic steatosis, including non-alcoholic fatty liver disease (NAFLD) and non-alcohol steatohepatitis disease (NASH).

WO 2019/046186 A1

TETRAZOLE CONTAINING APOPTOSIS SIGNAL-REGULATING KINASE 1 INHIBITORS AND METHODS OF USE THEREOF

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/550,951, filed on August 28, 2017. The entire teachings of the above application are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates generally to compounds and pharmaceutical compositions useful as ASK-1 inhibitors. Specifically, the present invention relates to compounds useful as inhibitors of ASK-1 and methods for their preparation and use.

BACKGROUND OF THE INVENTION

Apoptosis signal-regulating kinase 1 (ASK-1) is a member of the mitogen-activated protein kinase kinase kinase (MAPKKK, MAP3K) family, which when activated phosphorylates downstream MAP kinase kinases (MAPKK, MAP2K), which in turn activate MAP kinases (MAPK). MAPKs elicit a response by phosphorylating cellular substrates, thus regulating the activity of transcription factors that ultimately control gene expression. Specifically ASK-1, also known as MAPKKK5, phosphorylates MAPKK4/MAPKK7 or MAPKK3/MAPKK6, which subsequently phosphorylates and activates the c-Jun N-terminal protein kinase (JNK) and p38 MAPKs, respectively (H. Ichijo, et al., *Cell Comm. Signal* **2009**, *7*, 1-10; K. Takeda, et al., *Annu. Rev. Pharmacol. Toxicol.* **2008**, *48*, 199-225; H. Nagai, et al., *J. Biochem. Mol. Biol.* **2007**, *40*, 1-6). Activation of the JNK and p38 pathways triggers a downstream stress response such as apoptosis, inflammation, or differentiation (H. Ichijo, et al., *Science* **1997**, *275*, 90-94; K. Takeda, et al., *J. Biol. Chem.* **2000**, *275*, 9805-9813; K. Tobiume, et al., *EMBO Rep.* **2001**, *2*, 222-228; K. Sayama et al., *J. Biol. Chem.* **2001**, *276*, 999-1004).

The activity of ASK-1 is regulated by thioredoxin (Trx), which binds to the N-terminal end of ASK-1 (M. Saitoh, et al., *EMBO J.* **1998**, *17*, 2596-2606). ASK-1 is activated succeeding autophosphorylation at Thr838 in response to environmental stimuli including oxidative stress, lipopolysaccharides (LPS), reactive oxygen species (ROS), endoplasmic reticulum (ER) stress, an increase in cellular calcium ion concentrations, Fas ligand, and various cytokines such as tumor necrosis factor (TNF) (H. Nishitoh, et al., *Genes Dev.* **2002**,

16, 1345-1355; K. Takeda, et al., *EMBO Rep.* **2004**, *5*, 161-166; A. Matsuzawa, et al., *Nat. Immunol.* **2005**, *6*, 587-592).

ASK-1 has been associated with autoimmune disorders, neurodegenerative disorders, inflammatory diseases, chronic kidney disease, cardiovascular disease, metabolic disorders, and acute and chronic liver diseases (R. Hayakawa, et al., *Proc. Jpn. Acad., Ser. B* **2012**, *88*, 434-453).

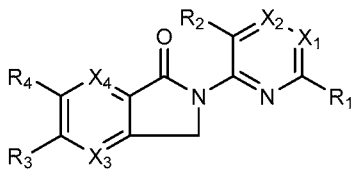
More specifically, ASK-1 has been associated with hepatic steatosis, including non-alcoholic fatty liver disease (NAFLD) and non-alcohol steatohepatitis (NASH). In a mouse model, high fat diets have caused induction of hepatic steatosis, ultimately causing fat accumulation and fatty acid oxidation. This led to the generation of ROS which caused hepatocyte dysfunction and death (S. K. Mantena, et al., *Free Radic. Biol. Med.* **2008**, *44*, 1259-1272; S. K. Mantena, et al., *Biochem. J.* **2009**, *417*, 183-193). Moreover, TNF was shown to be critical for apoptosis of hepatocytes through the ASK-1-JNK pathway, and TNF deficient mice showed reduced hepatic steatosis and fibrosis (W. Zhang, et al., *Biochem. Biophys. Res. Commun.* **2010**, *391*, 1731-1736).

Small molecule compounds which act as ASK-1 inhibitors have been disclosed in the following publications: WO 2008/016131, WO 2009/027283, WO 2009/0318425, WO 2009/123986, US 2009/0318425, WO 2011/041293, WO 2011/097079, US 2011/0009410, G.P. Volynets, et al., *J. Med. Chem.* **2011**, *54*, 2680-2686, WO 2012/003387, WO 2012/011548, WO 2012/080735, Y. Terao, et al., *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7326-7329, WO 2013/112741, G.P. Volynets, et al., *Eur. J. Med. Chem.* **2013**, *16*, 104-115, US 2014/0018370, WO 2014/100541, WO 2015/095059, WO 2016/049069, WO 2016/049070, WO 2018133865 and WO 2018133866.

There is a need for the development of ASK-1 inhibitors for the treatment and prevention of disease. The present invention has identified compounds which inhibit ASK-1 as well as methods of using these compounds to treat disease.

SUMMARY OF THE INVENTION

In one aspect, the invention provides compounds represented by Formula I, or a pharmaceutically acceptable salt, ester, or combination thereof:

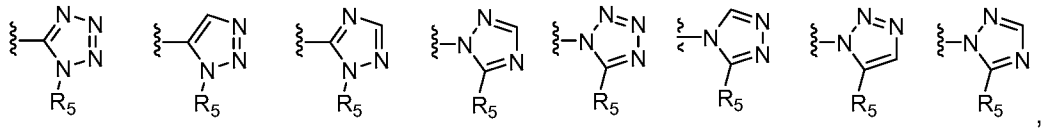


(I)

,

wherein

R_1 is selected from the groups below:



,

Each of which is optionally substiuted when possible;

R_5 is selected from the group consisting of:

1) Hydrogen;
2) Optionally substituted $-C_1$-C_8 alkyl;
3) Optionally substituted $-C_2$-C_8 alkenyl;
4) Optionally substituted $-C_2$-C_8 alkynyl;
5) Optionally substituted $-C_3$-C_8 cycloalkyl;
6) Optionally substituted aryl;
7) Optionally substituted arylalkyl;
8) Optionally substituted 3- to 8- membered heterocycloalkyl;
9) Optionally substituted heteroaryl; and
10) Optionally substituted heteroarylalkyl;

X_1, X_2, X_3 and X_4 are each independently selected from N and C(R_6);

R_2 and R_6 are each independently selected from the group consisting of:

1) Hydrogen;
2) Halogen;
3) $-NO_2$;
4) Cyano;
5) Optionally substituted $-C_1$-C_8 alkyl;
6) Optionally substituted $-C_1$-C_8 cycloalkyl; and
7) Optionally substituted 3- to 8- membered heterocycloalkyl;

R_3 and R_4 are each independently selected from the group consisting of:

1) Hydrogen;
2) Halogen;
3) $-NO_2$;
4) Cyano;
5) Optionally substituted $-C_1$-C_8 alkyl;
6) Optionally substituted $-C_2$-C_8 alkenyl;
7) Optionally substituted $-C_2$-C_8 alkynyl;
8) Optionally substituted $-C_3$-C_8 cycloalkyl;
9) Optionally substituted aryl;
10) Optionally substituted arylalkyl;
11) Optionally substituted 3- to 8- membered heterocycloalkyl;
12) Optionally substituted heteroaryl;
13) Optionally substituted heteroarylalkyl;
14) $-OR_7$;
15) $-N(R_7)(R_8)$;
16) $-S(O)_2N(R_7)(R_8)$;
17) $-N(R_7)C(O)R_8$; and
18) $-N(R_7)S(O)_2R_8$;

wherein R_7 and R_8 are independently selected from the group consisting of hydrogen; -C_1-C_{15} alkyl; cycloalkyl; heterocycloalkyl; aryl, and heteroaryl, each of which is optionally substituted with 1 to 3 substituents independently selected from halo; alkyl; alkylamino; dialkylamino; alkylC(O)NH-; arylC(O)NH-; heteroarylC(O)NH-amido; −CN, alkoxy; $-CF_3$; aryl, and heteroaryl, or R_7 and R_8 are taken together with the nitrogen atom to which they are attached to form a heterocyclic.

In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt, ester or combination thereof, in combination with a pharmaceutically acceptable carrier or excipient.

In another embodiment, the present invention provides a method for the prevention or treatment of an ASK-1 mediated disease or condition ion a subject in need thereof. The method comprises administering to the subject a therapeutically effective amount of a compound of Formula (I). The present invention also provides the use of a compound of

Formula (I) for the preparation of a medicament for the prevention or treatment of an ASK-1 mediated disease or condition. Such diseases include autoimmune disorders, neurodegenerative disorders, inflammatory diseases, chronic kidney disease, cardiovascular disease, metabolic disorders, and acute and chronic liver diseases.

DETAILED DESCRIPTION OF THE INVENTION

A first embodiment of the invention is a compound represented by Formula I as described above, or a pharmaceutically acceptable salt, ester, or combination thereof.

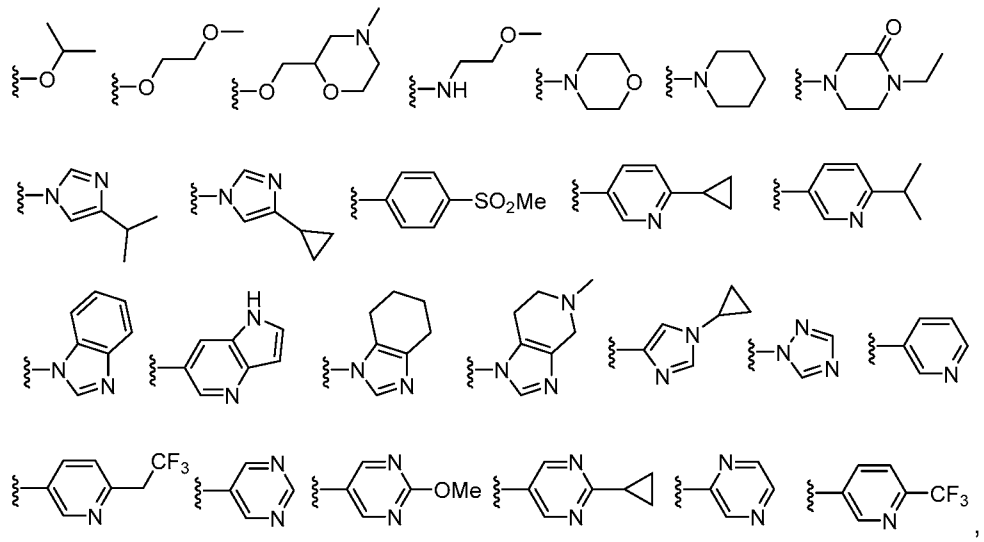
In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts and esters thereof, wherein X_1 is CH. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts and esters thereof, wherein X_2 is CH. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts, esters and combinations thereof, wherein X_1 is CH, and X_2 is CH.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts and esters thereof, wherein X_3 is CH. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts, esters and combinations thereof, wherein X_4 is CH. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts, esters and combinations thereof, wherein X_3 is CH and X_4 is CH.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts and esters thereof, wherein X_4 is N. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts, esters and combinations thereof, wherein X_3 is CH and X_4 is N.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts and esters thereof, wherein R_3 is hydrogen. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts, esters and combinations thereof, wherein R_3 is halogen. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts and esters thereof, wherein R_3 is CH_3, CF_3, NH_2, NH(Me), $N(Me)_2$, or F.

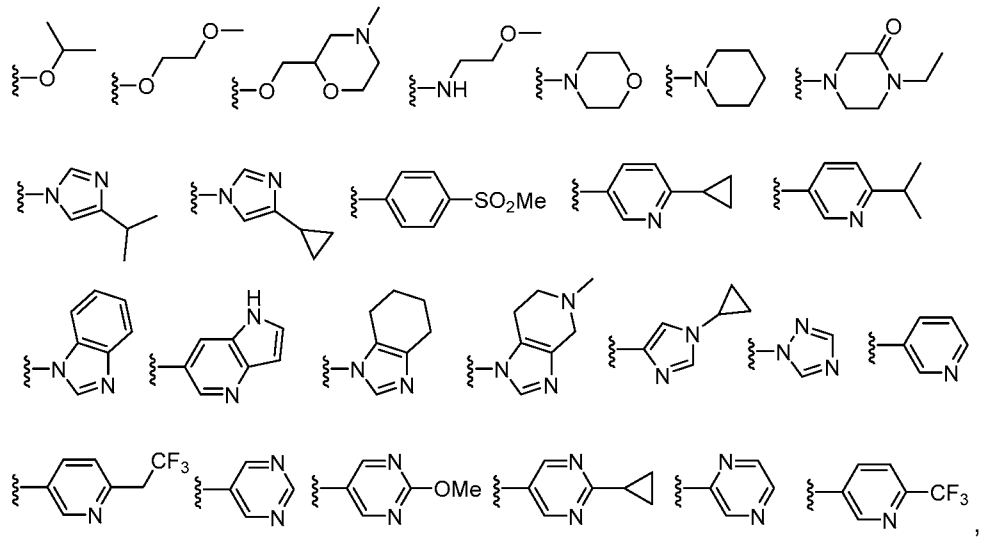
In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts, esters and combinations thereof, wherein R_3 is selected from:



wherein each of the above shown groups is optionally substituted.

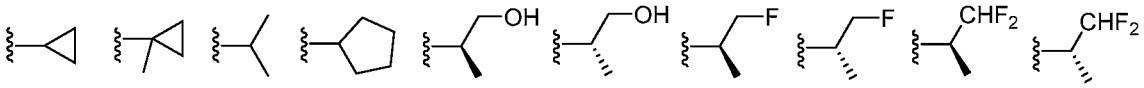
In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts, esters and combinations thereof, wherein R_4 is hydrogen. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts, esters and combinations thereof, wherein R_4 is halogen. In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts, esters and combinations thereof, wherein R_4 is CH_3, CF_3, NH_2, NHMe, $N(Me)_2$, or F.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salts, esters and combinations thereof, wherein R_4 is selected from:



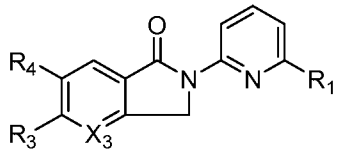
wherein each of the above shown groups is optionally substituted.

In certain embodiments, the present invention relates to compounds of Formula (**I**), and pharmaceutically acceptable salt, ester and combination thereof, wherein R_5 is selected from:



wherein each of the above shown groups is optionally substituted.

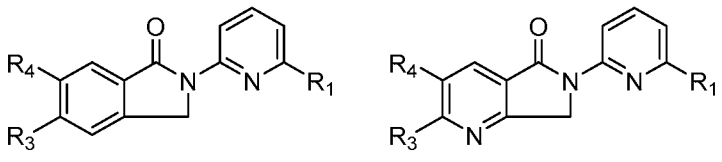
In one embodiment of the invention is represented by Formula (II) or a pharmaceutically acceptable salt, ester, or combination thereof:



(II)

wherein R_1, R_3, R_4 and X_3 are as previously defined.

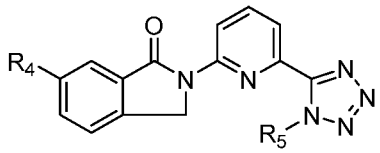
In another embodiment of the invention is represented by Formula (IIIa) or Formula (IIIb), or a pharmaceutically acceptable salt, or ester, or combination thereof:



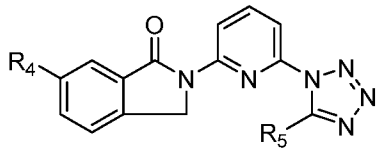
(IIIa) (IIIb)

wherein R_1, R_3, and R_4 are as previously defined.

In another embodiment of the invention is represented by Formula (IVa) or (IVb), or a pharmaceutically acceptable salt, or combination thereof:



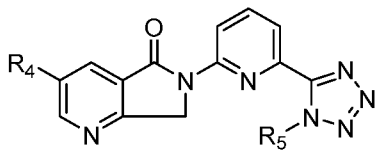
(IVa)



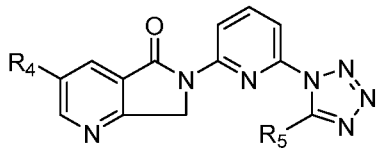
(IVb)

wherein R_4 and R_5 are as previously defined.

In another embodiment of the invention is represented by Formula (Va) or (Vb), or a pharmaceutically acceptable salt, or combination thereof:



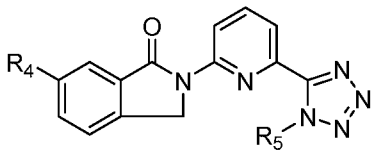
(Va)



(Vb)

wherein R_4 and R_5 are as previously defined.

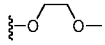
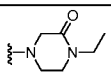
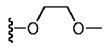
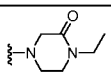
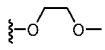
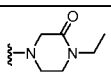
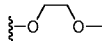
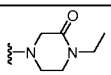
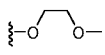
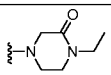
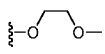
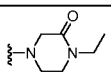
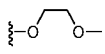
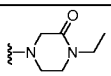
Representative compounds of the invention include, but are not limited to, the following compounds (compound 1 to compound 100 in Table 1) according to Formula (IVa), and pharmaceutically acceptable salts, esters and combinations thereof, wherein R_4 and R_5 are delineated for each compound in Table 1.

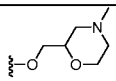
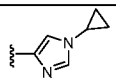
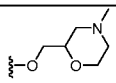
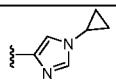
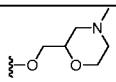
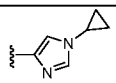
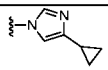
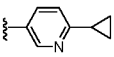
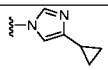
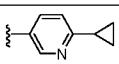
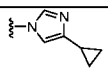
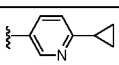
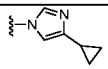
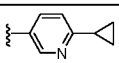
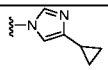
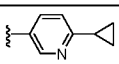
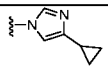
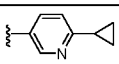
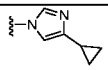
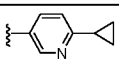


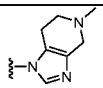
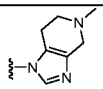
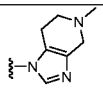
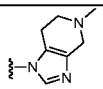
(IVa)

Table 1

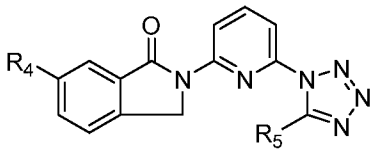
compound	R_5	R_4	compound	R_5	R_4
1			51		
2			52		
3			53		
4			54		
5			55		
6			56		
7			57		

8			58		
9			59		
10			60		
11			61		
12			62		
13			63		
14			64		
15			65		
16			66		
17			67		
18			68		
19			69		
20			70		
21			71		
22			72		
23			73		
24			74		
25			75		
26			76		
27			77		

28			78		
29			79		
30			80		
31			81		
32			82		
33			83		
34			84		
35			85		
36			86		
37			87		
38			88		
39			89		
40			90		
41			91		
42			92		
43			93		
44			94		
45			95		
46			96		

47			97		
48			98		
49			99		
50			100		

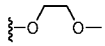
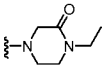
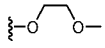
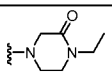
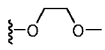
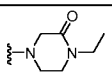
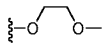
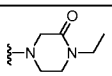
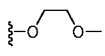
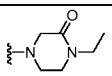
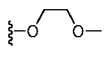
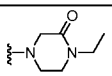
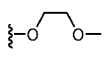
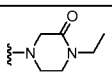
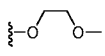
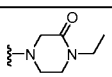
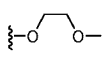
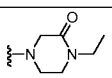
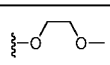
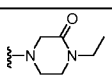
Representative compounds of the invention include, but are not limited to, the following compounds (compound 101 to compound 200 in Table 2) according to Formula (IVb), and pharmaceutically acceptable salts, esters and combinations thereof, wherein R_4 and R_5 are delineated for each compound in Table 2.

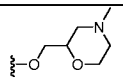
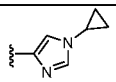
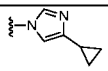
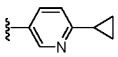
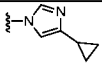
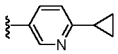
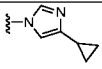
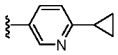
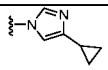
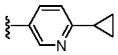
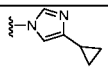
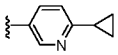
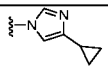
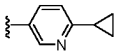
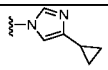
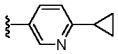
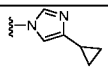
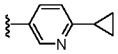
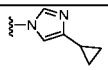
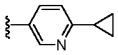


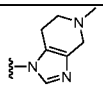
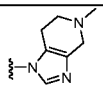
(IVb)

Table 2

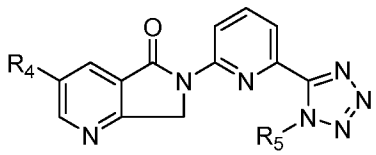
compound	R_5	R_4	compound	R_5	R_4
101			151		
102			152		
103			153		
104			154		
105			155		
106			156		
107			157		
108			158		
109			159		
110			160		

111			161		
112			162		
113			163		
114			164		
115			165		
116			166		
117			167		
118			168		
119			169		
120			170		
121			171		
122			172		
123			173		
124			174		
125			175		
126			176		
127			177		
128			178		
129			179		

130			180		
131			181		
132			182		
133			183		
134			184		
135			185		
136			186		
137			187		
138			188		
139			189		
140			190		
141			191		
142			192		
143			193		
144			194		
145			195		
146			196		
147			197		
148			198		

149			199		
150			200		

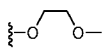
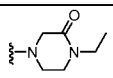
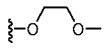
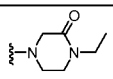
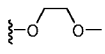
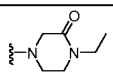
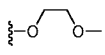
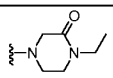
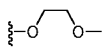
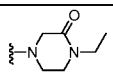
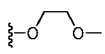
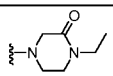
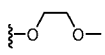
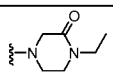
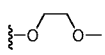
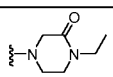
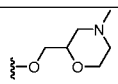
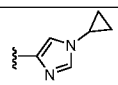
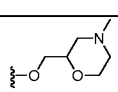
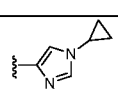
Representative compounds of the invention include, but are not limited to, the following compounds (compound 201 to compound 300 in Table 3) according to Formula (Va), and pharmaceutically acceptable salts, esters and combinations thereof, wherein R_4 and R_5 are delineated for each compound in Table 3.

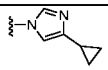
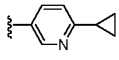
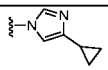
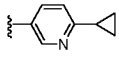
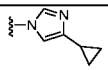
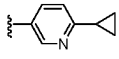
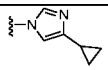
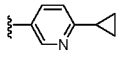
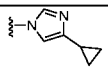
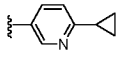
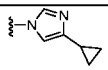
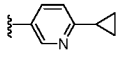
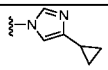
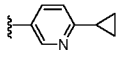
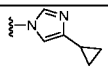
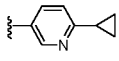
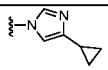
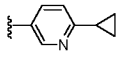
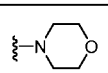
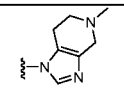


(Va)

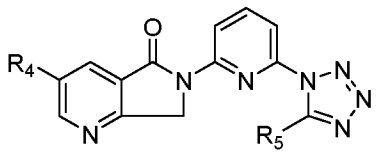
Table 3

compound	R_5	R_4	compound	R_5	R_4
201			251		
202			252		
203			253		
204			254		
205			255		
206			256		
207			257		
208			258		
209			259		
210			260		
211			261		
212			262		

213			263		
214			264		
215			265		
216			266		
217			267		
218			268		
219			269		
220			270		
221			271		
222			272		
223			273		
224			274		
225			275		
226			276		
227			277		
228			278		
229			279		
230			280		
231			281		

232			282		
233			283		
234			284		
235			285		
236			286		
237			287		
238			288		
239			289		
240			290		
241			291		
242			292		
243			293		
244			294		
245			295		
246			296		
247			297		
248			298		
249			299		
250			300		

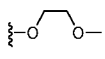
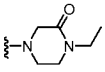
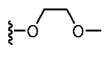
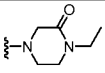
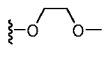
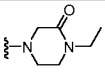
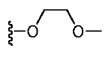
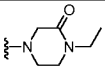
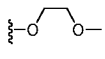
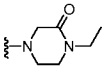
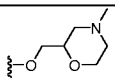
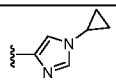
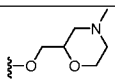
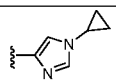
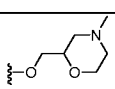
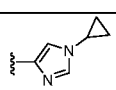
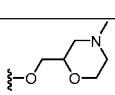
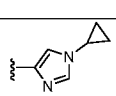
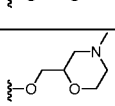
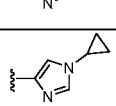
Representative compounds of the invention include, but are not limited to, the following compounds (compound 301 to compound 400 in Table 4) according to Formula (Vb), and pharmaceutically acceptable salts, esters and combinations thereof, wherein R_4 and R_5 are delineated for each compound in Table 4.

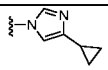
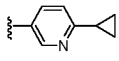
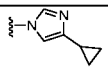
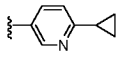
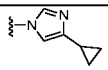
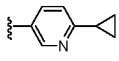
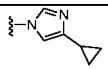
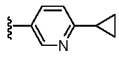
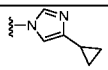
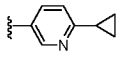
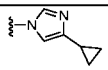
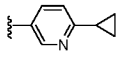
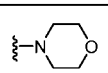
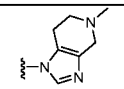
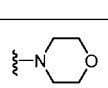
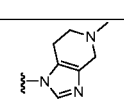
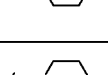
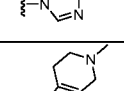
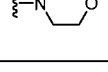
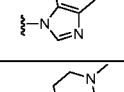


(Vb)

Table 4

compound	R_5	R_4	compound	R_5	R_4
301			351		
302			352		
303			353		
304			354		
305			355		
306			356		
307			357		
308			358		
309			359		
310			360		
311			361		
312			362		
313			363		
314			364		
315			365		

316			366		
317			367		
318			368		
319			369		
320			370		
321			371		
322			372		
323			373		
324			374		
325			375		
326			376		
327			377		
328			378		
329			379		
330			380		
331			381		
332			382		
333			383		
334			384		

335			385		
336			386		
337			387		
338			388		
339			389		
340			390		
341			391		
342			392		
343			393		
344			394		
345			395		
346			396		
347			397		
348			398		
349			399		
350			400		

In certain embodiments, the present invention provides a method for the prevention or treatment of an ASK-1 mediated disease or condition. The method comprises administering a therapeutically effective amount of a compound of Formula (I). The present

invention also provides the use of a compound of Formula (I) for the preparation of a medicament for the prevention or treatment of an ASK-1 mediated disease or condition.

In certain embodiments, the ASK-1 mediated disease or condition is an autoimmune disorder, a neurodegenerative disorder, an inflammatory disease, chronic kidney disease, renal disease, cardiovascular disease, a metabolic disease, or an acute or chronic liver disease.

In certain embodiments, the chronic liver disease is primary biliary cirrhosis (PBC), cerebrotendinous xanthomatosis (CTX), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver transplant associated graft versus host disease, living donor transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, Sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, or alpha 1-antitrypsin deficiency. In certain embodiments, the gastrointestinal disease is inflammatory bowel disease (IBD) (including Crohn's disease and ulcerative colitis), irritable bowel syndrome (IBS), bacterial overgrowth, malabsorption, post-radiation colitis, or microscopic colitis.

In certain embodiments, the renal disease is diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, or polycystic kidney disease.

In certain embodiments, the cardiovascular disease is atherosclerosis, arteriosclerosis, dyslipidemia, hypercholesterolemia, or hypertriglyceridemia.

In certain embodiments, the metabolic disease is insulin resistance, Type I and Type II diabetes, or obesity.

Yet a further aspect of the present invention is a process of making any of the compounds delineated herein employing any of the synthetic means delineated herein.

DEFINITIONS

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "alkyl" as used herein, refers to saturated, straight- or branched-chain hydrocarbon radicals. "C_1-C_3 alkyl","C_1-C_6 alkyl", "C_1-C_{10} alkyl", "C_2-C_4 alkyl" or "C_3-C_6 alkyl", refer to alkyl groups containing from one to three, one to six, one to ten carbon atoms, 2 to 4 and 3 to 6 carbon atoms respectively. Examples of C_1-C_8 alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, n-hexyl, heptyl and octyl radicals.

The term "alkenyl" as used herein, refers to straight- or branched-chain hydrocarbon radicals having at least one carbon-carbon double bond by the removal of a single hydrogen atom. "C_2-C_{10} alkenyl", "C_2-C_8 alkenyl", "C_2-C_4 alkenyl", or "C_3-C_6 alkenyl", refer to alkenyl groups containing from two to ten, two to eight, two to four or three to six carbon atoms respectively. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl, and the like.

The term "alkynyl" as used herein, refers to straight- or branched-chain hydrocarbon radicals having at least one carbon-carbon triple bond by the removal of a single hydrogen atom. "C_2-C_{10} alkynyl", "C_2-C_8 alkynyl", "C_2-C_4 alkynyl", or "C_3-C_6 alkynyl" refer to alkynyl groups containing from two to ten, two to eight, two to four or three to six carbon atoms respectively. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl, and the like.

The term "cycloalkyl", as used herein, refers to a monocyclic or polycyclic saturated carbocyclic ring or a bi- or tri-cyclic group fused, bridged or spiro system, and the carbon atoms may be optionally oxo-substituted or optionally substituted with exocyclic olefinic, iminic or oximic double bond. Preferred cycloalkyl groups include C_3-C_{12} cycloalkyl, C_3-C_6 cycloalkyl, C_3-C_8 cycloalkyl and C_4-C_7 cycloalkyl. Examples of C_3-C_{12} cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl, cyclooctyl, 4-methylene-cyclohexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.0]hexyl, spiro[2.5]octyl, 3-methylenebicyclo[3.2.1]octyl, spiro[4.4]nonanyl, and the like.

The term "cycloalkenyl", as used herein, refers to monocyclic or polycyclic carbocyclic ring or a bi- or tri-cyclic group fused, bridged or spiro system having at least one carbon-carbon double bond and the carbon atoms may be optionally oxo-substituted or optionally substituted with exocyclic olefinic, iminic or oximic double bond. Preferred

cycloalkenyl groups include C_3-C_{12} cycloalkenyl, C_3-C_8 cycloalkenyl or C_5-C_7 cycloalkenyl groups. Examples of C_3-C_{12} cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, bicyclo[2.2.1]hept-2-enyl, bicyclo[3.1.0]hex-2-enyl, spiro[2.5]oct-4-enyl, spiro[4.4]non-1-enyl, bicyclo[4.2.1]non-3-en-9-yl, and the like.

The term "aryl," as used herein, refers to a mono- or polycyclic carbocyclic ring system comprising at least one aromatic ring, including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, and indenyl. A polycyclic aryl is a polycyclic ring system that comprises at least one aromatic ring. Polycyclic aryls can comprise fused rings, covalently attached rings or a combination thereof.

The term "heteroaryl," as used herein, refers to a mono- or polycyclic aromatic radical having one or more ring atom selected from S, O and N; and the remaining ring atoms are carbon, wherein any N or S contained within the ring may be optionally oxidized. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, quinoxalinyl. A polycyclic heteroaryl can comprise fused rings, covalently attached rings or a combination thereof.

In accordance with the invention, aromatic groups can be substituted or unsubstituted. The term “bicyclic aryl” or “bicyclic heteroaryl” refers to a ring system consisting of two rings wherein at least one ring is aromatic; and the two rings can be fused or covalently attached.

As used herein, the term “arylalkyl” means a functional group wherein an alkylene chain is attached to an aryl group, e.g., -CH_2CH_2-phenyl. The term “substituted arylalkyl” means an arylalkyl functional group in which the aryl group is substituted. Similarly, the term “heteroarylalkyl” means a functional group wherein an alkylene chain is attached to a heteroaryl group. The term “substituted heteroarylalkyl” means a heteroarylalkyl functional group in which the heteroaryl group is substituted.

The term “alkylene” as used herein, refers to a diradical of a branched or unbranched saturated hydrocarbon chain, typically having from 1 to 20 carbon atoms (e.g. 1-10 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms). This term is exemplified by groups such as methylene (−CH_2−), ethylene (−CH_2CH_2−), the propylene isomers (e.g., −$CH_2CH_2CH_2$− and −$CH(CH_3)CH_2$−), and the like.

The term “substituted” as used herein, refers to independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited

to, deuterium, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO_2, -CN, -NH_2, N_3, protected amino, alkoxy, thioalkoxy, oxo, -C_1-C_{12}-alkyl; -C_2-C_{12}-alkenyl, -C_2-C_{12}-alkynyl, -C_3-C_{12}-cycloalkyl, -heterocycloalkyl, -halo- C_1-C_{12}-alkyl, -halo- C_2-C_{12}-alkenyl, -halo- C_2-C_{12}-alkynyl, -halo-C_3-C_{12}-cycloalkyl, -NH -C_1-C_{12}-alkyl, -NH -C_2-C_{12}-alkenyl, -NH -C_2-C_{12}-alkynyl, -NH -C_3-C_{12}-cycloalkyl, -NH -aryl, -NH -heteroaryl, -NH -heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C_1-C_{12}-alkyl, -O-C_2-C_{12}-alkenyl, -O-C_2-C_{12}-alkynyl, -O-C_3-C_{12}-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)- C_1-C_{12}-alkyl, -C(O)- C_2-C_{12}-alkenyl, -C(O)- C_2-C_{12}-alkynyl, -C(O)-C_3-C_{12}-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -$CONH_2$, -CONH- C_1-C_{12}-alkyl, -CONH- C_2-C_{12}-alkenyl, -CONH- C_2-C_{12}-alkynyl, -CONH-C_3-C_{12}-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO_2- C_1-C_{12}-alkyl, -OCO_2- C_2-C_{12}-alkenyl, -OCO_2-C_2-C_{12}-alkynyl, -OCO_2-C_3-C_{12}-cycloalkyl, -OCO_2-aryl, -OCO_2-heteroaryl, -OCO_2-heterocycloalkyl, -$OCONH_2$, -OCONH- C_1-C_{12}-alkyl, -OCONH- C_2-C_{12}-alkenyl, -OCONH-C_2-C_{12}-alkynyl, -OCONH- C_3-C_{12}-cycloalkyl, -OCONH- aryl, -OCONH- heteroaryl, -OCONH- heterocycloalkyl, -NHC(O)- C_1-C_{12}-alkyl, -NHC(O)-C_2-C_{12}-alkenyl, -NHC(O)-C_2-C_{12}-alkynyl, -NHC(O)-C_3-C_{12}-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -$NHCO_2$- C_1-C_{12}-alkyl, -$NHCO_2$- C_2-C_{12}-alkenyl, -$NHCO_2$- C_2-C_{12}-alkynyl, -$NHCO_2$- C_3-C_{12}-cycloalkyl, -$NHCO_2$- aryl, -$NHCO_2$- heteroaryl, -$NHCO_2$-heterocycloalkyl, -$NHC(O)NH_2$, -NHC(O)NH- C_1-C_{12}-alkyl, -NHC(O)NH-C_2-C_{12}-alkenyl, -NHC(O)NH-C_2-C_{12}-alkynyl, -NHC(O)NH-C_3-C_{12}-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, $NHC(S)NH_2$, -NHC(S)NH- C_1-C_{12}-alkyl, -NHC(S)NH-C_2-C_{12}-alkenyl, -NHC(S)NH-C_2-C_{12}-alkynyl, -NHC(S)NH-C_3-C_{12}-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -$NHC(NH)NH_2$, -NHC(NH)NH- C_1-C_{12}-alkyl, -NHC(NH)NH-C_2-C_{12}-alkenyl, -NHC(NH)NH-C_2-C_{12}-alkynyl, -NHC(NH)NH-C_3-C_{12}-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C_1-C_{12}-alkyl, -NHC(NH)-C_2-C_{12}-alkenyl, -NHC(NH)-C_2-C_{12}-alkynyl, -NHC(NH)-C_3-C_{12}-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C_1-C_{12}-alkyl, -C(NH)NH-C_2-C_{12}-alkenyl, -C(NH)NH-C_2-C_{12}-alkynyl, -C(NH)NH-C_3-C_{12}-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C_1-C_{12}-alkyl, -S(O)-C_2-C_{12}-alkenyl, - S(O)-C_2-C_{12}-alkynyl, - S(O)-C_3-C_{12}-cycloalkyl, - S(O)-aryl, - S(O)-heteroaryl, - S(O)-heterocycloalkyl -SO_2NH_2, -SO_2NH- C_1-C_{12}-alkyl, -SO_2NH- C_2-C_{12}-alkenyl, -SO_2NH- C_2-C_{12}-alkynyl, -SO_2NH- C_3-C_{12}-cycloalkyl, -SO_2NH- aryl, -SO_2NH-heteroaryl, -SO_2NH- heterocycloalkyl, -$NHSO_2$-C_1-C_{12}-alkyl, -$NHSO_2$-C_2-C_{12}-alkenyl, -

$NHSO_2$-C_2-C_{12}-alkynyl, -$NHSO_2$-C_3-C_{12}-cycloalkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -$NHSO_2$-heterocycloalkyl, -CH_2NH_2, -$CH_2SO_2CH_3$, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C_3-C_{12}-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C_1-C_{12}-alkyl, -S-C_2-C_{12}-alkenyl, -S-C_2-C_{12}-alkynyl, -S-C_3-C_{12}-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, methylthiomethyl, or –L'–R', wherein L' is C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, and R' is aryl, heteroaryl, heterocyclic, C_3-C_{12}cycloalkyl or C_3-C_{12}cycloalkenyl. In certain embodiments, the substituents are independently selected from halo, preferably Cl and F; C_1-C_4-alkyl, preferably methyl and ethyl; C_2-C_4-alkenyl; halo-C_1-C_4-alkyl, such as fluoromethyl, difluoromethyl, and trifluoromethyl; halo-C_2-C_4-alkenyl; C_3-C_6-cycloalkyl, such as cyclopropyl; -CN; -OH; NH_2; C_1-C_4-alkylamino; di(C_1-C_4-alkyl)amino; and NO_2. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted. In some cases, each substituent in a substituted moiety is additionally optionally substituted with one or more groups, each group being independently selected from C_1-C_4-alkyl, -F, -Cl, -Br, -I, -OH, -NO_2, -CN, or -NH_2.

In accordance with the invention, any of the aryls, substituted aryls, heteroaryls and substituted heteroaryls described herein, can be any aromatic group. Aromatic groups can be substituted or unsubstituted.

It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl moiety described herein can also be an aliphatic group, an alicyclic group or a heterocyclic group. An "aliphatic group" is non-aromatic moiety that may contain any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen or other atoms, and optionally contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight chained, branched or cyclic and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, aliphatic groups include, for example, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Such aliphatic groups may be further substituted. It is understood that aliphatic groups may be used in place of the alkyl, alkenyl, alkynyl, alkylene, alkenylene, and alkynylene groups described herein.

The term "alicyclic" as used herein, denotes a monovalent group derived from a monocyclic or polycyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Examples include, but are not limited to, cyclopropyl, cyclobutyl,

cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, and bicyclo[2.2.2]octyl. Such alicyclic groups may be further substituted.

As used herein, the term "alkoxy" employed alone or in combination with other terms means, unless otherwise stated, an alkyl group having the designated number of carbon atoms connected to the rest of the molecule via an oxygen atom, such as, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy (isopropoxy) and the higher homologs and isomers. Preferred alkoxy are (C_1-C_3) alkoxy.

The term "aryloxy" refers to the group aryl-O− wherein the aryl group is as defined above, and includes optionally substituted aryl groups as also defined above. The term "arylthio" refers to the group R−S−, where R is as defined for aryl.

The terms "heterocyclic" or "heterocycloalkyl" can be used interchangeably and referred to a non-aromatic ring or a bi- or tri-cyclic group fused, bridged or spiro system, where (i) each ring system contains at least one heteroatom independently selected from oxygen, sulfur and nitrogen, (ii) each ring system can be saturated or unsaturated (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, (v) any of the above rings may be fused to an aromatic ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted or optionally substituted with exocyclic olefinic, iminic or oximic double bond. Representative heterocycloalkyl groups include, but are not limited to, 1,3-dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, 2-azabicyclo[2.2.1]-heptyl, 8-azabicyclo[3.2.1]octyl, 5-azaspiro[2.5]octyl, 1-oxa-7-azaspiro[4.4]nonanyl, 7-oxooxepan-4-yl, and tetrahydrofuryl. Such heterocyclic groups may be further substituted. Heteroaryl or heterocyclic groups can be C-attached or N-attached (where possible).

It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic and cycloalkenyl moiety described herein can also be an aliphatic group or an alicyclic group.

It will be apparent that in various embodiments of the invention, the substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, arylalkyl, heteroarylalkyl, and heterocycloalkyl are intended to be monovalent or divalent. Thus, alkylene, alkenylene, and alkynylene, cycloaklylene, cycloalkenylene, cycloalkynylene, arylalkylene, heteroarylalkylene and heterocycloalkylene groups are to be included in the above definitions and are applicable to provide the Formulas herein with proper valency.

The terms "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine and chlorine.

The term "optionally substituted", as used herein, means that the referenced group may be substituted or unsubstituted. In one embodiment, the referenced group is optionally substituted with zero substituents, i.e., the referenced group is unsubstituted. In another embodiment, the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from groups described herein.

The term "hydrogen" includes hydrogen and deuterium. In addition, the recitation of an atom includes other isotopes of that atom so long as the resulting compound is pharmaceutically acceptable.

In certain embodiments, the compounds of each formula herein are defined to include isotopically labelled compounds. An "isotopically labelled compound" is a compound in which at least one atomic position is enriched in a specific isotope of the designated element to a level which is significantly greater than the natural abundance of that isotope. For example, one or more hydrogen atom positions in a compound can be enriched with deuterium to a level which is significantly greater than the natural abundance of deuterium, for example, enrichment to a level of at least 1%, preferably at least 20% or at least 50%. Such a deuterated compound may, for example, be metabolized more slowly than its non-deuterated analog, and therefore exhibit a longer half-life when administered to a subject. Such compounds can synthesize using methods known in the art, for example by employing deuterated starting materials. Unless stated to the contrary, isotopically labelled compounds are pharmaceutically acceptable.

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, *et al.*, Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds, other unsaturation, or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds

include both *E* and *Z* geometric isomers or cis- and trans- isomers. Likewise, all tautomeric forms are also intended to be included. Tautomers may be in cyclic or acyclic. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus, a carbon-carbon double bond or carbon-heteroatom double bond depicted arbitrarily herein as *trans* may be *cis, trans*, or a mixture of the two in any proportion.

The term "subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a human. When the subject is a human, the subject may be referred to herein as a patient.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art.

Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reaction of the free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts e.g., salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when

appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, esters of C_1-C_6-alkanoic acids, such as acetate, propionate, butyrate and pivalate esters.

The term "hydroxy activating group," as used herein, refers to a labile chemical moiety which is known in the art to activate a hydroxyl group so that it will depart during synthetic procedures such as in a substitution or an elimination reaction. Examples of hydroxyl activating group include, but not limited to, mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate and the like.

The term "activated hydroxyl," as used herein, refers to a hydroxy group activated with a hydroxyl activating group, as defined above, including mesylate, tosylate, triflate, p-nitrobenzoate, phosphonate groups, for example.

The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxyl group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxyl protecting groups include benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, tert-butoxy-carbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, t-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, allyl, benzyl, triphenyl-methyl (trityl), methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-(trimethylsilyl)-ethoxymethyl, methanesulfonyl, trimethylsilyl, triisopropylsilyl, and the like.

The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

The term "hydroxy prodrug group," as used herein, refers to a promoiety group which is known in the art to change the physicochemical, and hence the biological properties of a parent drug in a transient manner by covering or masking the hydroxy group. After said synthetic procedure(s), the hydroxy prodrug group as described herein must be capable of reverting back to hydroxy group *in vivo*. Hydroxy prodrug groups as known in the art are described generally in Kenneth B. Sloan, Prodrugs, Topical and Ocular Drug Delivery, (Drugs and the Pharmaceutical Sciences; Volume 53), Marcel Dekker, Inc., New York (1992) and in "Prodrugs of Alcohols and Phenols" by S. S. Dhareshwar and V. J. Stella, in Prodrugs Challenges and Rewards Part-2, (Biotechnology: Pharmaceutical Aspects), edited by V. J. Stella, et al, Springer and AAPSPress, 2007, pp 31-99.

The term "amino" as used herein, refers to the group $-NH_2$.

The term "substituted amino" as used herein, refers to the group –NRR where each R is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocycloalkyl provided that both R groups are not hydrogen, or a group –Y–Z, in which Y is optionally substituted alkylene and Z is alkenyl, cycloalkenyl, or alkynyl.

The term "amino protecting group" as used herein, refers to a labile chemical moiety which is known in the art to protect an amino group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting groups as known in the art described generally in T.H. Greene and P.G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl, and the like.

The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

As used herein, the term "pharmaceutically acceptable ester" refers to esters of the compounds formed by the process of the present invention which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and

alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound, which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to afford any compound delineated by the Formulae of the instant invention. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed.), *Methods in Enzymology*, Vol. 4, Academic Press (1985); Krogsgaard-Larsen, *et al.*, (ed). "Design and Application of Prodrugs, *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991); Bundgaard, *et al.*, *Journal of Drug Deliver Reviews, 8*:1-38(1992); Bundgaard, J. of *Pharmaceutical Sciences, 77*:285 et seq. (1988); Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, *American Chemical Society* (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry and Enzymology," John Wiley and Sons, Ltd. (2002).

The term "treating", as used herein, means relieving, lessening, reducing, eliminating, modulating, or ameliorating, i.e. causing regression of the disease state or condition. Treating can also include inhibiting, i.e. arresting the development, of an existing disease state or condition, and relieving or ameliorating, i.e. causing regression of an existing disease state or condition, for example when the disease state or condition may already be present.

The term "preventing", as used herein means, to completely or almost completely stop a disease state or condition, from occurring in a patient or subject, especially when the patient or subject is predisposed to such or at risk of contracting a disease state or condition.

Additionally, the compounds of the present invention, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

"Solvates" means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water, the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H_2O, such combination being able to form one or more hydrate.

As used herein, the term "analog" refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar to or comparable in function and appearance to the reference compound.

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as, for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and *N*-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such solvents are well known to those skilled in the art, and individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: *Organic Solvents Physical Properties and Methods of Purification*, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the *Techniques of Chemistry Series*, John Wiley & Sons, NY, 1986.

The terms "protogenic organic solvent" or "protic solvent" as used herein, refer to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: *Organic Solvents Physical Properties and Methods of*

Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the *Techniques of Chemistry Series*, John Wiley & Sons, NY, 1986.

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 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. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, etc. delineated herein are for purposes of illustration only and variation of the reaction conditions can produce the desired isoxazole products of the present invention. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995).

The compounds of this invention may be modified by appending various functionalities via synthetic means delineated herein to enhance selective biological properties. Such modifications include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention Formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or Formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose

and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the Formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

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.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants

such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic 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 water, Ringer's solution, U.S.P. 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 can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable Formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable Formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragées, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical Formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be

required. Ophthalmic Formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art. All publications, patents, published patent applications, and other references mentioned herein are hereby incorporated by reference in their entirety.

ABBREVIATIONS

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are:

BOP-Cl for bis(2-oxo-3-oxazolidinyl)phosphinic chloride;

CDI for carbonyldiimidazole;

DBU for 1,8-diazabicycloundec-7-ene;

DCC for *N,N'*-dicyclohexylcarbodiimide;

DCM for dichloromethane;

DIPEA for *N,N*-diisopropylethylamine;

DMAP for *N,N*-dimethylaminopyridine;

DME for 1,2-dimethoxyethane;

DMF for *N,N*-dimethyl formamide;

DMPU for 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone;

EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

Et_3N for triethylamine;

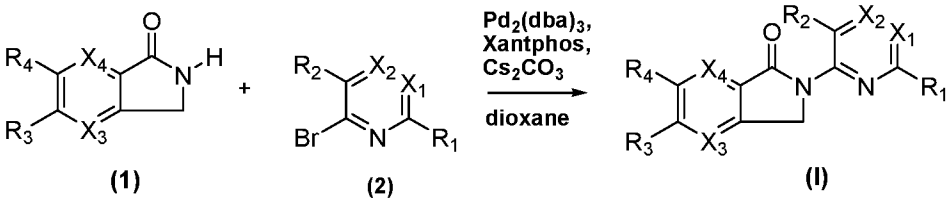
EtOAc for ethyl acetate;
HATU for 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate;
HCl for hydrochloric acid;
*m*CPBA for meta-chloroperoxybenzoic acid;
NMO for *N*-methylmorpholine-*N*-oxide;
PhMe for toluene;
PyAOP for 7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate;
PyBOP for benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate;
THF for tetrahydrofuran;
CuTC for Copper(I)-thiophene-2-carboxylate;
Xantphos for 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene;
Me4tButylXphos for 2-Di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl;
Pd2(dba)3 for Tris(dibenzylideneacetone)dipalladium(0);
PMBCl for p-methoxybenzyl chloride.

SYNTHETIC METHODS

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared, which are intended as an illustration only and not to limit the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

As shown in Scheme 1, the compound of Formula (I) can be prepared by C-N coupling, wherein R_1, R_2, R_3, R_4, X_1, X_2, X_3 and X_4 are as previously defined. The lactam compound (1) and aromatic bromide compound (2) are subjected to suitable C-N coupling conditions, such as but not limited to, mixed with $Pd_2(dba)_3$, Cs_2CO_3 and Xantphos in dioxane at elevated temperature. Alternative reagents and reaction conditions may be used, including but not limited to, a suspension of compound (1) and compound (2) with CuTC, K_2CO_3 in DMSO under microwave irradiation.

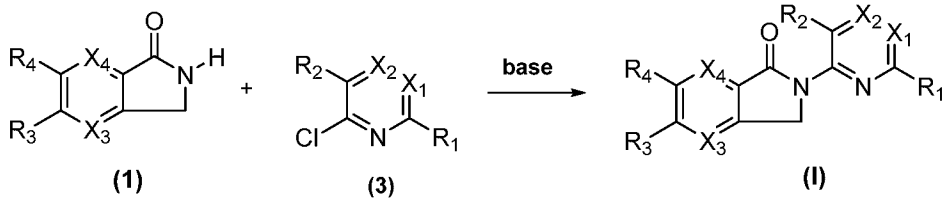
Scheme 1



(1) (2) (I)

Alternatively, the compound of Formula (**I**) may also be prepared from nucleophilic aromatic substitution of lactam compound (1) and aromatic chloride compound (3) under suitable conditions. Thus, suitable base is slowly added to a solution of lactam compound (1) in an aprotic solvent at low temperature. The base can be, such as but not limited to, nBuLi, KHMDS, NaH and KOtBu. The aprotic solvent can be, such as, but not limited to, THF and DMF. Then the aromatic chloride compound (2) is slowly added to the resulting reaction mixture. The reaction temperature is from 0 °C to 80 °C.

Scheme 2

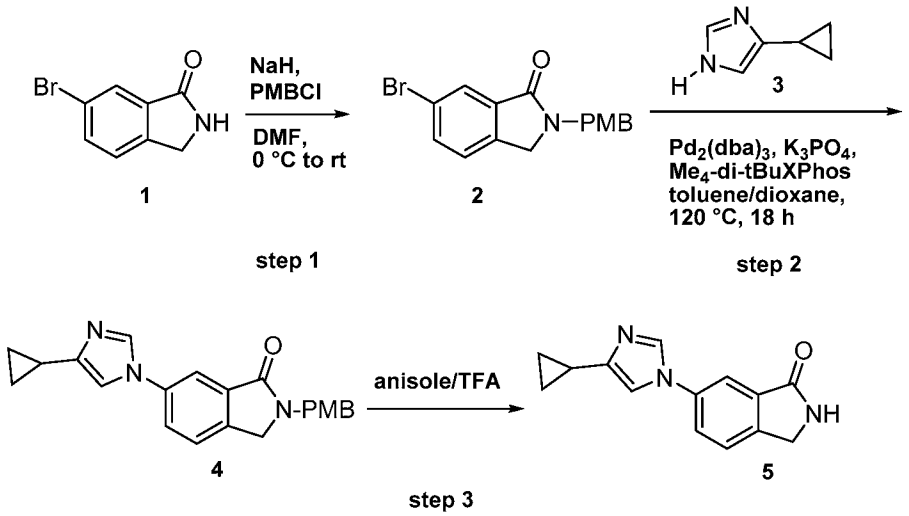


(1) (3) (I)

EXAMPLES

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting of the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, Formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Synthesis of 6-(4-cyclopropyl-1H-imidazol-1-yl)isoindolin-1-one (compound 5)



Step 1: synthesis of 6-bromo-2-(4-methoxybenzyl)isoindolin-1-one (compound 2)

To a solution of 6-bromoisoindolin-1-one (2.418 g, 11.4 mmol) in DMF (57 mL) at 0 °C was added NaH (0.547 g, 13.68 mmol). The resulting dark suspension was allowed to stir for 60 min before addition of PMBCl (1.86 mL, 13.68 mmol). The reaction was then allowed to stir at room temperature for 3 hours. The crude was diluted by EtOAc, washed with water and brine. The organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel using 0->50% EtOAc in hexanes to afford 3.18 g yellow solid as compound 2 (84% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 1.9 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.75 (s, 2H), 4.22 (s, 2H), 3.82 (s, 3H).

Step 2: synthesis of 6-(4-cyclopropyl-1H-imidazol-1-yl)-2-(4-methoxybenzyl)isoindolin-1-one (compound 4)

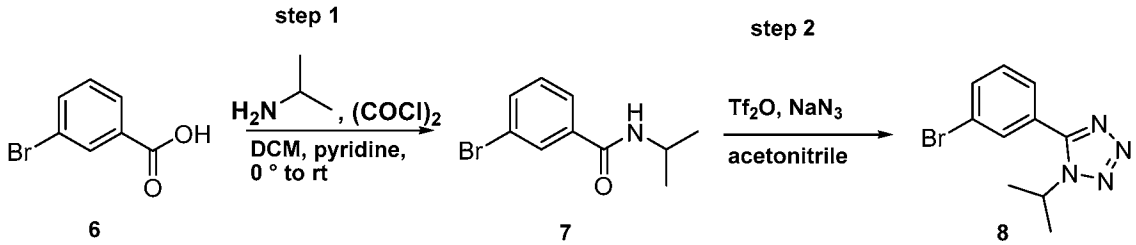
To a solution of 6-bromo-2-(4-methoxybenzyl)isoindolin-1-one (1 g, 3.01 mmol) in toluene (12 mL) and dioxane (3 mL) was added 4-cyclopropyl-1H-imidazole (0.651 g, 6.02 mmol), K_3PO_4 (1.278 g, 6.02 mmol), $Pd_2(dba)_3$ (110 mg, 0.12 mmol) and Me_4-di-*t*BuXPhos (145 mg, 0.301 mmol). The reaction was degassed and allowed to stir at 120 °C for overnight. The crude was filtered and concentrated. The residue was purified by chromatography on silica gel using 0->10% MeOH in DCM to afford 490 mg white solid as compound 4 (45% yield). ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.22 (d, *J* = 1.5 Hz, 1H), 7.92 (d, *J* = 2.1 Hz, 1H), 7.83 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.24 (d, *J* = 8.7

Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 4.69 (s, 2H), 4.36 (s, 2H), 3.74 (s, 3H), 1.84 (td, J = 8.4, 4.2 Hz, 1H), 0.81 (dt, J = 8.3, 2.9 Hz, 2H), 0.73 – 0.69 (m, 2H).

Step 3: synthesis of 6-(4-cyclopropyl-1H-imidazol-1-yl)isoindolin-1-one (compound 5)

The solution of 6-(4-cyclopropyl-1H-imidazol-1-yl)-2-(4-methoxybenzyl)isoindolin-1-one (490 mg, 1.36 mmol) in 10% anisole in TFA (6 mL) was allowed to stir at 85 °C for 3 days. The reaction was cooled to room temperature and concentrated. The residue was purified by chromatography on silica gel using 0->20% MeOH in DCM to afford 340 mg white solid as compound 5 (quant. yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.36 – 9.17 (m, 1H), 8.82 (s, 1H), 8.04 (dd, J = 9.0, 1.8 Hz, 2H), 7.95 (dd, J = 8.2, 2.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 4.47 (s, 2H), 1.97 (m, 1H), 1.06 – 0.96 (m, 2H), 0.87 – 0.81 (m, 2H).

Synthesis of 5-(3-bromophenyl)-1-isopropyl-1H-tetrazole (compound 8)



Step 1: synthesis of 3-bromo-N-isopropylbenzamide (compound 7)

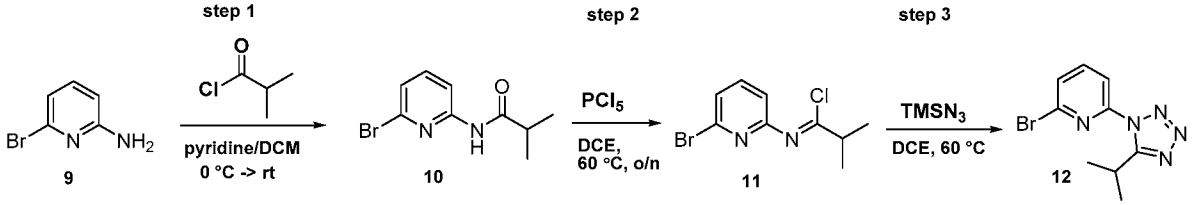
To a suspension of 3-bromobenzoic acid (1.04 g, 5.18 mmol) in DCM (6.6 mL) was added oxalyl chloride (0.5 mL, 5.7 mmol) and DMF (0.02 mL, 0.259 mmol) at 0 °C. The reaction was allowed to stir 4 hours before turning to clear solution. The crude was concentrated and redissolved in pyridine (6.6 mL). A solution of propan-2-amine (0.49 mL, 5.7 mmol) in DCM (6.6 mL) was slowly added at 0 °C. The reaction was allowed to stir for overnight. The crude was concentrated and purified by chromatography on silica gel using 0->50% EtOAc in hexanes to afford 1.17 g pale yellow oil as compound 7 (93% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 (dd, J = 7.5, 1.0 Hz, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.62 (dd, J = 7.9, 1.0 Hz, 1H), 4.29 (dp, J = 8.1, 6.6 Hz, 1H), 1.32 (d, J = 6.6 Hz, 6H).

Step 2: synthesis of 5-(3-bromophenyl)-1-isopropyl-1H-tetrazole (compound 8)

To suspension of 6-bromo-N-isopropylpicolinamide (413.5 mg, 1.701 mmol) and NaN_3 (166 mg, 2.55 mmol) in acetonitrile (5.7 mL) at 0 °C was added Tf_2O (1M in DCM, 2.55 mL, 2.55 mmol) dropwise. The resulting mixture was stirred for 30 min then warmed up to room

temperature for additional 1 hour. The crude was diluted with EA, and quenched with $NaHCO_3$ aq. Solution. The organic layer was separated and washed with brine, dried, filtered and concentrated. The residue was purified by chromatography on silica gel using 0->40% EtOAc in hexanes to afford 56 mg oil as compound 8 (12% yield). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.34 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.7 (d, *J* = 7.7 Hz, 1H), 5.82 (p, J = 6.7 Hz, 1H), 1.72 (d, J = 6.7 Hz, 6H).

Synthesis of 2-bromo-6-(5-isopropyl-1H-tetrazol-1-yl) pyridine (compound 12)



Step 1: synthesis of N-(6-bromopyridin-2-yl)isobutyramide (compound 10)

To a solution of 6-bromopyridin-2-amine (883.6 mg, 5.11 mmol) in DCM (6.4 mL) and pyridine (6.4 mL) was slowly added isobutyryl chloride (0.59 mL, 5.62 mmol) at 0 °C. The reaction was allowed to stir at room temperature for 2 hours and concentrated. The residue was purified by chromatography on silica gel using 0->40% EtOAc in hexanes to afford 1.1612 g white solid as compound 10 (94% yield). ^1H NMR (400 MHz, Chloroform-d) δ 8.22 (d, *J* = 8.2 Hz, 1H), 7.87 (br, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 2.55 (m, 1H), 1.28 (d, *J* = 6.9 Hz, 6H).

Step 2: synthesis of (Z)-N-(6-bromopyridin-2-yl)isobutyrimidoyl chloride (compound 11)

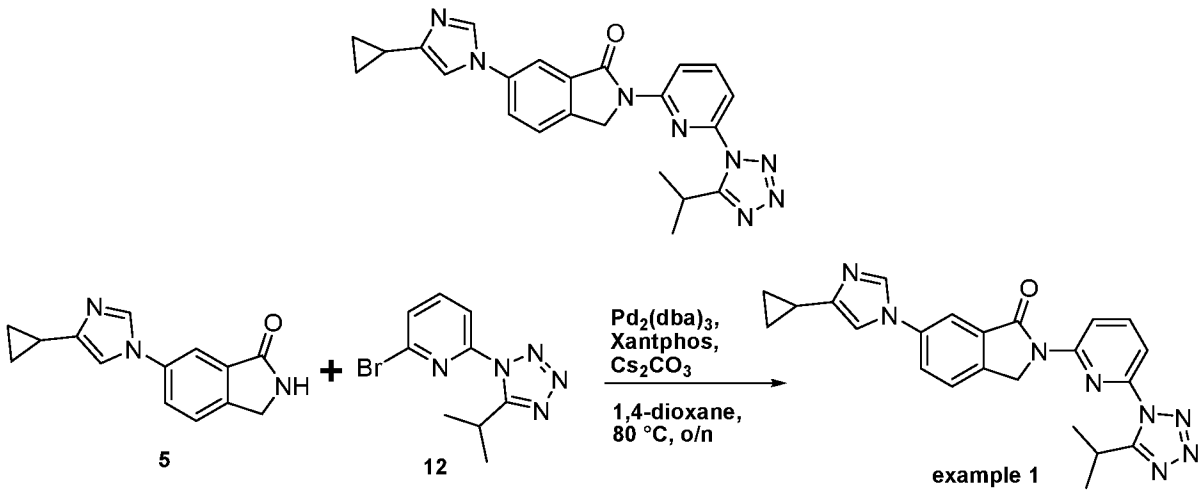
To a solution of N-(6-bromopyridin-2-yl)isobutyramide (179.5 mg, 0.738 mmol) in DCE (2.23 mL) was added PCl_5 (184 mg, 0.886 mmol). The resulting suspension became clear solution upon heating. The reaction was allowed to stir at 60 °C for overnight. Concentrate to afford light yellow solid. The crude was directly used in the next step without any purification.

Step 3: synthesis of 2-bromo-6-(5-isopropyl-1H-tetrazol-1-yl)pyridine (compound 12)

To a solution of (Z)-N-(6-bromopyridin-2-yl)isobutyrimidoyl chloride (193 mg, 0.738 mmol) in DCE (3.7 mL) was added $TMSN_3$ (94 mg, 0.812 mmol). The reaction was allowed to stir at 60 °C for 1 day. The reaction was quenched by aq. $NaHCO_3$, extracted with EtOAc (X3). The combined organic layers were washed by brine, dried over Na_2SO_4, filtered and concentrate. The residue was purified by chromatography on silica gel using 0->20% EtOAc

in hexanes to afford 66 mg white solid as compound 12 (33% yield). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 4.05 – 3.94 (m, 1H), 1.51 (d, *J* = 6.9 Hz, 6H).

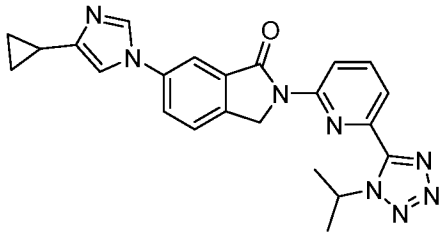
Example 1: 6-(4-cyclopropyl-1H-imidazol-1-yl)-2-(6-(5-isopropyl-1H-tetrazol-1-yl)42yridine-2-yl)isoindolin-1-one



5 12 example 1

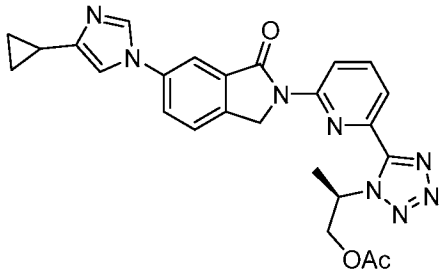
To a solution of 6-(4-cyclopropyl-1H-imidazol-1-yl)isoindolin-1-one (70.7 mg, 0.295 mmol) in 1,4-dioxane (0.8 mL) was added 2-bromo-6-(5-isopropyl-1H-tetrazol-1-yl)pyridine (66.0 mg, 0.246 mmol), $Pd_2(dba)_3$ (11.3 mg, 0.012 mmol), Xantphos (14.2 mg, 0.025 mmol) and Cs_2CO_3 (160 mg, 0.492 mmol). The reaction was purged with N_2 and allowed to stir at 80 °C for overnight. The reaction was concentrated, and the residue was purified by chromatography on silica gel using 0->70% acetone in hexanes to afford 32.1 mg white solid as Example 1 (31% yield). LC-MS [M+H] = 427.19, Calcd. 427.19. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.76 (d, *J* = 8.4 Hz, 1H), 8.33 – 8.26 (m, 2H), 8.08 (d, *J* = 2.1 Hz, 1H), 8.01 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.77 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 5.17 (s, 2H), 3.94 (p, *J* = 6.8 Hz, 1H), 1.90 – 1.81 (m, 1H), 0.85 – 0.80 (m, 2H), 0.75 – 0.70 (m, 2H).

Example 2: 6-(4-cyclopropyl-1H-imidazol-1-yl)-2-(6-(1-isopropyl-1H-tetrazol-5-yl)42yridine-2-yl)isoindolin-1-one



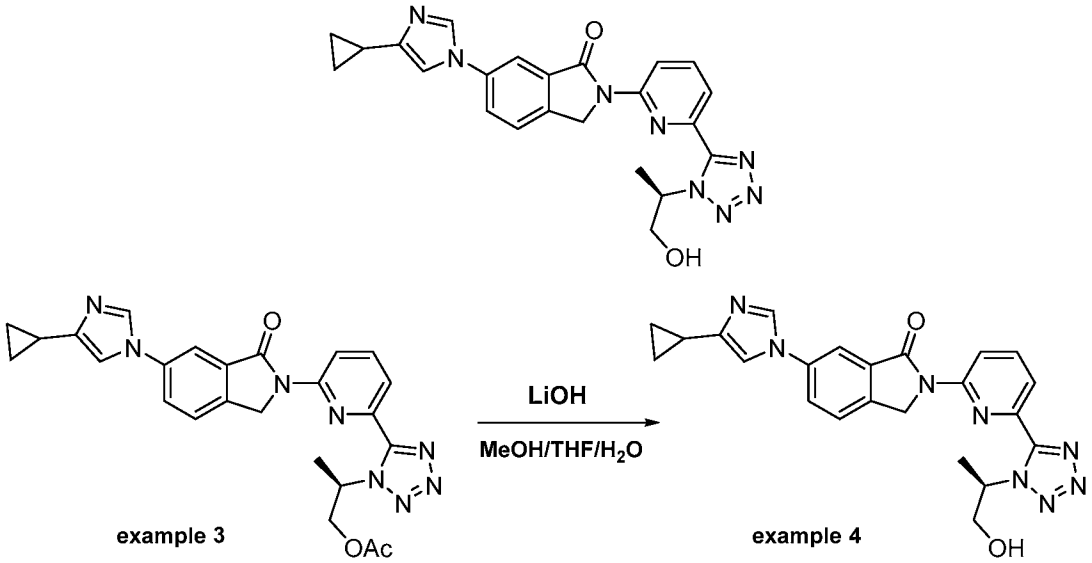
Example 2 was prepared by using similar procedure as described for compound of example 1. LC-MS observed [M+H], 427.19, Calcd. 427.19. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.78 (d, *J* = 8.5 Hz, 1H), 8.30 (d, *J* = 1.5 Hz, 1H), 8.22 (dd, *J* = 8.5, 7.6 Hz, 1H), 8.09 (d, *J* = 2.2 Hz, 1H), 8.05 – 8.00 (m, 2H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 5.90 – 5.79 (m, 1H), 5.25 (s, 2H), 1.93 – 1.82 (m, 1H), 1.70 (d, *J* = 6.9 Hz, 6H), 0.88 – 0.80 (m, 2H), 0.76 – 0.72 (m, 2H).

Example 3: I-2-(5-(6-(6-(4-cyclopropyl-1H-imidazol-1-yl)-1-oxoisoindolin-2-yl)43yridine-2-yl)-1H-tetrazol-1-yl)propyl acetate



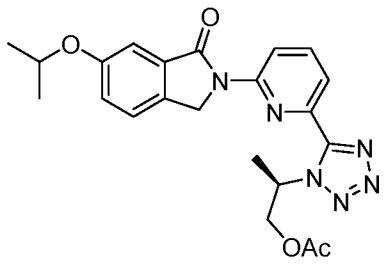
Example 3 was prepared by using similar procedure as described for Example 1. LC-MS observed [M+H], 485.20, Calcd. 485.20. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.78 (dd, *J* = 8.5, 0.9 Hz, 1H), 8.29 (d, *J* = 1.5 Hz, 1H), 8.23 (dd, *J* = 8.5, 7.6 Hz, 1H), 8.09 (d, *J* = 2.1 Hz, 1H), 8.07 (dd, *J* = 7.6, 0.9 Hz, 1H), 8.03 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 6.13 (td, *J* = 7.5, 4.0 Hz, 1H), 5.22 (s, 2H), 4.64 (dd, *J* = 11.6, 4.0 Hz, 1H), 4.50 (dd, *J* = 11.6, 8.1 Hz, 1H), 1.87 (td, *J* = 8.4, 4.2 Hz, 1H), 1.81 (s, 3H), 1.75 (d, *J* = 6.9 Hz, 3H), 0.88 – 0.80 (m, 2H), 0.75 – 0.68 (m, 2H).

Example 4: I-6-(4-cyclopropyl-1H-imidazol-1-yl)-2-(6-(1-(1-hydroxypropan-2-yl)-1H-tetrazol-5-yl)43yridine-2-yl)isoindolin-1-one



To a solution of Example 3 (49.7 mg, 0.103 mmol) in MeOH/H_2O/THF (1:1:1, 0.6 mL) was added LiOH (4.9 mg, 0.205 mmol). The reaction was allowed to stir at room temperature for 2 hours. The reaction was concentrated, and the residue was purified by chromatography on silica gel using 0->10% MeOH in DCM to afford 33.8 mg white solid as Example 4 (75% yield). LC-MS observed [M+H], 443.18, Calcd. 443.19. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.76 (d, *J* = 8.5 Hz, 1H), 8.29 (s, 1H), 8.21 (t, *J* = 8.0 Hz, 1H), 8.08 (s, 1H), 8.02 (d, *J* = 7.3 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.69 (s, 1H), 5.85 – 5.74 (m, 1H), 5.24 (d, *J* = 3.5 Hz, 2H), 5.04 (t, *J* = 5.6 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.88 – 3.74 (m, 1H), 1.91 – 1.82 (m, 1H), 1.68 (d, J = 6.8 Hz, 3H), 0.88 – 0.81 (m, 2H), 0.76 – 0.69 (m, 2H).

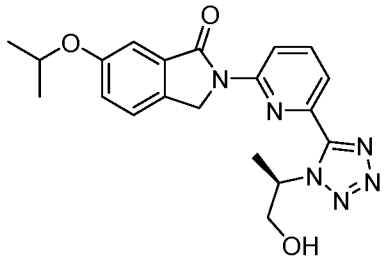
Example 5: I-2-(5-(6-(6-isopropoxy-1-oxoisoindolin-2-yl)44yridine-2-yl)-1H-tetrazol-1-yl)propyl acetate



Example 5 was prepared by using similar procedure as described for Example 1. LC-MS observed [M+H], 437.18, Calcd. 437.19. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.75 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.20 (dd, *J* = 8.6, 7.5 Hz, 1H), 8.04 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.35 – 7.23 (m, 2H), 5.10 (s, 2H), 4.77 (p, *J* = 6.0 Hz, 1H), 4.63 (dd, *J* = 11.6, 4.1 Hz,

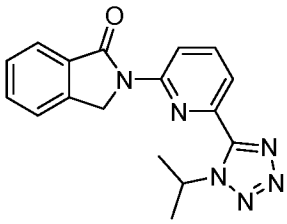
1H), 4.48 (dd, *J* = 11.6, 8.2 Hz, 1H), 1.80 (s, 3H), 1.73 (d, *J* = 6.8 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 6H).

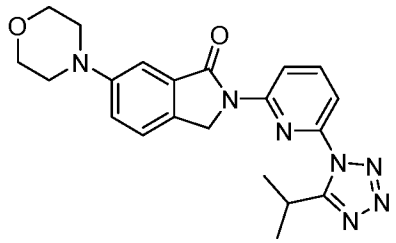
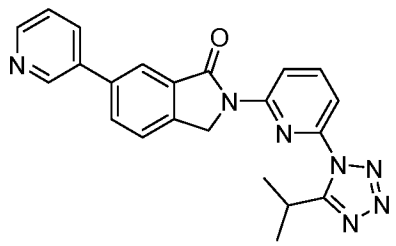
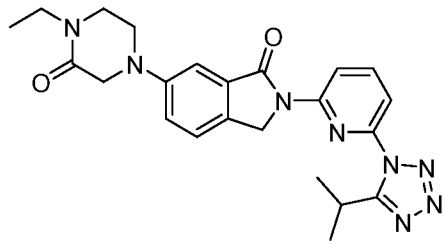
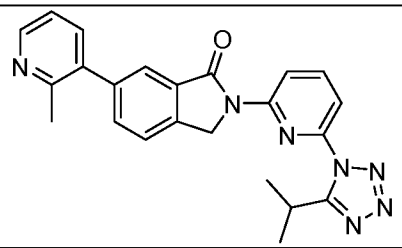
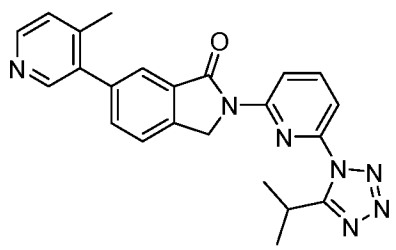
Example 6: I-2-(6-(1-(1-hydroxypropan-2-yl)-1H-tetrazol-5-yl)45yridine-2-yl)-6-isopropoxyisoindolin-1-one

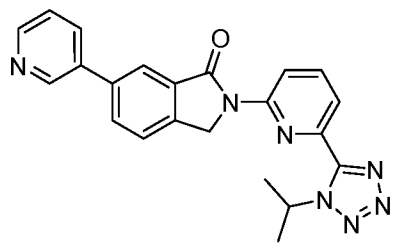
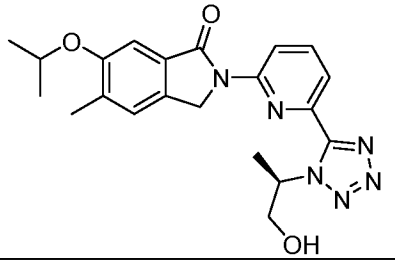
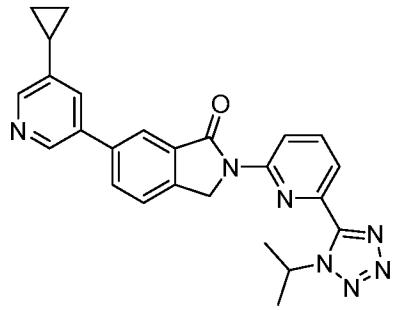
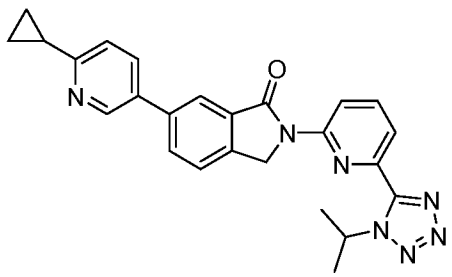


Example 6 was prepared by using similar procedure as described for Example 4. LC-MS observed [M+H], 395.17, Calcd. 395.18. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 8.74 (dd, *J* = 8.5, 0.8 Hz, 1H), 8.18 (dd, *J* = 8.6, 7.5 Hz, 1H), 7.99 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.33 – 7.25 (m, 2H), 5.83 – 5.75 (m, 1H), 5.18 – 5.06 (m, 2H), 5.03 (t, *J* = 5.6 Hz, 1H), 4.77 (p, *J* = 6.0 Hz, 1H), 3.91 (ddd, *J* = 11.1, 8.0, 5.9 Hz, 1H), 3.82 (dt, *J* = 10.8, 5.0 Hz, 1H), 1.66 (d, *J* = 6.7 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 6H).

The following examples were prepared using procedures similar to those described above:

Example	Structure	HNMR	ESIMS (M-H)$^-$ or (M+H)$^+$
7		^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.89 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.12 (dd, *J* = 7.6, 0.9 Hz, 1H), 8.05 – 7.95 (m, 2H), 7.71 (td, *J* = 7.4, 1.2 Hz, 1H), 7.64 – 7.52 (m, 2H), 5.85 (p, *J* = 6.8 Hz, 1H), 5.11 (s, 2H), 1.80 (d, *J* = 6.7 Hz, 6H).	321.13

8		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J = 8.4 Hz, 1H), 8.25 (t, J = 8.1 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.41 (dd, J = 8.6, 2.5 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 5.03 (s, 2H), 3.93 (p, J = 6.7 Hz, 1H), 3.78 (t, J = 4.8 Hz, 4H), 3.21 (t, J = 4.9 Hz, 4H), 1.43 (d, J = 6.8 Hz, 6H).	406.18
9		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.78 (d, J = 8.4 Hz, 1H), 8.64 (d, J = 5.0 Hz, 1H), 8.29 (t, J = 8.1 Hz, 1H), 8.24 (d, J = 7.7 Hz, 1H), 8.18 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.55 (dd, J = 8.1, 4.7 Hz, 1H), 5.21 (s, 2H), 4.01 – 3.80 (m, 1H), 1.45 (d, J = 6.8 Hz, 6H).	398.15
10		^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (d, J = 8.4 Hz, 1H), 8.25 (t, J = 8.1 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.39 (dd, J = 8.5, 2.5 Hz, 1H), 7.27 (d, J = 2.4 Hz, 1H), 5.03 (s, 2H), 3.99 – 3.90 (m, 1H), 3.87 (s, 2H), 3.62 – 3.57 (m, 2H), 3.48 (t, J = 5.4 Hz, 2H), 3.40 (t, J = 7.2 Hz, 2H), 1.43 (d, J = 6.9 Hz, 6H), 1.08 (t, J = 7.1 Hz, 3H).	447.21
11			412.17
12		^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (d, J = 8.3 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.45 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.85 (s, 1H), 7.79 (dd, J = 7.8, 1.7 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 5.2 Hz, 1H), 5.22 (s, 2H), 3.95 (p, J = 6.9 Hz, 1H), 2.31 (s, 3H), 1.45 (d, J = 6.9 Hz, 6H).	412.17

13		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (d, J = 2.4 Hz, 1H), 8.80 (dd, J = 8.5, 0.9 Hz, 1H), 8.64 (dd, J = 4.7, 1.6 Hz, 1H), 8.27 – 8.17 (m, 3H), 8.14 (dd, J = 7.9, 1.8 Hz, 1H), 8.04 (dd, J = 7.5, 0.9 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.59 – 7.51 (m, 1H), 5.85 (p, J = 6.6 Hz, 1H), 5.29 (s, 2H), 1.71 (d, J = 6.6 Hz, 6H).	398.15
14			409.20
15		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (d, J = 8.5 Hz, 1H), 8.77 (d, J = 2.2 Hz, 1H), 8.46 (d, J = 2.2 Hz, 1H), 8.24 – 8.18 (m, 2H), 8.13 (dd, J = 7.9, 1.8 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 2.2 Hz, 1H), 5.85 (p, J = 6.6 Hz, 1H), 5.28 (s, 2H), 2.14 – 2.02 (m, 1H), 1.71 (d, J = 6.6 Hz, 6H), 1.10 – 1.04 (m, 2H), 0.93 (dd, J = 5.1, 2.2 Hz, 2H).	438.19
16		^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (d, J = 2.4 Hz, 1H), 8.81 – 8.77 (m, 1H), 8.21 (dd, J = 8.7, 7.6 Hz, 1H), 8.12 (d, J = 1.8 Hz, 1H), 8.08 (dt, J = 8.3, 2.5 Hz, 2H), 8.03 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 5.84 (p, J = 6.6 Hz, 1H), 5.27 (s, 2H), 2.22 – 2.16 (m, 1H), 1.71 (d, J = 6.6 Hz, 6H), 1.01 – 0.98 (m, 4H).	438.19

ASSAYS

The ability (IC_{50}) of compounds to inhibit ASK1 kinase activity was determined by HTRF® KinEASE™ Assay System

ASK1 kinase was from Thermofisher (Catalogue # PV4011), ATP was from Sigma (Catalogue # A7699), HTRF® KinEASE™ Assay System was obtained from Cisbio (Bedford, Mass). ½ Area plate was from Perkin Elmer (Catalogue # #6005560). HTRF® KinEASE™-STK is a generic method for measuring serine/threonine kinase activities using time-resolved fluorescence resonance energy transfer (TR-FRET) immunoassay. The IC_{50} value for each compound was determined in the presence of compound (various concentration from 0 to 10 uM) and a fixed amount of ATP, peptide substrates. Test compound, 1uM STK3 peptide substrate, 5nM of ASK1 kinase are incubated with kinase reaction buffer, containing 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, and 1 mM EGTA for 30 minutes, then 100uM ATP is added to start kinase reaction and incubated for 3 hours. The STK3-antibody labeled with Eu^{3+}-Cryptate and 125 nM streptavidin-XL665 are mixed in a single addition with stop reagents provided by the Cisbio kit used to stop the kinase reaction. Fluorescence is detected using Envision Multilabeled 2014 reader from PerkinElmer. The Fluorescence is measured at 615 nm (Cryptate) and 665 nm (XL665) and a ratio of 665 nm/ 615nm is calculated for each well. The resulting TR-FRET is proportional to the phosphorylation level. Staurosporine was used as the positive control. IC_{50} was determined by Xlfit 5.3.

By using above method, the inhibition of ASK1 was tested for the compound of formula (I). IC_{50} ranges are as follows: A < 1 nM; 1 nM < B < 10 nM; 10 nM < C < 100 nM; 100 nM < D < 1 μM; E > 1 μM.

Example No.	IC_{50}
1	B
2	C
3	D
4	C
5	E
6	B
7	C
8	D

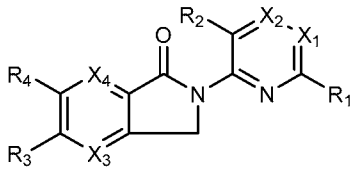
9	C
10	C
11	D
12	D
13	B
14	B
15	C
16	C

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

WHAT IS CLAIMED:

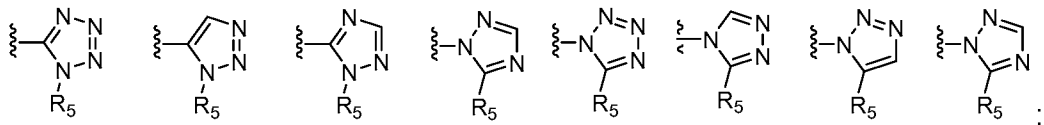
1. A compound represented by Formula I or a pharmaceutically acceptable salt, ester, or combination thereof:



(I) ,

wherein

R_1 is selected from:



;

each of which is optionally further substituted when possible,

wherein R_5 is selected from the group consisting of:

1) Hydrogen;
2) Optionally substituted –C_1-C_8 alkyl;
3) Optionally substituted –C_2-C_8 alkenyl;
4) Optionally substituted –C_2-C_8 alkynyl;
5) Optionally substituted –C_3-C_8 cycloalkyl;
6) Optionally substituted aryl;
7) Optionally substituted arylalkyl;
8) Optionally substituted 3- to 8- membered heterocycloalkyl;
9) Optionally substituted heteroaryl; and
10) Optionally substituted heteroarylalkyl;

X_1, X_2, X_3 and X_4 are each independently selected from N and C(R_6);

R_2 and R_6 are each independently selected from the group consisting of:

1) Hydrogen;
2) Halogen;
3) –NO_2;
4) Cyano;
5) Optionally substituted –C_1-C_8 alkyl;
6) Optionally substituted –C_1-C_8 cycloalkyl; and

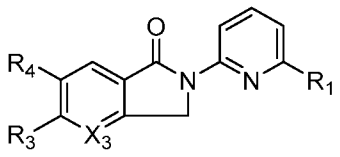
7) Optionally substituted 3- to 8- membered heterocycloalkyl;

R_3 and R_4 are each independently selected from the group consisting of:

1) Hydrogen;
2) Halogen;
3) $-NO_2$;
4) Cyano;
5) Optionally substituted $-C_1$-C_8 alkyl;
6) Optionally substituted $-C_2$-C_8 alkenyl;
7) Optionally substituted $-C_2$-C_8 alkynyl;
8) Optionally substituted $-C_3$-C_8 cycloalkyl;
9) Optionally substituted aryl;
10) Optionally substituted arylalkyl;
11) Optionally substituted 3- to 8- membered heterocycloalkyl;
12) Optionally substituted heteroaryl;
13) Optionally substituted heteroarylalkyl;
14) $-OR_7$;
15) $-N(R_7)(R_8)$;
16) $-S(O)_2N(R_7)(R_8)$;
17) $-N(R_7)\,C(O)\,R_8$; and
18) $-N(R_7)\,S(O)_2R_8$;

wherein R_7 and R_8 are independently selected from the group consisting of hydrogen, $-C_1$-C_{15} alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, all of which are optionally substituted with 1-3 substituents selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, $-CN$, lower alkoxy, $-CF_3$, aryl, and heteroaryl, or R_7 and R_8 are taken together with the nitrogen atom to which they are attached to form a heterocyclic.

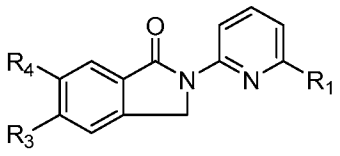
2. The compound of claim 1, represented by Formula (II) or a pharmaceutically acceptable salt, ester or combination thereof:



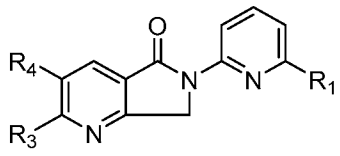
(II) ,

wherein R_1, R_3, R_4 and X_3 are as defined in claim 1.

3. The compound of claim 1, represented by Formula (IIIa) or Formula (IIIb), or a pharmaceutically acceptable salt, ester or combination thereof:



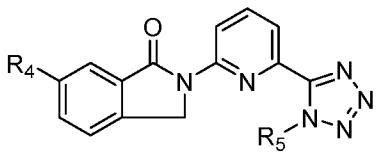
(IIIa)



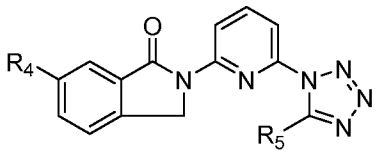
(IIIb) ,

wherein R_1, R_3, and R_4 are as defined in claim 1.

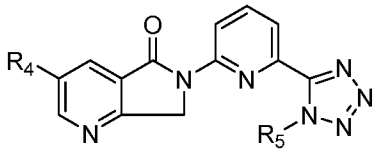
4. The compound of claim 1, represented by Formula (Iva), (Ivb), (Va), (Vb), or a pharmaceutically acceptable salt, ester or combination thereof:



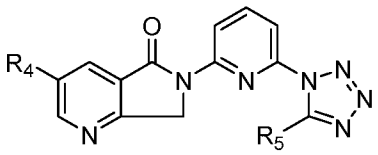
(IVa)



(IVb)



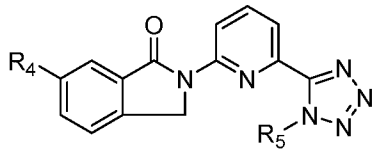
(Va)



(Vb) ,

wherein R_4 and R_5 are as defined in claim 1.

5. The compound according to claim 1, which is selected from compounds of Formula (Iva) or a pharmaceutically acceptable salt, ester or combination thereof:

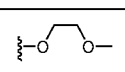
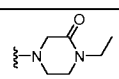


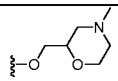
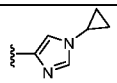
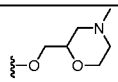
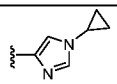
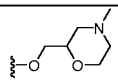
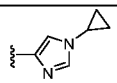
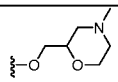
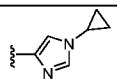
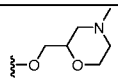
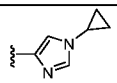
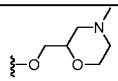
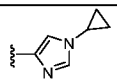
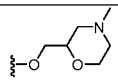
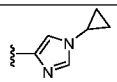
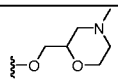
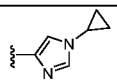
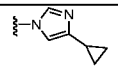
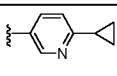
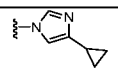
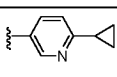
(IVa) ,

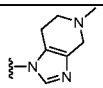
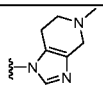
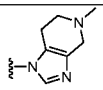
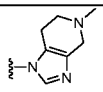
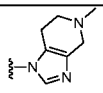
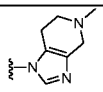
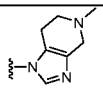
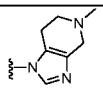
wherein R^1 and R^2 are delineated for each example in Table 1,

Table 1

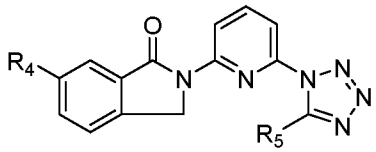
compound	R_5	R_4	compound	R_5	R_4
1			51		

2			52		
3			53		
4			54		
5			55		
6			56		
7			57		
8			58		
9			59		
10			60		
11			61		
12			62		
13			63		
14			64		
15			65		
16			66		
17			67		
18			68		
19			69		
20			70		
21			71		
22			72		

23			73		
24			74		
25			75		
26			76		
27			77		
28			78		
29			79		
30			80		
31			81		
32			82		
33			83		
34			84		
35			85		
36			86		
37			87		
38			88		
39			89		
40			90		
41			91		

42			92		
43			93		
44			94		
45			95		
46			96		
47			97		
48			98		
49			99		
50			100		

6. The compound according to claim 1, which is selected from compounds of Formula (IVb) or a pharmaceutically acceptable salt, ester or combination thereof:

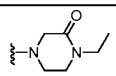
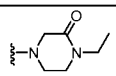
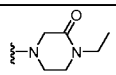


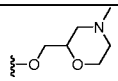
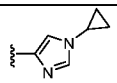
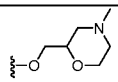
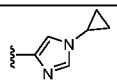
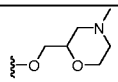
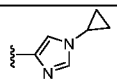
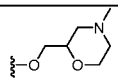
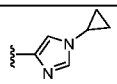
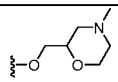
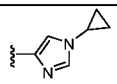
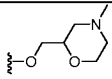
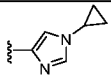
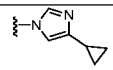
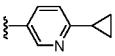
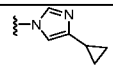
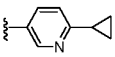
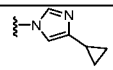
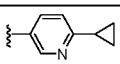
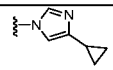
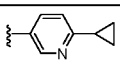
(IVb)

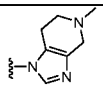
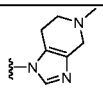
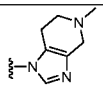
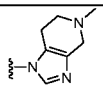
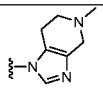
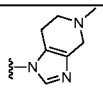
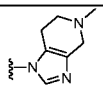
wherein R^1 and R^2 are delineated for each example in Table 2,

Table 2

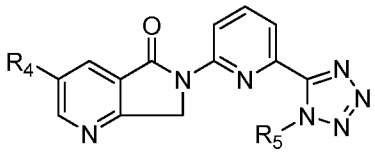
compound	R_5	R_4	compound	R_5	R_4
101			151		
102			152		
103			153		

104			154		
105			155		
106			156		
107			157		
108			158		
109			159		
110			160		
111			161		
112			162		
113			163		
114			164		
115			165		
116			166		
117			167		
118			168		
119			169		
120			170		
121			171		
122			172		
123			173		
124			174		

125			175		
126			176		
127			177		
128			178		
129			179		
130			180		
131			181		
132			182		
133			183		
134			184		
135			185		
136			186		
137			187		
138			188		
139			189		
140			190		
141			191		
142			192		
143			193		

144			194		
145			195		
146			196		
147			197		
148			198		
149			199		
150			200		

7. The compound according to claim 1, which is selected from compounds of Formula (Va) or a pharmaceutically acceptable salt, ester or combination thereof:

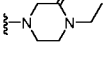
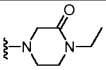


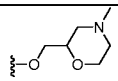
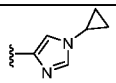
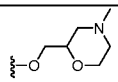
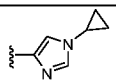
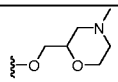
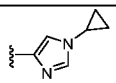
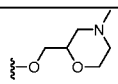
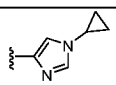
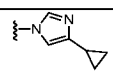
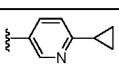
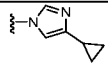
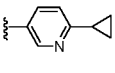
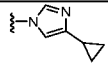
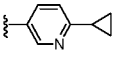
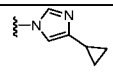
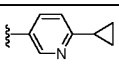
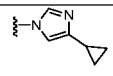
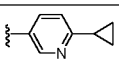
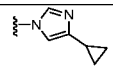
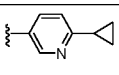
(Va)

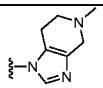
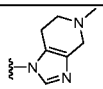
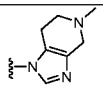
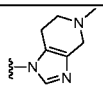
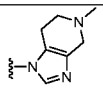
wherein R^1 and R^2 are delineated for each example in Table 3,

Table 3

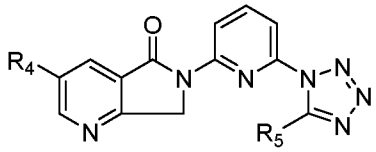
compound	R_5	R_4	compound	R_5	R_4
201			251		
202			252		
203			253		
204			254		
205			255		
206			256		

207			257		
208			258		
209			259		
210			260		
211			261		
212			262		
213			263		
214			264		
215			265		
216			266		
217			267		
218			268		
219			269		
220			270		
221			271		
222			272		
223			273		
224			274		
225			275		
226			276		

227			277		
228			278		
229			279		
230			280		
231			281		
232			282		
233			283		
234			284		
235			285		
236			286		
237			287		
238			288		
239			289		
240			290		
241			291		
242			292		
243			293		
244			294		
245			295		

246			296		
247			297		
248			298		
249			299		
250			300		

8. The compound according to claim 1, which is selected from compounds of Formula (Vb) or a pharmaceutically acceptable salt, ester or combination thereof:

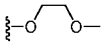
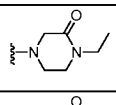
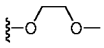
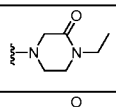
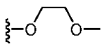
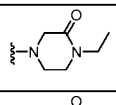
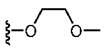
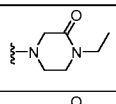
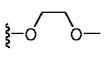
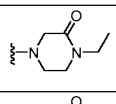
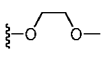
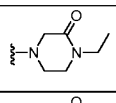
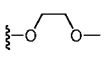
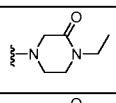
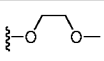
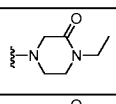
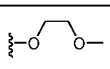
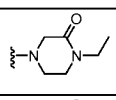


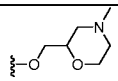
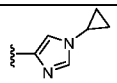
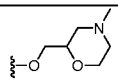
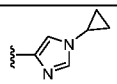
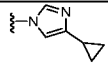
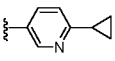
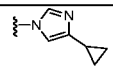
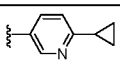
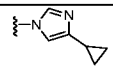
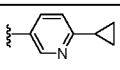
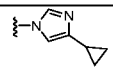
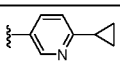
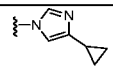
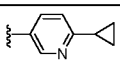
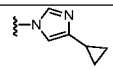
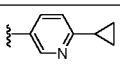
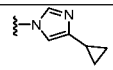
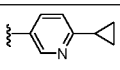
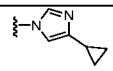
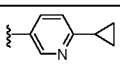
(Vb)

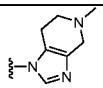
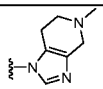
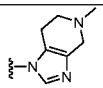
wherein R^1 and R^2 are delineated for each example in Table 4,

Table 4

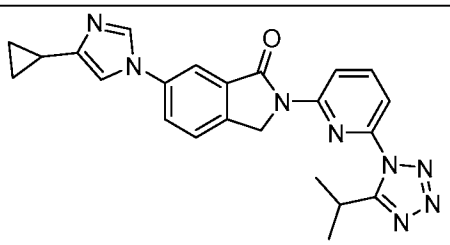
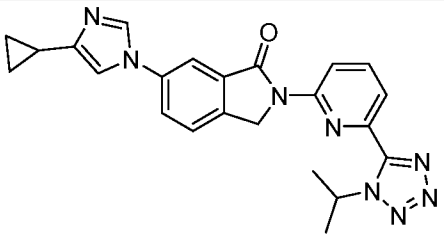
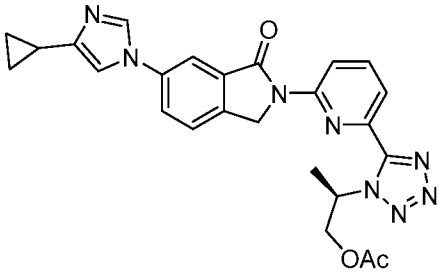
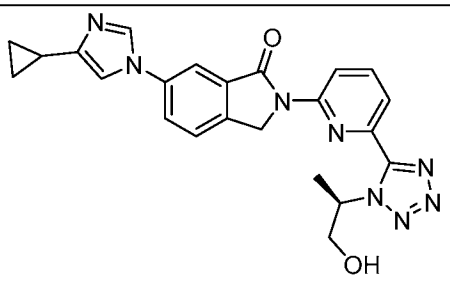
compound	R_5	R_4	compound	R_5	R_4
301			351		
302			352		
303			353		
304			354		
305			355		
306			356		
307			357		
308			358		
309			359		

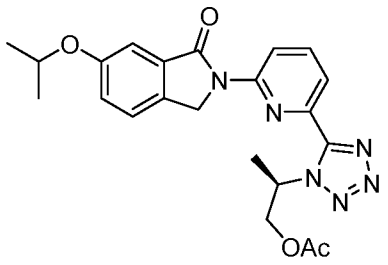
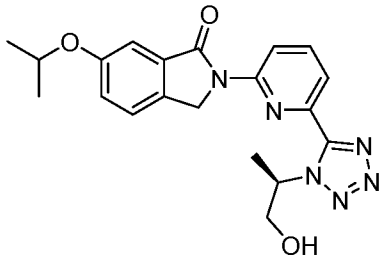
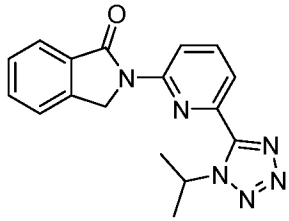
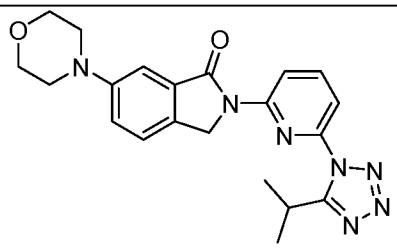
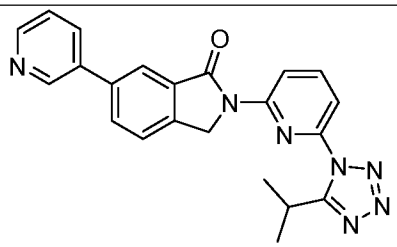
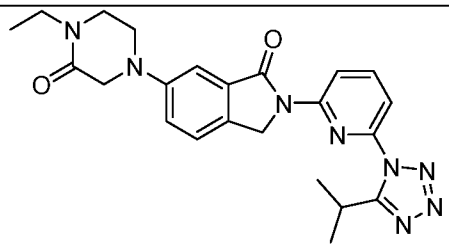
310			360		
311			361		
312			362		
313			363		
314			364		
315			365		
316			366		
317			367		
318			368		
319			369		
320			370		
321			371		
322			372		
323			373		
324			374		
325			375		
326			376		
327			377		
328			378		

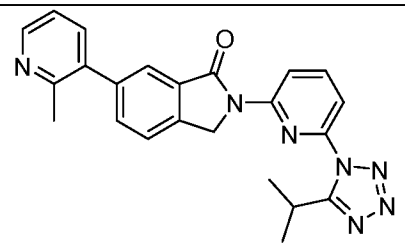
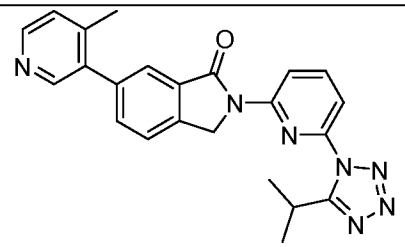
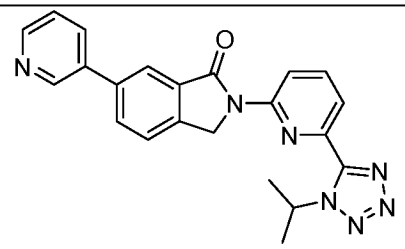
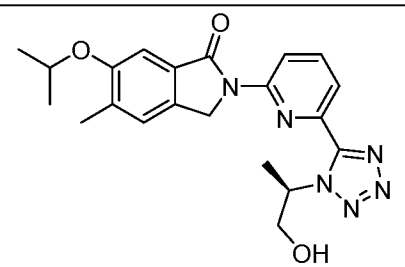
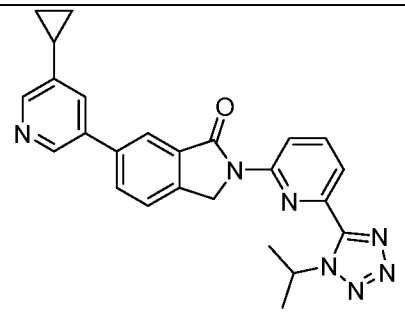
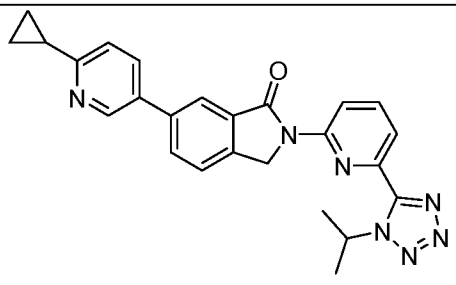
329			379		
330			380		
331			381		
332			382		
333			383		
334			384		
335			385		
336			386		
337			387		
338			388		
339			389		
340			390		
341			391		
342			392		
343			393		
344			394		
345			395		
346			396		
347			397		

348			398		
349			399		
350			400		

9. The compound of claim 1, selected from the compounds set forth below or a pharmaceutically acceptable salt thereof:

Compound	Structure
1	
2	
3	
4	

5	
6	
7	
8	
9	
10	

11	
12	
13	
14	
15	
16	

10. A pharmaceutical composition comprising a compound according to any one of claims 1-8 and a pharmaceutically acceptable carrier or excipient.

11. A method for treating an ASK-1 mediated disease or condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of one or more compounds according to any one of claims 1-8.

12. The method according to claim 10, wherein the ASK-1 mediated disease or condition is selected from the group consisting of an autoimmune disorder, a neurodegenerative disorder, an inflammatory disease, chronic kidney disease, renal disease, cardiovascular disease, a metabolic disease, and an acute or chronic liver disease.

13. The method according to claim 11, wherein the chronic liver disease is selected from the group consisting of primary biliary cirrhosis (PBC), cerebrotendinous xanthomatosis (CTX), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver transplant associated graft versus host disease, living donor transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, Sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, and alpha 1-antitrypsin deficiency.

14. The method according to claim 11, wherein the renal disease is selected from the group consisting of diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, kidney fibrosis and polycystic kidney disease.

15. The method according to claim 11, wherein the cardiovascular disease is selected from the group consisting of atherosclerosis, arteriosclerosis, dyslipidemia, hypercholesterolemia, and hypertriglyceridemia.

16. The method according to claim 11, wherein the metabolic disease is selected from the group consisting of insulin resistance, Type I and Type II diabetes, and obesity.

17. Use of a compound of any one of claims 1-8 in the preparation of a medicament for treating an ASK-1 mediated disease or condition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/48131

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-***-Please See Within the Next Supplemental Box-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-5, 10/1-5, 11/1-5, 12/10/1-5, 17/1-5

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/48131

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/165; C07D 209/46 (2018.01)
CPC - A61K 31/165; C07D 209/46

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/000339 A1 (J. URIACH Y COMPANIA S.A.) 04 January 2007; page 2, lines 15-24; page 3, lines 11, 13-14; page 5, lines 21-23; page 6, lines 1-4; page 7, lines 4-6, 9-10; page 9, lines 29-31; page 30, lines 15-17	1-5, 10/1-5, 11/1-5, 12/10/1-5, 17/1-5
Y	US 2013/0210810 A1 (RIGEL PHARMACEUTICALS, INC.) 15 August 2013; paragraphs [0053], [0439], [0445], [0450]	1-5, 10/1-5, 11/1-5, 12/10/1-5, 17/1-5
Y	US 6,534,651 B2 (JAGTAP, P et al.) 18 March 2003; column 4, lines 44-64; column 5, lines 3-6, 13	1-5, 10/1-5, 11/1-5, 12/10/1-5, 17/1-5
P, X	WO 2018/151830 A1 (FRONTHERA U.S. PHARMACEUTICALS LLC) 23 August 2018; claim 1	1-5, 10/1-5, 11/1-5, 12/10/1-5, 17/1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 October 2018 (01.10.2018)	26 NOV 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

-***-Continued from Box No. III Observations where unity of invention is lacking -***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-17 (in-part); compound represented by Formula I, as shown, wherein R1 is the first shown moiety wherein R5 is -C3-C8 cycloalkyl; X1, X2, X3 and X4 are each C(R6) wherein R6 is hydrogen; R2 is hydrogen; R3 is hydrogen; and R4 is –OR7 wherein R7 is –C1-C15 alkyl, which is compound 1 in table 1, for use in the treatment of an autoimmune disorder (first exemplary compound structure and method).

The compound, compositions and methods will be searched to the extent the compound encompasses a compound represented by Formula I, as shown, wherein R1 is the first shown moiety wherein R5 is -C3-C8 cycloalkyl; X1, X2, X3 and X4 are each C(R6) wherein R6 is hydrogen; R2 is hydrogen; R3 is hydrogen; and R4 is –OR7 wherein R7 is –C1-C15 alkyl, which is compound 1 in table 1, for use in the treatment of an autoimmune disorder (first exemplary compound structure and method). Applicant is invited to elect additional compound(s) and/or method(s), with fully specified structure (e.g. no optional or variable atoms or substituents) for each, to be searched. Additional compound(s) and/or method(s) will be searched upon the payment of additional fees. It is believed that claims 1-5 (in-part), 10-12 (in-part), and 17 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound represented by Formula I, as shown, wherein R1 is the first shown moiety wherein R5 is -C3-C8 cycloalkyl; X1, X2, X3 and X4 are each C(R6) wherein R6 is hydrogen; R2 is hydrogen; R3 is hydrogen; and R4 is –OR7 wherein R7 is –C1-C15 alkyl, which is compound 1 in table 1, for use in the treatment of an autoimmune disorder (first exemplary compound structure and method). Applicants must specify the claims that encompass any additionally elected compound structure(s) and/or method(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound represented by Formula I, as shown, wherein R1 is the first shown moiety wherein R5 is -C3-C8 cycloalkyl; X1, X2, X3 and X4 are each C(R6) wherein R6 is hydrogen; R2 is hydrogen; R3 is hydrogen; and R4 is –OR7 wherein R7 is –C1-C15 alkyl, which is compound 1 in table 1, for use in the treatment of an neurodegenerative disorder (first exemplary elected compound structure and method).

Groups I+ share the technical features including: a compound represented by Formula I, as shown, wherein R1 is the first shown moiety wherein R5 is -C3-C8 cycloalkyl; X1, X2, X3 and X4 are each C(R6) wherein R6 is hydrogen; R2 is hydrogen; R3 is hydrogen; and R4 is –OR7 wherein R7 is –C1-C15 alkyl, which is compound 1 in table 1, for use in the treatment of an autoimmune disorder.

However, these shared technical features are previously disclosed by WO 2007/000339 A1 (J. URIACH Y COMPANIA S.A.) (hereinafter 'Uriach') in view of US 2013/0210810 A1 (RIGEL PHARMACEUTICALS, INC.) (hereinafter 'Rigel') and in further view of US 6,534,651 B2 to Jagtap, et al. (hereinafter 'Jagtap').