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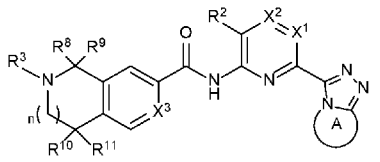

(I)

(57) Abstract: The present invention discloses compounds of Formula (I), and pharmaceutically acceptable salts and esters thereof, 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).

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

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 62/823,195, filed on March 25, 2019. 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).

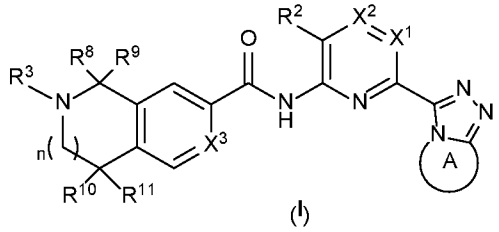
More specifically, ASK-1 has been associated with hepatic steatosis, including non-alcoholic fatty liver disease (NAFLD) and non-alcohol steatohepatitis (NASH). In a mouse model, high fat diets have caused induction of hepatic steatosis, ultimately causing fat accumulation and fatty acid oxidation. This 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, *J. Med. Chem.* **2011**, *54*, 2680-2686, *Bioorg. Med. Chem.* **2011**, *19*, 486-489, WO 2012/003387, WO 2012/011548, WO 2012/080735, Y. Terao, et al., *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7326-7329, WO 2013/112741, *Eur. J. Med. Chem.* **2013**, *16*, 104-115, US 2014/0018370, WO 2014/100541, WO 2015/095059, *Bioorg. Med. Chem. Lett.* **2015**, *23*, 2489-2497, WO 2016/049069, WO 2016/049070, WO 2016/106384, *ACS Med. Chem. Lett.* **2017**, *8*, 316-320, WO 2018/090869, WO 2018/133865, WO 2018/133866, WO 2018/148204, WO 2018/149284, WO 2018/151830, WO 2018/157277, WO 2018/157856, WO 2018/157857, WO 2018/160406, WO 2018/169742, WO 2018/183122, WO 2018/187506, WO 2018/218042, WO 2018/218044, WO 2018/218051, WO 2018/233553, *Bioorg. Med. Chem. Lett.* **2018**, *28*, 400-404, *Eur. J. Med. Chem.* **2018**, *145*, 606-621.

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 or ester thereof:



(I)

wherein:

one of X^1 and X^2 is $C(R^6)$, and the other is $C(R^6)$ or N;

X^3 is $C(R^7)$ or N, wherein R^7 is selected from the group consisting of hydrogen, optionally substituted $-C_1$-C_8 alkyl, optionally substituted $-C_1$-C_8 alkoxy and halo;

A is optionally substituted heterocycloalkyl or optionally substituted heteroaryl which is fused with the 1,2,4-triazolyl ring;

R^2 and R^6 are each independently selected from the group consisting of:

1) Hydrogen;
2) Halogen;
3) $-NO_2$;
4) Cyano;
5) Substituted or unsubstituted $-C_1$-C_8 alkyl;
6) Substituted or unsubstituted $-C_2$-C_8 alkenyl;
7) Substituted or unsubstituted $-C_2$-C_8 alkynyl;
8) Substituted or unsubstituted $-C_3$-C_8 cycloalkyl;
9) Substituted or unsubstituted aryl;
10) Substituted or unsubstituted arylalkyl;
11) Substituted or unsubstituted 3- to 8- membered heterocycloalkyl;
12) Substituted or unsubstituted heteroaryl;
13) Substituted or unsubstituted heteroarylalkyl;
14) $-N(R^4)(R^5)$;
15) $-S(O)_2N(R^4)(R^5)$;
16) $-N(R^4)C(O)R^5$; and
17) $-N(R^4)S(O)_2R^5$;

R^3 is selected from the group consisting of:

1) Hydrogen;

2) Substituted or unsubstituted $-C_1$-C_8 alkyl;

3) Substituted or unsubstituted $-C_2$-C_8 alkenyl;

4) Substituted or unsubstituted $-C_2$-C_8 alkynyl;

5) Substituted or unsubstituted $-C_3$-C_8 cycloalkyl;

6) Substituted or unsubstituted aryl;

7) Substituted or unsubstituted arylalkyl;

8) Substituted or unsubstituted 3- to 8- membered heterocycloalkyl;

9) Substituted or unsubstituted heteroaryl;

10) Substituted or unsubstituted heteroarylalkyl;

11) $-C(O)R^4$;

12) $-C(O)OR^4$;

13) $-C(O)N(R^4)(R^5)$; and

14) $-SO_2R^4$;

R^4 and R^5 are independently hydrogen, $-C_1$-C_8 alkyl, $-C_1$-C_8 alkenyl, $-C_1$-C_8 alkynyl, $-C_3$-C_8 cycloalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroarylalkyl, wherein the $-C_1$-C_8 alkyl, $-C_1$-C_8 alkenyl, $-C_1$-C_8 alkynyl, $-C_3$-C_8 cycloalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroarylalkyl is optionally substituted with 1-3 substituents independently selected from halo, oxo, alkyl, $-C_3$-C_8 cycloalkyl, alkylamino, dialkylamino, alkyl-C(O)-NH-, aryl-C(O)NH-, heteroaryl-C(O)NH-, heterocycloalkyl, heterocycloalkyl-C(O)-, -OH, $-CN$, alkoxy, $-CF_3$, aryl, and heteroaryl; or R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocycloalkyl;

R^8 and R^9 are each independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted $-C_1$-C_8 alkyl; alternatively, R^8 and R^9 are taken together with the carbon atom to which they are attached to form C(O), spiro–C_3-C_8 cycloalkyl, or spiro-3- to 8- membered heterocycloalkyl;

R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, halo, and optionally substituted $-C_1$-C_8 alkyl; and

n is 0, 1 or 2; preferably n is 0 or 1.

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 form, stereoisomer, solvate,

hydrate 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. The method comprises administering a therapeutically effective amount of a compound of Formula (I) to a subject in need thereof. 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 or ester thereof.

In certain embodiments of the compounds of the invention, R^2 is hydrogen or halogen.

In certain embodiments of the compounds of the invention, n is 0 or 1, preferably 1.

In certain embodiments of the compounds of the invention, R^2 is hydrogen and n is 0 or 1.

In certain embodiments of the compounds of the invention, R^8 is hydrogen.

In certain embodiments of the compounds of the invention, R^9 is hydrogen.

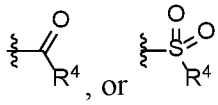
In certain embodiments of the compounds of the invention, R^8 and R^9 are both hydrogen.

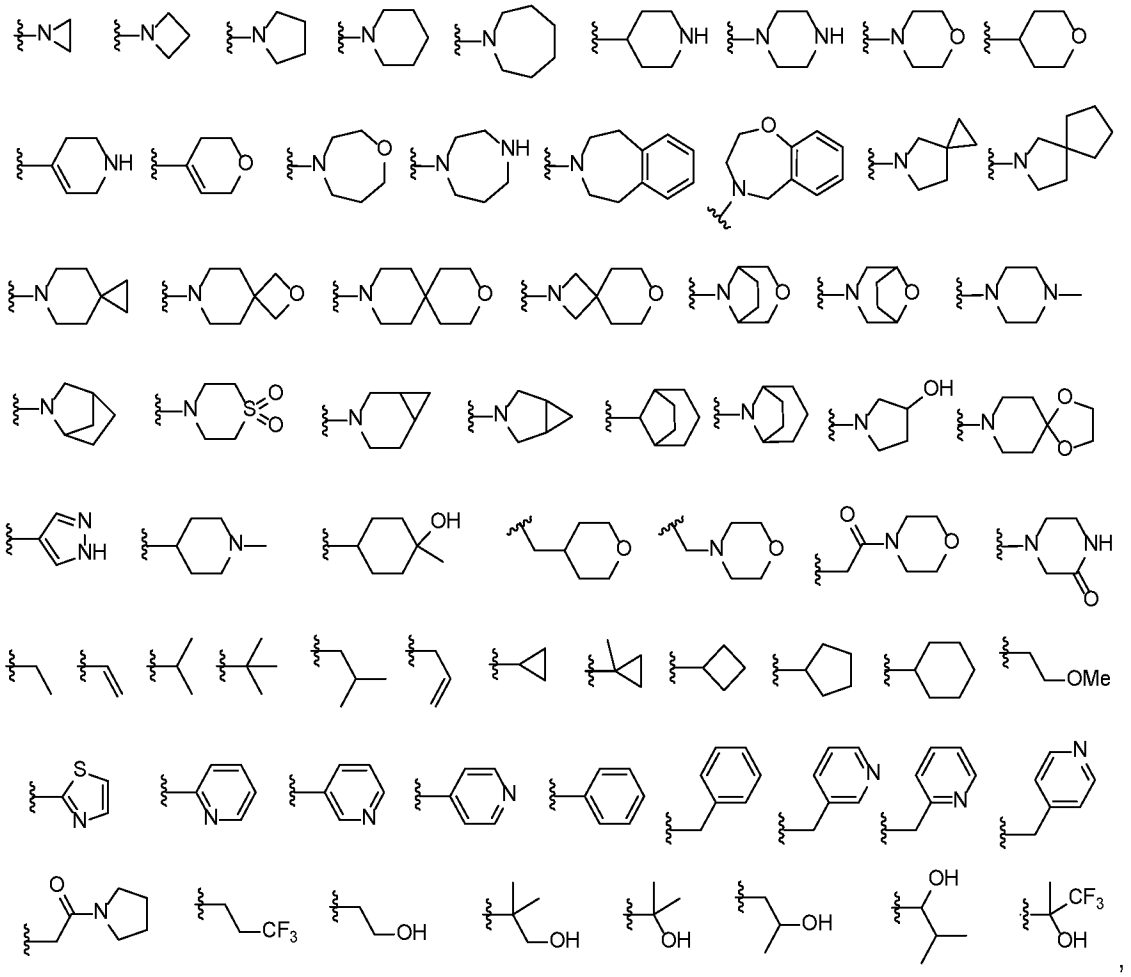
In certain embodiments of the compounds of the invention, R^{10} is hydrogen, halogen or optionally substituted methyl.

In certain embodiments of the compounds of the invention, R^{11} is hydrogen, halogen or optionally substituted methyl.

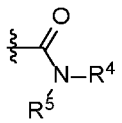
In certain embodiments of the compounds of the invention, R^{10} and R^{11} are both hydrogen.

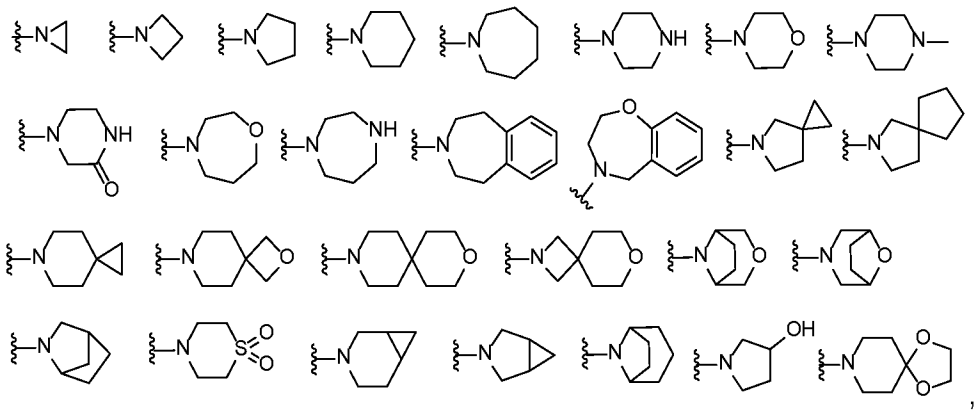
In certain embodiments of the compounds of the invention, R^8, R^9, R^{10} and R^{11} are all hydrogen.

In certain embodiments of the compounds of the invention, R^3 is  , wherein R^4 is selected from the groups below:

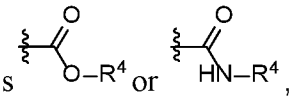


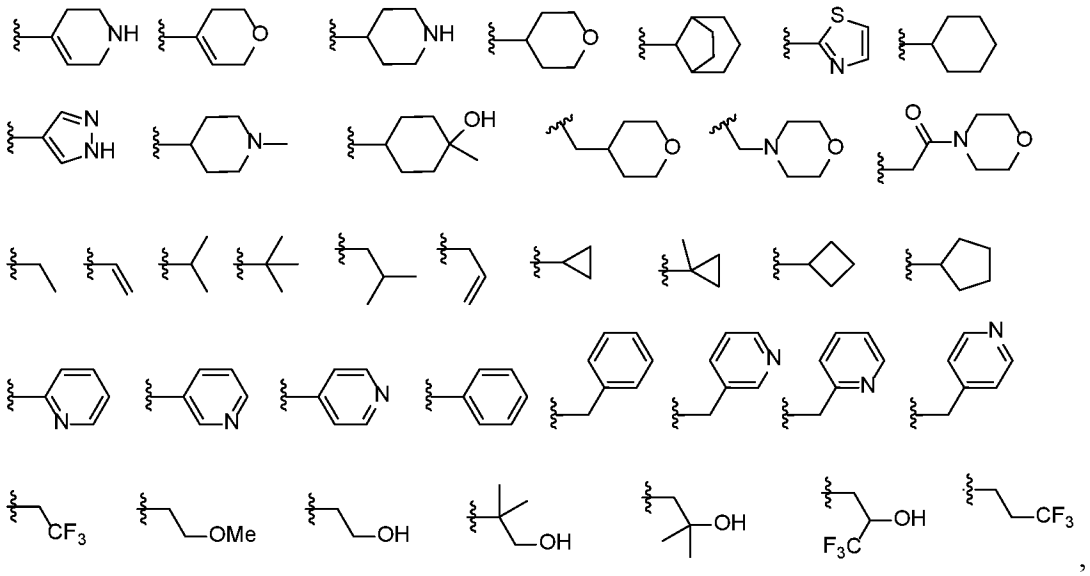
wherein each of the above shown groups is optionally substituted.

In certain embodiments of the compounds of the invention, R^3 is  , wherein R^4 and R^5 are taken together with the nitrogen atom to which they are they attached to form a heterocycloalkyl which is selected from the groups below:



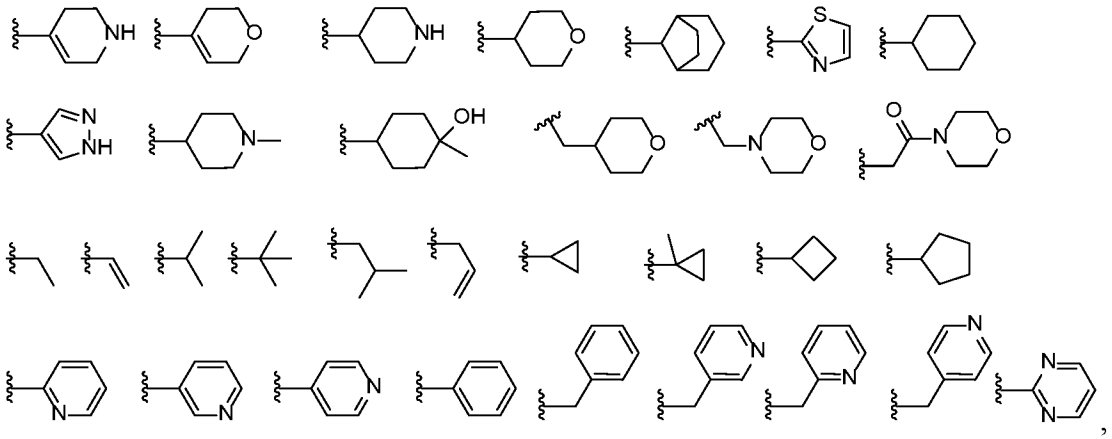
wherein each of the above shown groups is optionally substituted.

In certain embodiments of the compounds of the invention, R^3 is  wherein R^4 is selected from the groups below:



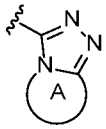
wherein each of the above shown groups is optionally substituted.

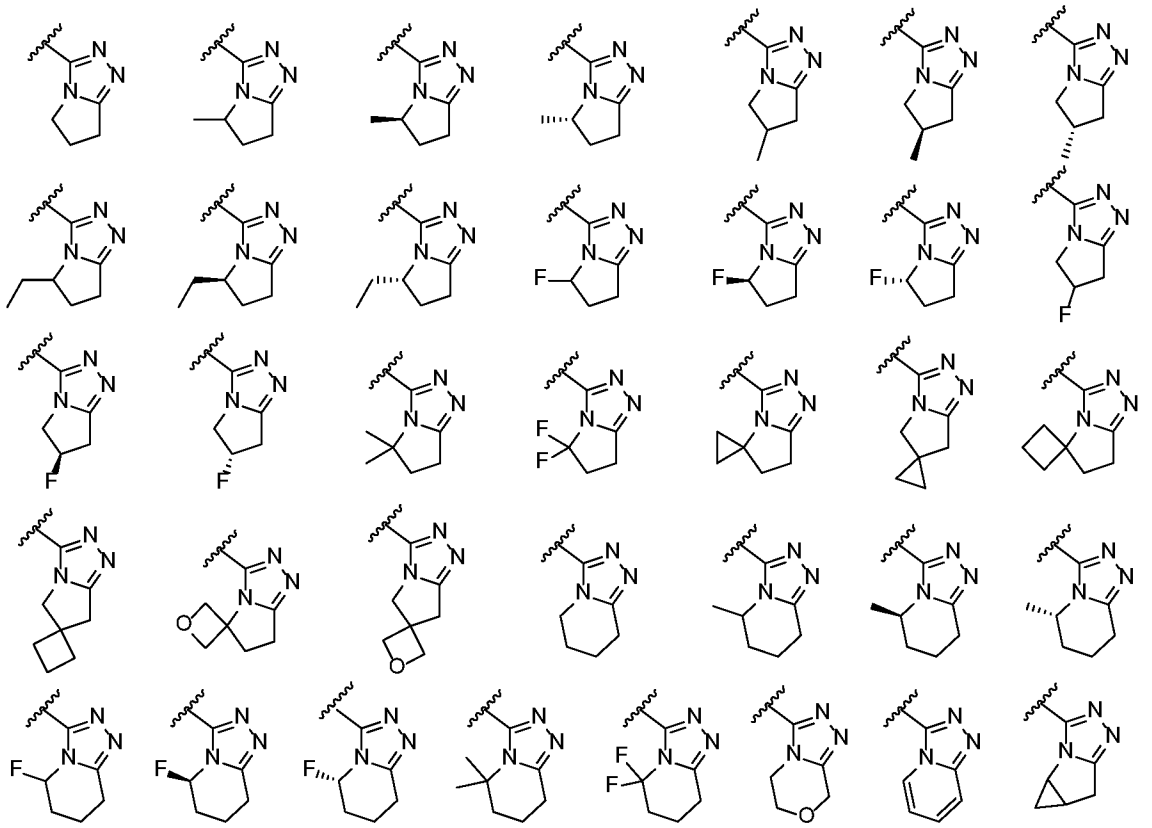
In certain embodiments of the compounds of the invention, R^3 is selected from the groups below:



wherein each of these groups is optionally substituted.

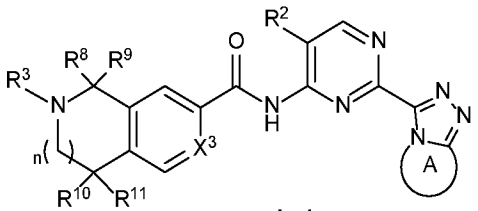
In certain embodiments of the compounds of the invention, X^3 is selected from C-H, C-F, C-OMe, and N.

In certain embodiments of the compounds of the invention,  is selected from the groups below:

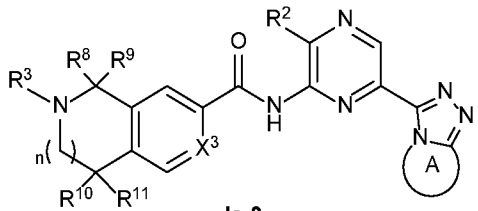


wherein each of the above shown groups is optionally substituted.

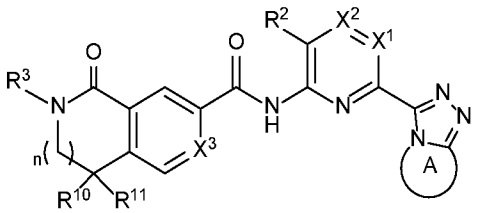
In certain embodiments, the invention provides compounds of Formula Ia-1, Ia-2, Ib-1, Ib-2, Ic-1, Ic-2, and Ie, and pharmaceutically acceptable salts and esters thereof:



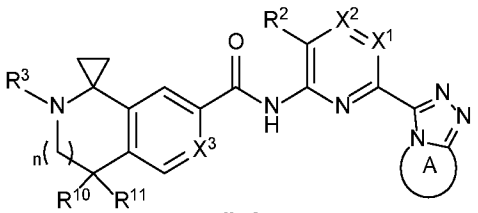
(Ia-1)



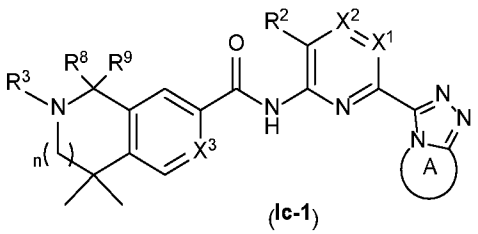
(Ia-2)



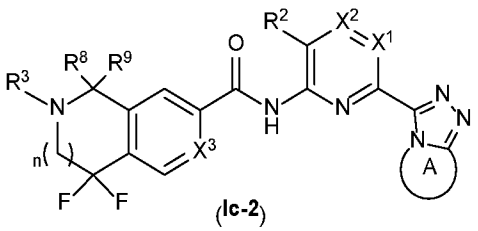
(Ib-1)



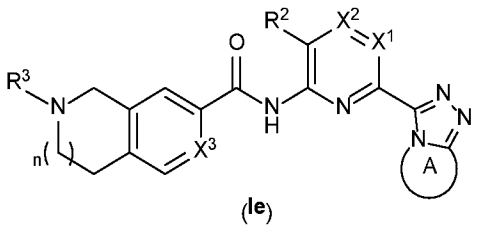
(Ib-2)



(Ic-1)



(Ic-2)

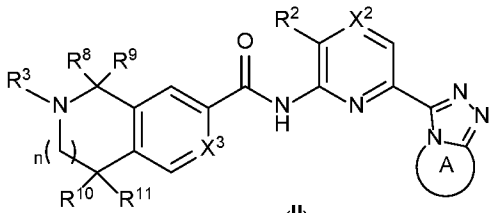


(Ie)

,

wherein A, R^2, R^3, R^8, R^9, R^{10}, R^{11}, X^1, X^2, X^3, and n are as previously defined.

In certain embodiments, the compound of Formula I is represented by Formula II or a pharmaceutically acceptable salt or ester thereof:

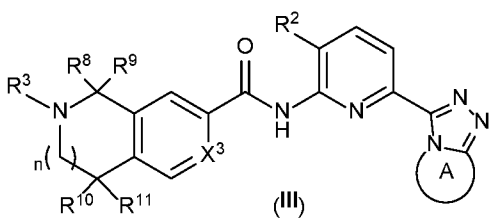


(II)

,

wherein A, R^2, R^3, R^8, R^9, R^{10}, R^{11}, X^2, X^3 and n are as previously defined.

In certain embodiments, the compound of Formula I is represented by Formula III or a pharmaceutically acceptable salt or ester thereof:

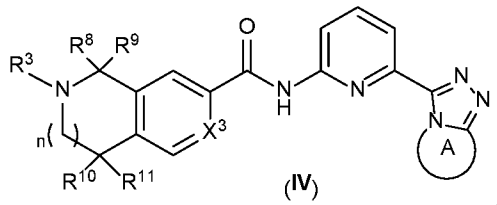


(III)

,

wherein A, R^2, R^3, R^8, R^9, R^{10}, R^{11}, X^3 and n are as previously defined.

In certain embodiments, the compound of Formula I is represented by Formula IV or a pharmaceutically acceptable salt or ester thereof:

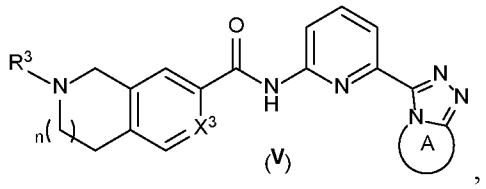


(IV)

,

wherein A, R^3, R^8, R^9, R^{10}, R^{11}, X^3 and n are as previously defined.

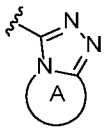
In certain embodiments, the compound of Formula I is represented by Formula V or a pharmaceutically acceptable salt or ester thereof:

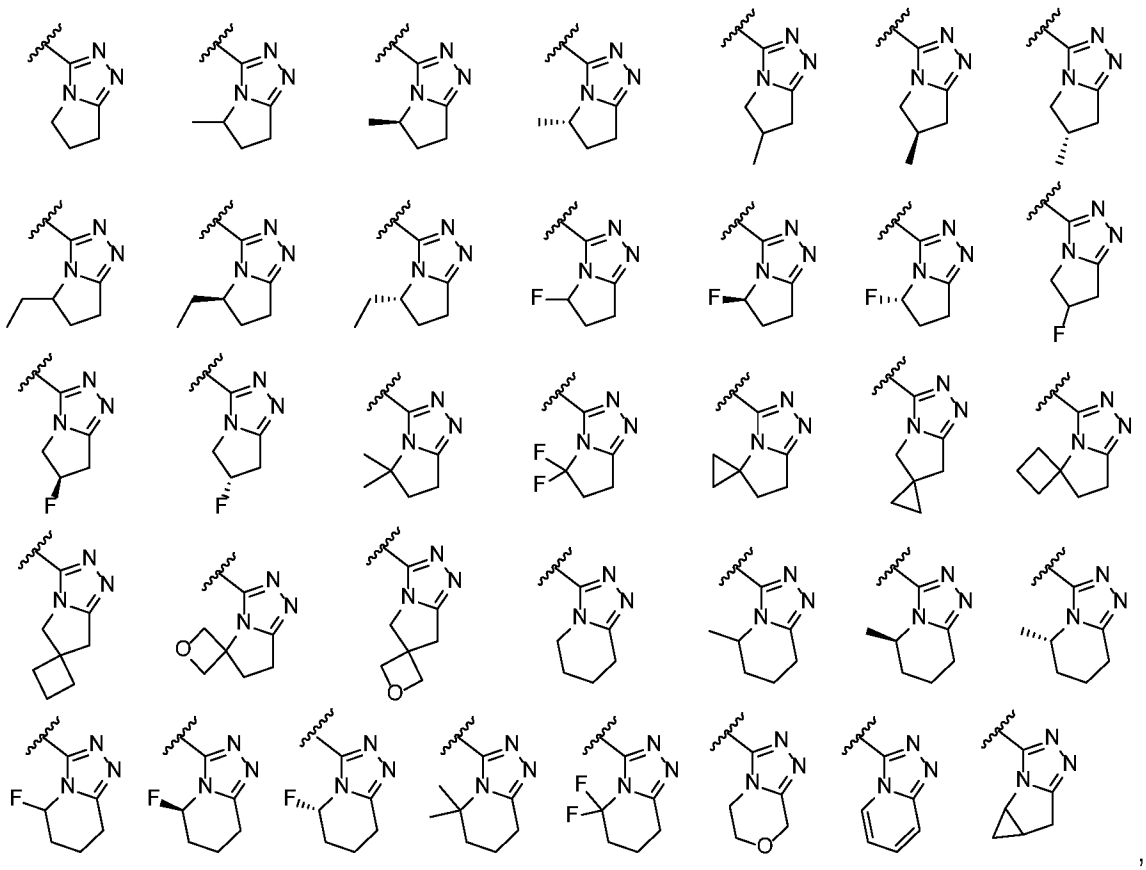


(V)

,

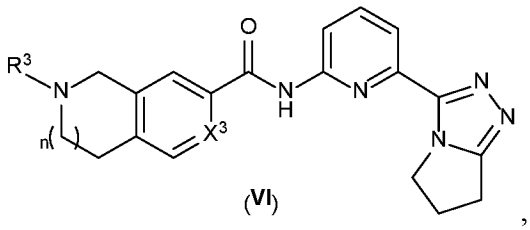
wherein A, R^3, X^3, and n are as previously defined.

In certain embodiments, the present invention relates to compounds of Formula I, Ia-1, Ia-2, Ib-1, Ib-2, Ic-1, Ic-2, Ie, II, III, IV, and V, and pharmaceutically acceptable salts and esters thereof, wherein  is selected from the groups below:



wherein each of the above shown groups is optionally substituted.

In certain embodiments, the compound of Formula I is represented by Formula VI or a pharmaceutically acceptable salt or ester thereof:

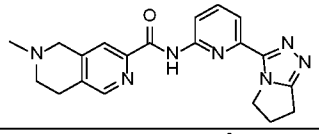
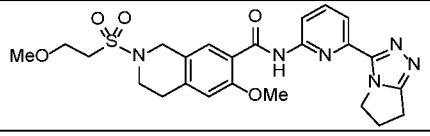
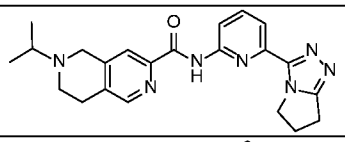
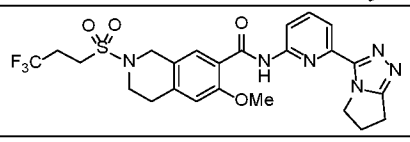
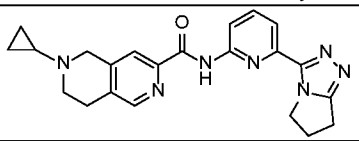
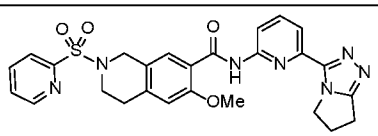
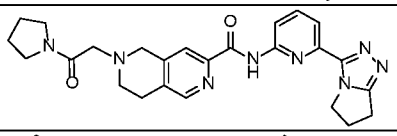
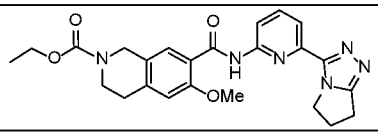
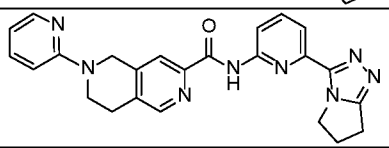
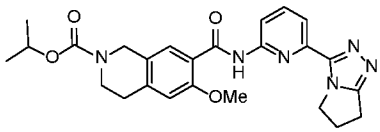
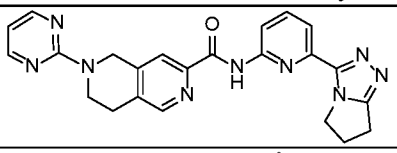
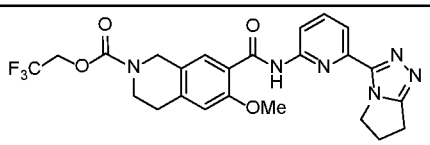
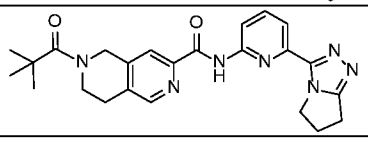
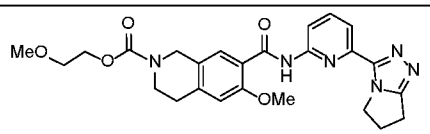
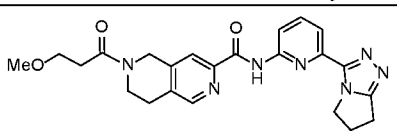
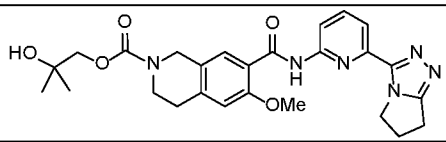
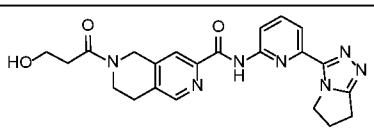
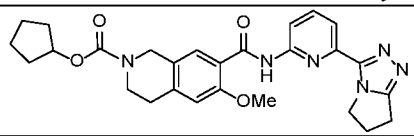
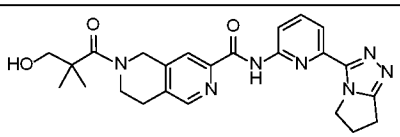
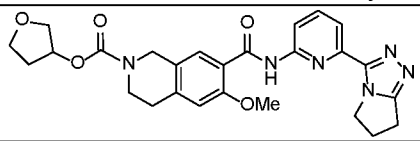
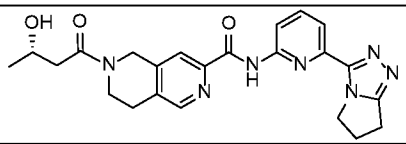
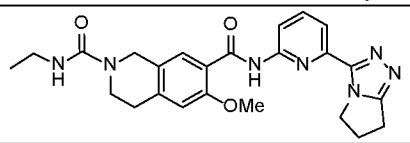
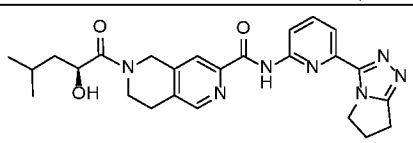
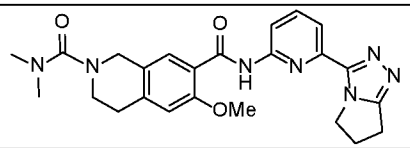
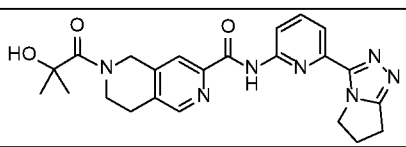
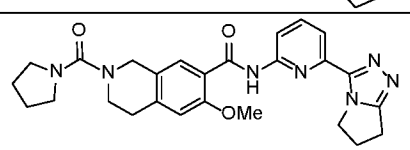


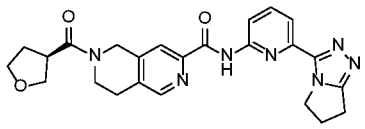
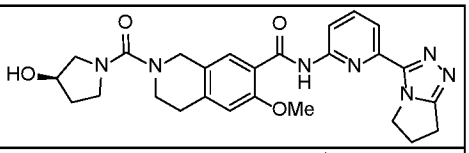
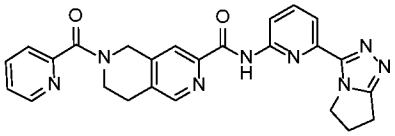
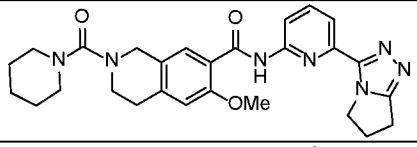
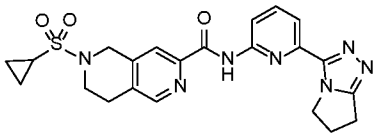
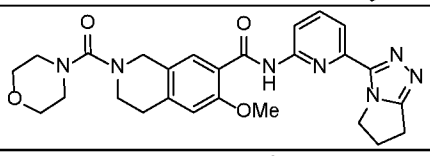
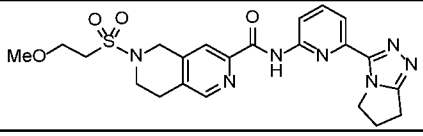
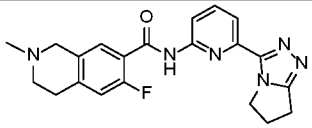
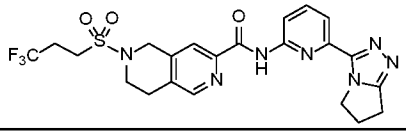
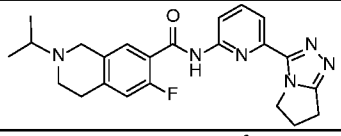
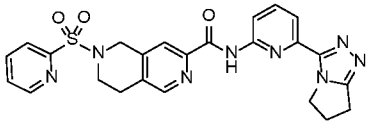
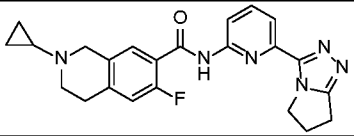
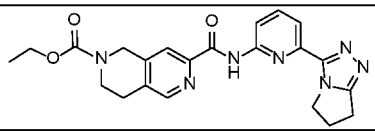
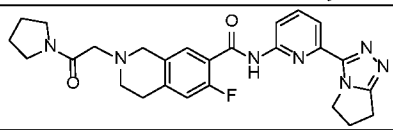
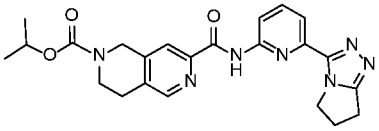
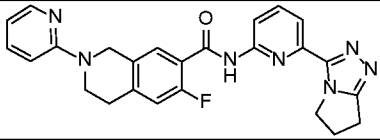
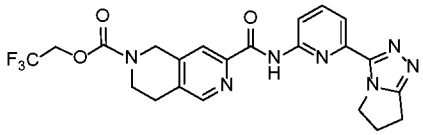
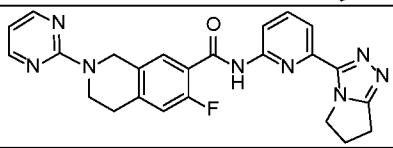
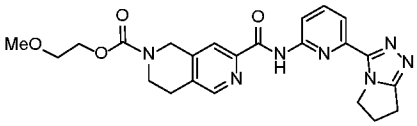
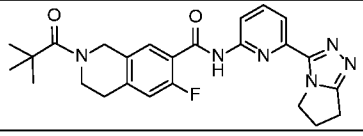
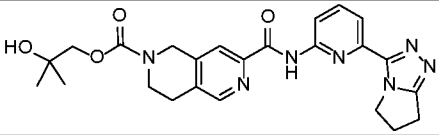
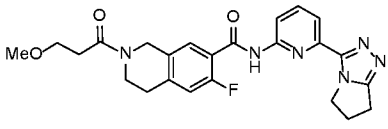
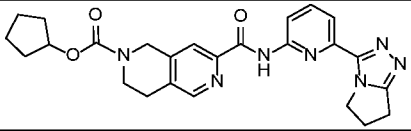
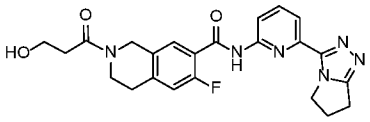
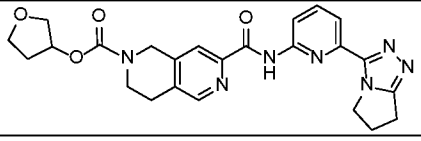
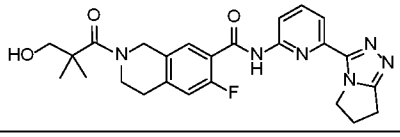
(VI)

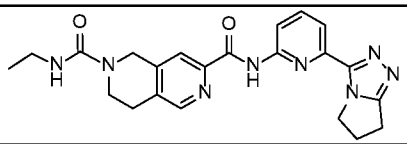
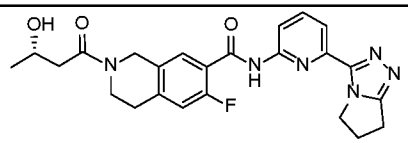
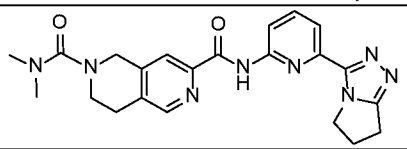
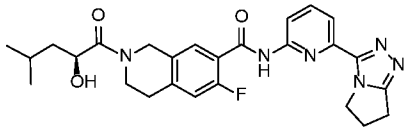
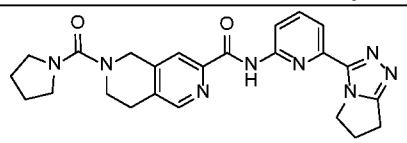
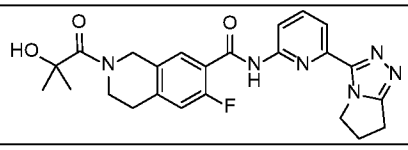
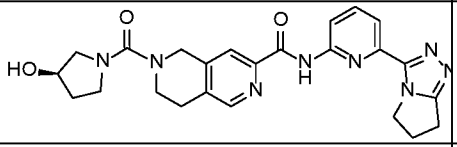
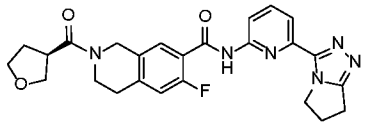
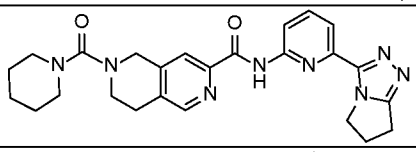
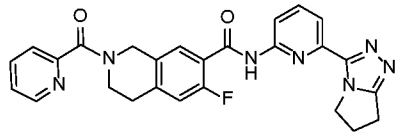
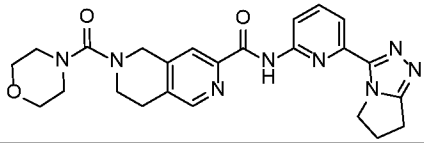
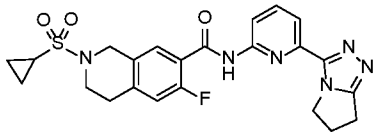
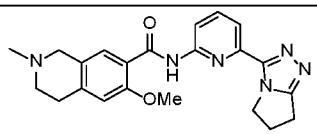
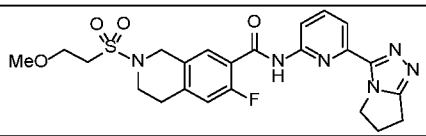
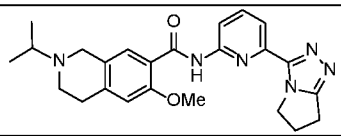
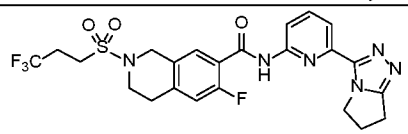
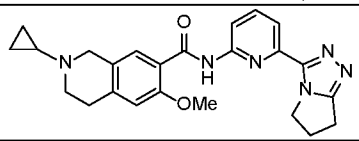
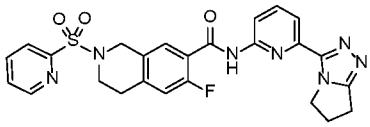
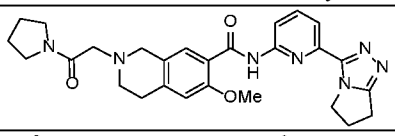
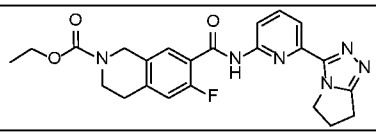
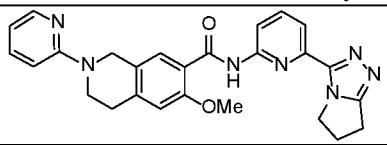
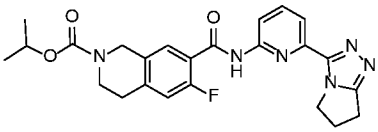
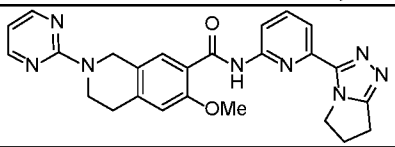
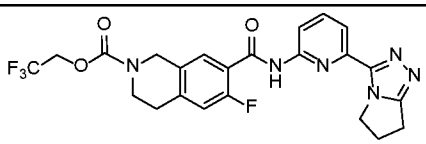
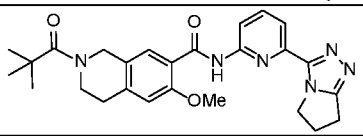
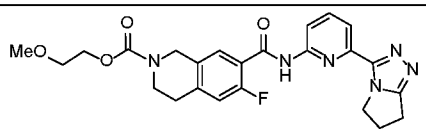
wherein R^3, X^3, and n are as previously defined.

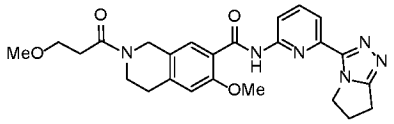
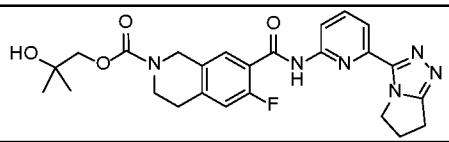
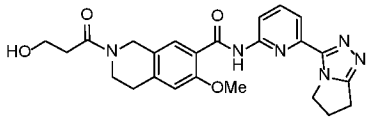
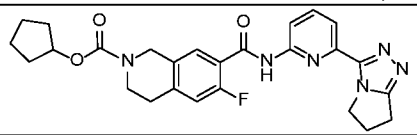
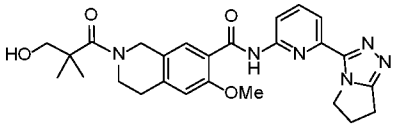
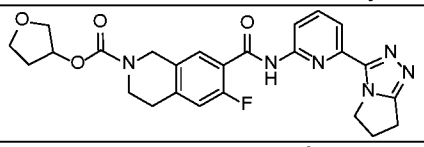
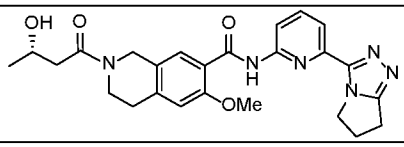
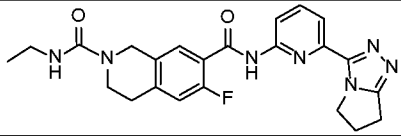
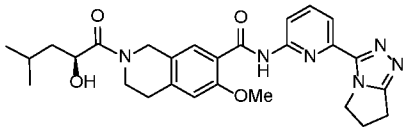
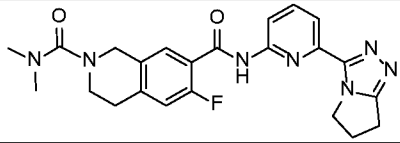
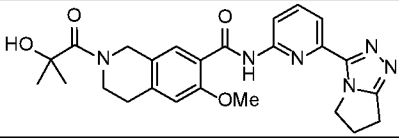
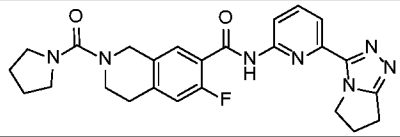
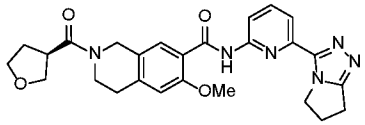
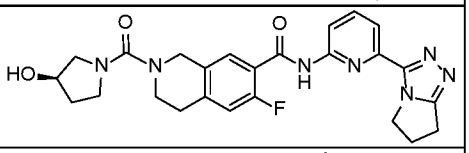
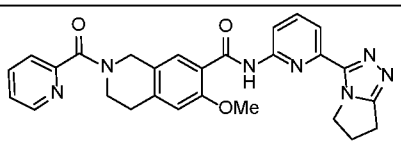
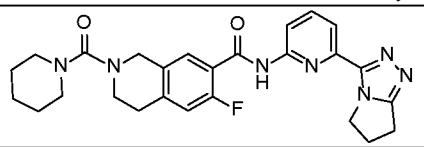
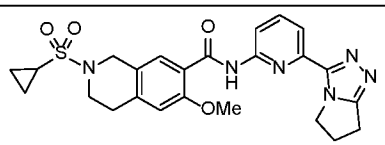
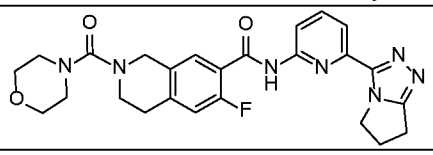
Representative compounds of the invention include, but are not limited to, the following compounds (compound 1 to compound 96 in Table 1) and pharmaceutically acceptable salts thereof.

Table 1

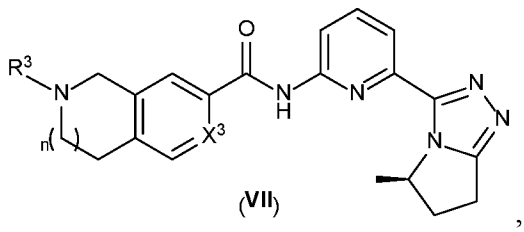
Compound	Structure	Compound	Structure
1		49	
2		50	
3		51	
4		52	
5		53	
6		54	
7		55	
8		56	
9		57	
10		58	
11		59	
12		60	
13		61	

14		62	
15		63	
16		64	
17		65	
18		66	
19		67	
20		68	
21		69	
22		70	
23		71	
24		72	
25		73	
26		74	

27		75	
28		76	
29		77	
30		78	
31		79	
32		80	
33		81	
34		82	
35		83	
36		84	
37		85	
38		86	
39		87	

40		88	
41		89	
42		90	
43		91	
44		92	
45		93	
46		94	
47		95	
48		96	

In certain embodiments, the compound of Formula I is represented by Formula VII or a pharmaceutically acceptable salt or ester thereof:

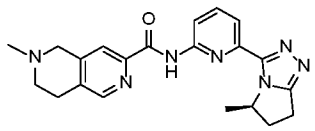
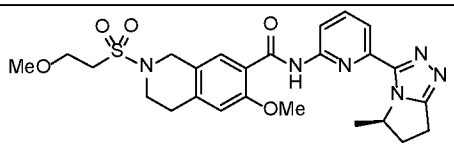
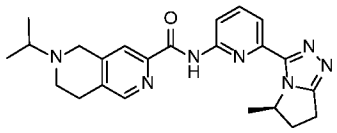
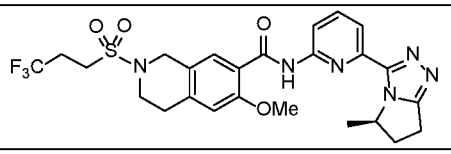
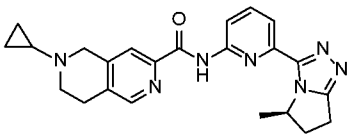
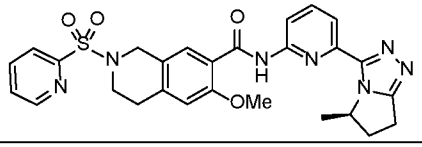
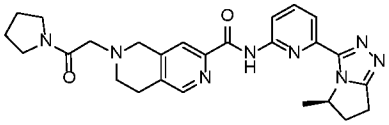
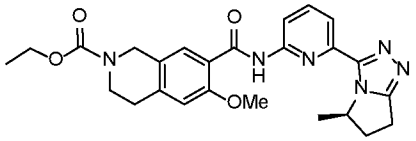
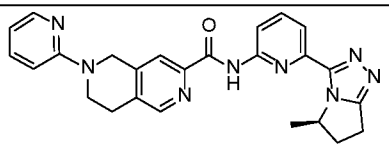
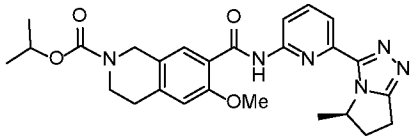
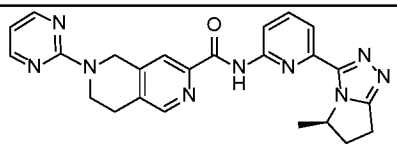
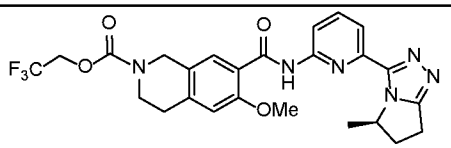
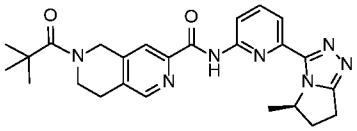
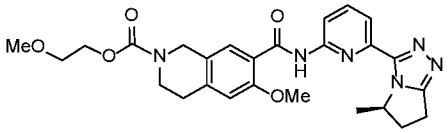
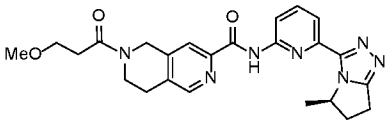
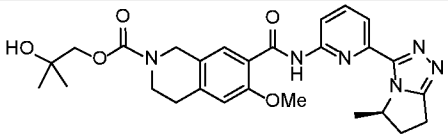
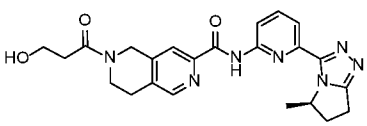
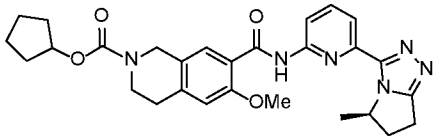
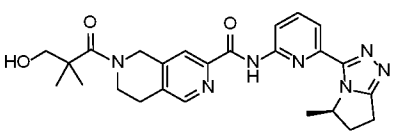
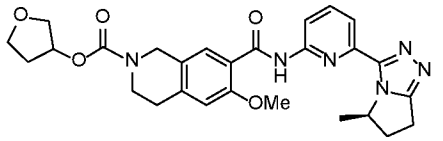


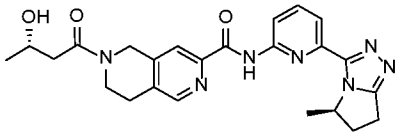
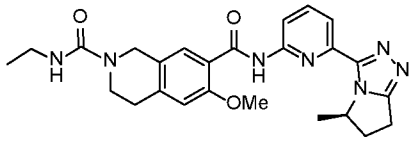
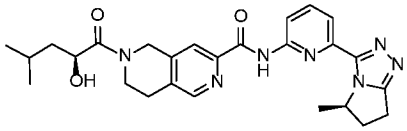
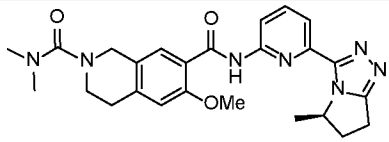
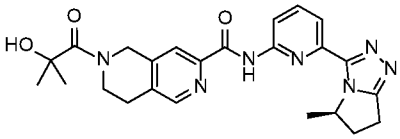
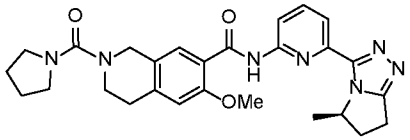
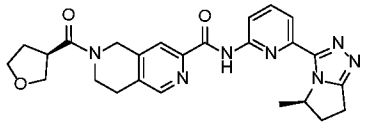
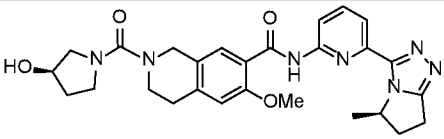
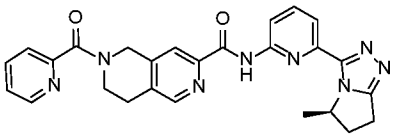
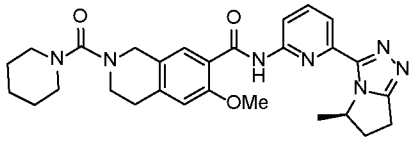
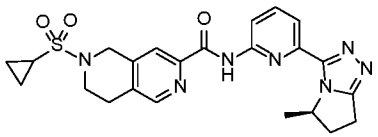
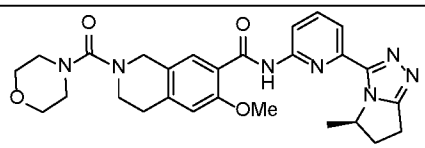
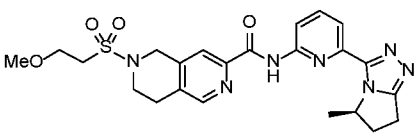
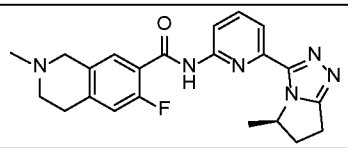
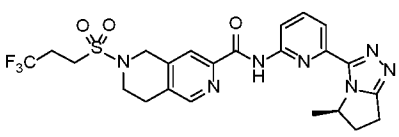
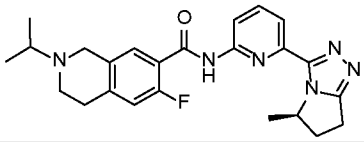
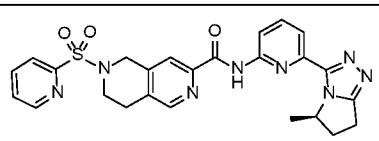
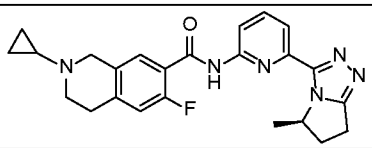
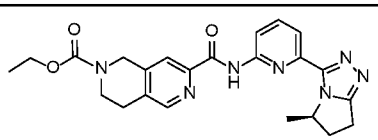
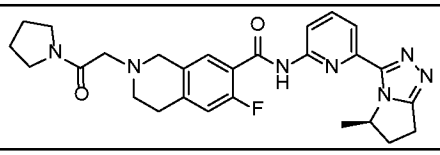
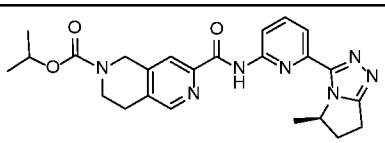
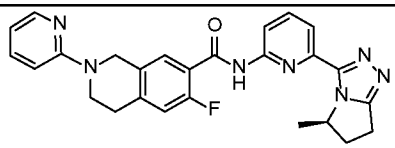
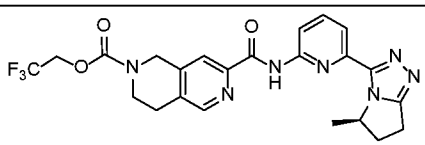
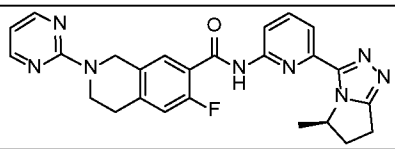
(VII),

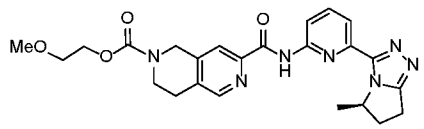
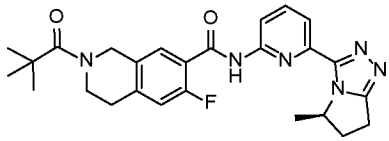
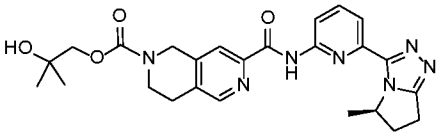
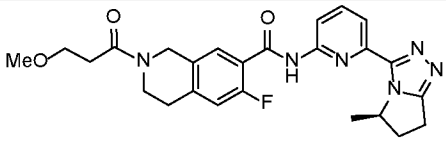
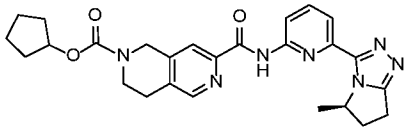
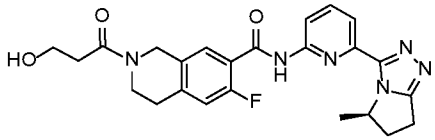
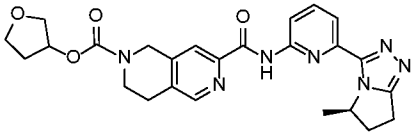
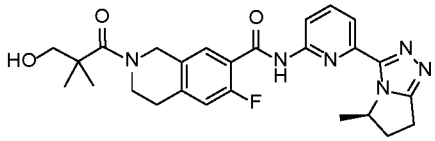
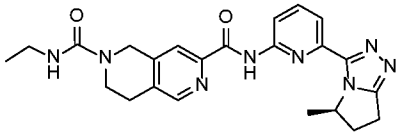
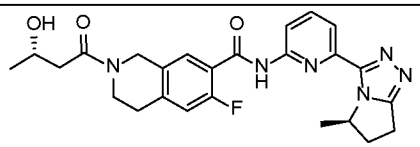
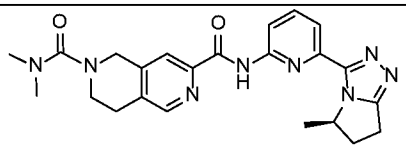
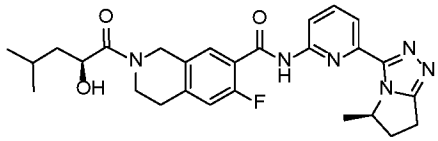
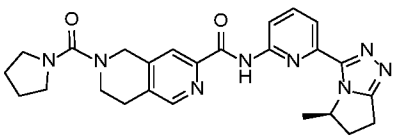
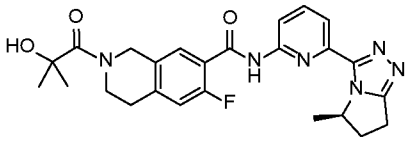
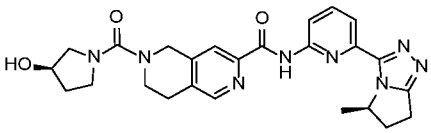
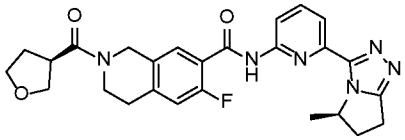
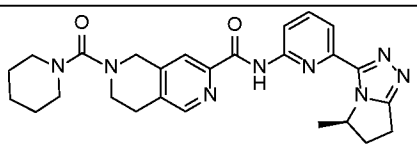
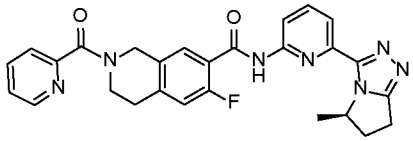
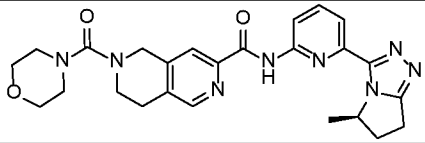
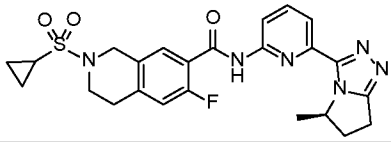
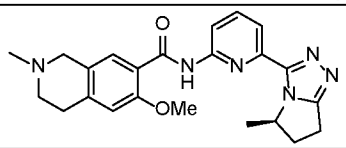
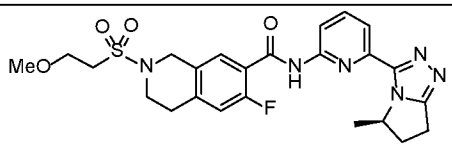
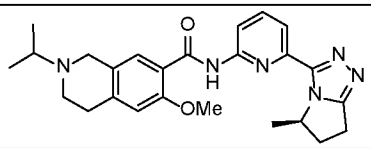
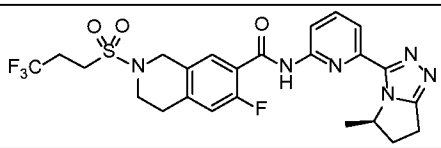
wherein R^3, X^3, and n are as previously defined.

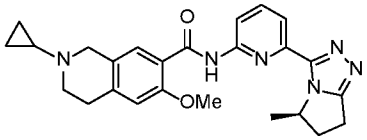
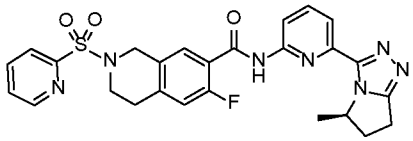
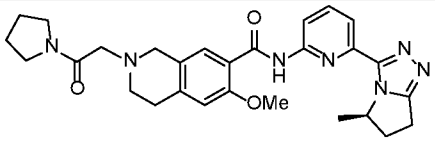
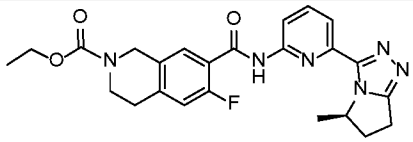
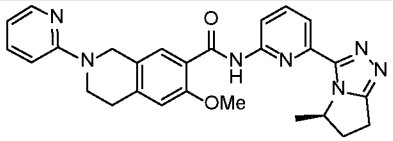
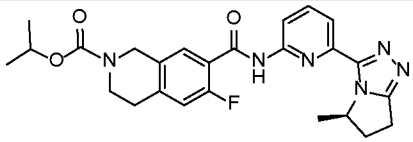
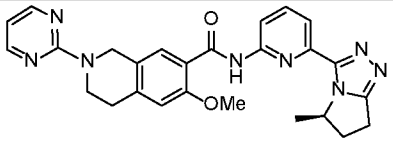
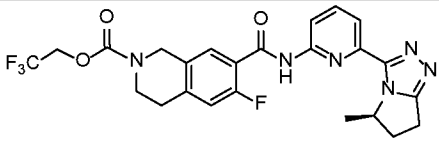
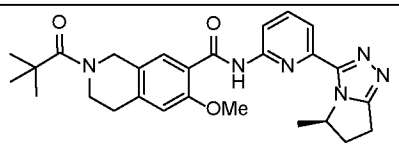
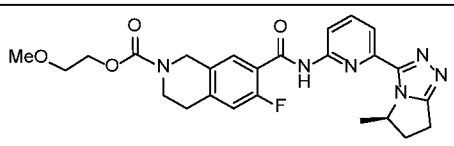
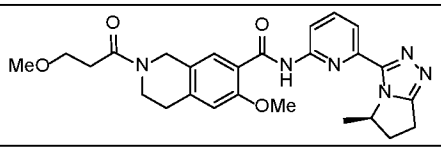
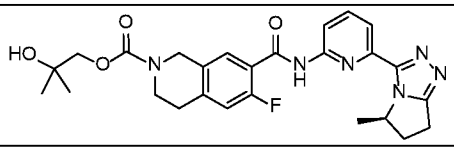
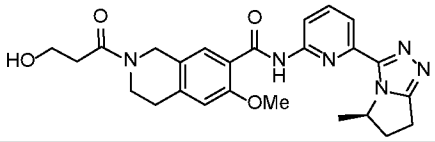
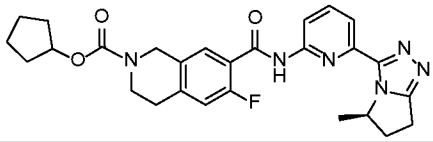
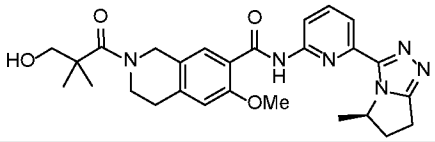
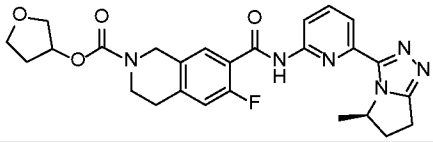
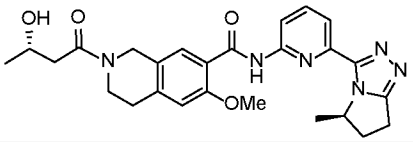
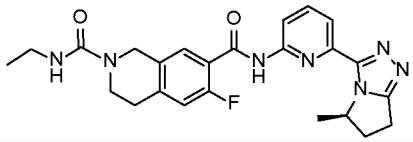
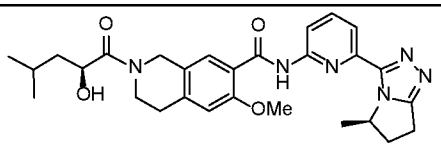
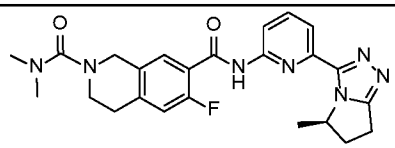
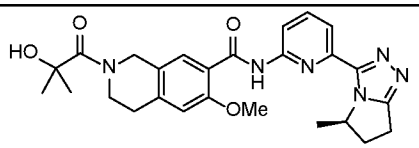
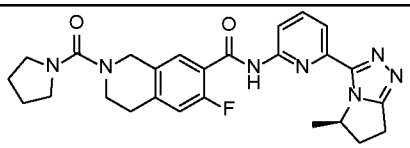
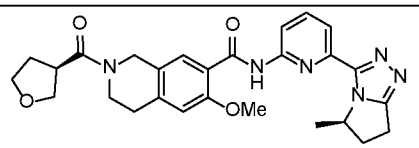
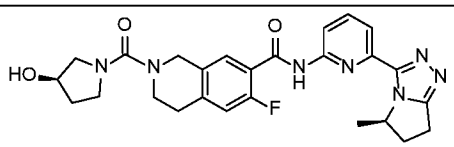
Representative compounds of the invention include, but are not limited to, the following compounds (compound 97 to compound 192 in Table 2) and pharmaceutically acceptable salts thereof.

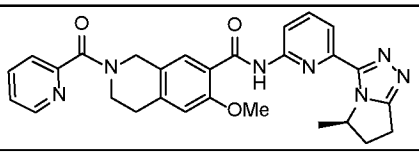
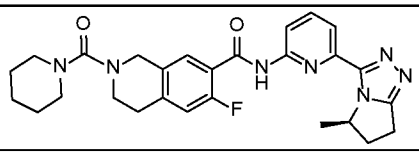
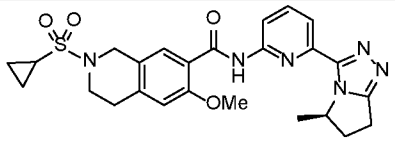
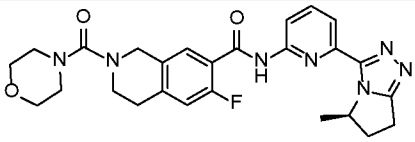
Table 2

Compound	Structure	Compound	Structure
97		145	
98		146	
99		147	
100		148	
101		149	
102		150	
103		151	
104		152	
105		153	
106		154	

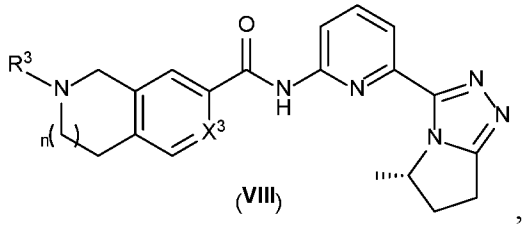
107		155	
108		156	
109		157	
110		158	
111		159	
112		160	
113		161	
114		162	
115		163	
116		164	
117		165	
118		166	

119		167	
120		168	
121		169	
122		170	
123		171	
124		172	
125		173	
126		174	
127		175	
128		176	
129		177	
130		178	

131		179	
132		180	
133		181	
134		182	
135		183	
136		184	
137		185	
138		186	
139		187	
140		188	
141		189	
142		190	

143		191	
144		192	

In certain embodiments, the compound of Formula I is represented by Formula VIII or a pharmaceutically acceptable salt or ester thereof:

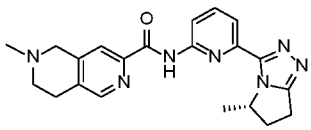
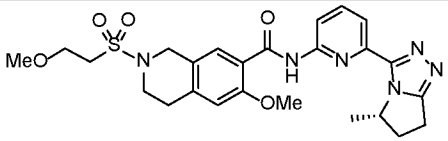
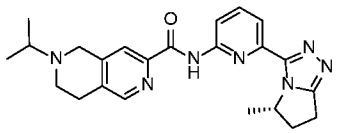
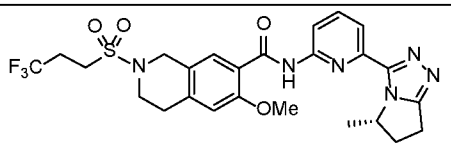
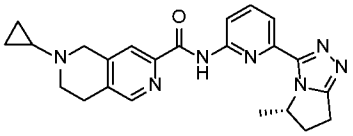
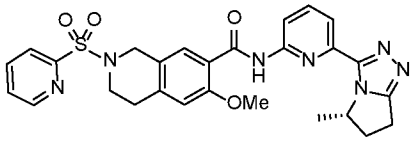
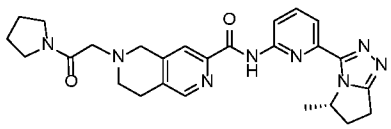
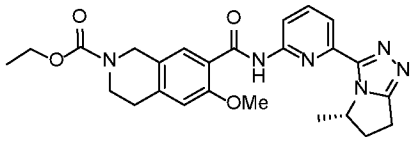
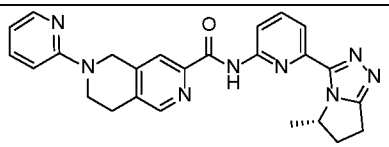
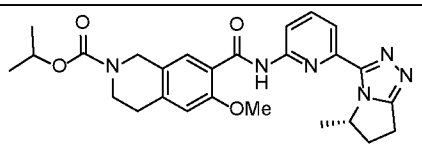


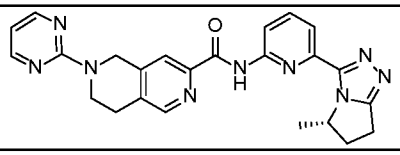
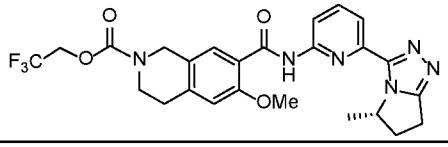
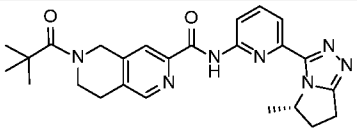
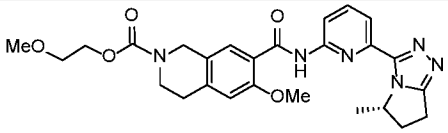
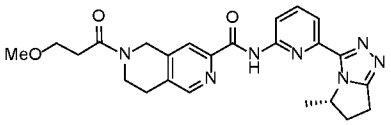
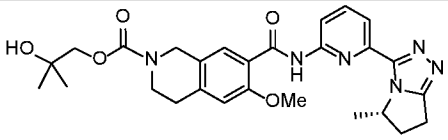
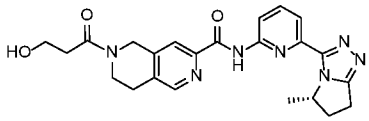
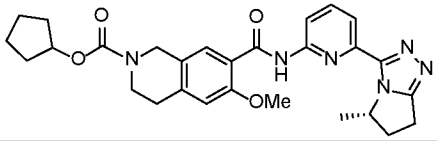
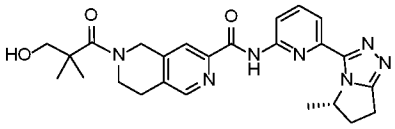
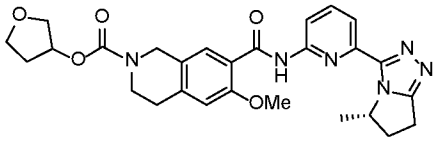
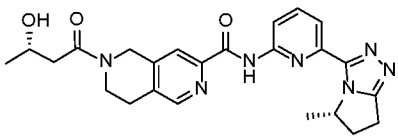
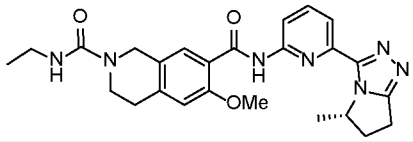
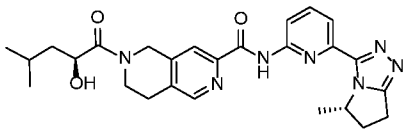
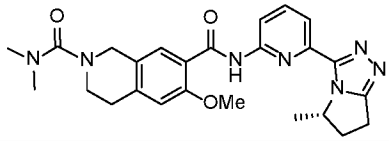
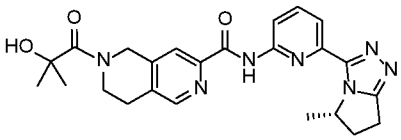
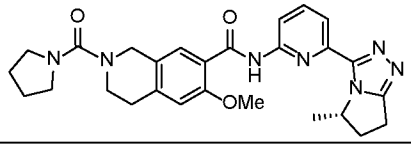
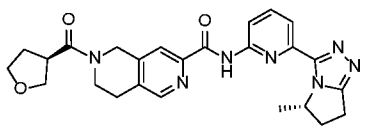
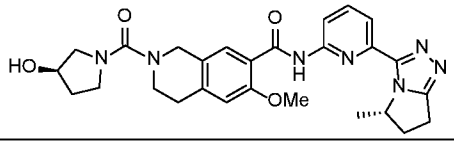
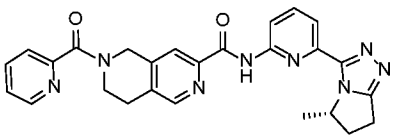
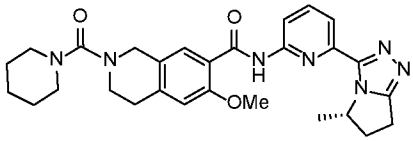
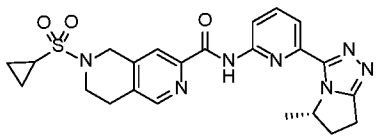
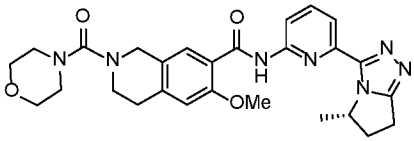
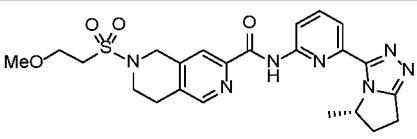
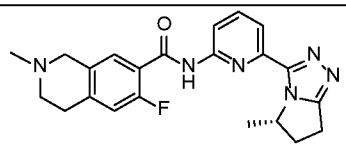
(VIII),

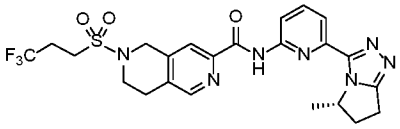
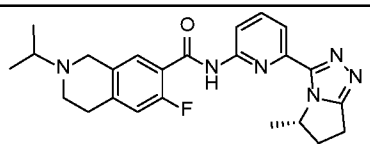
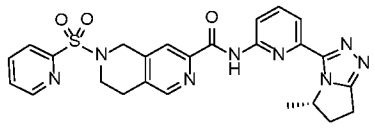
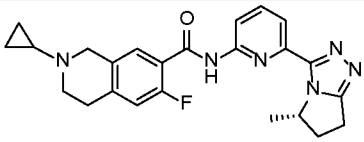
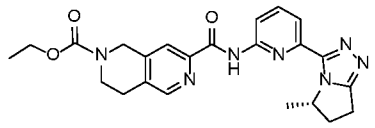
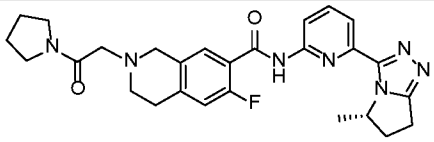
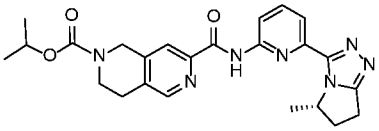
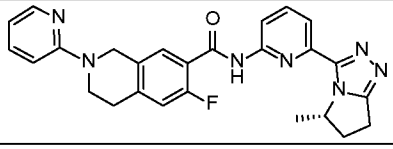
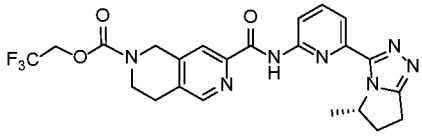
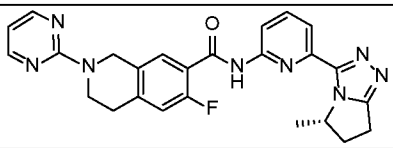
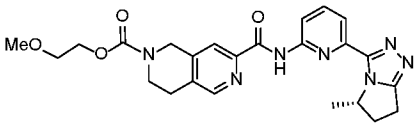
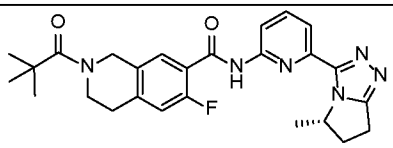
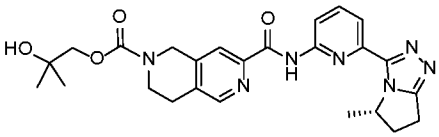
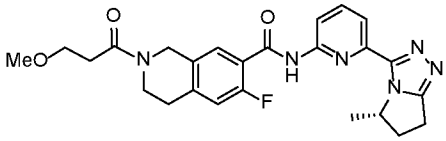
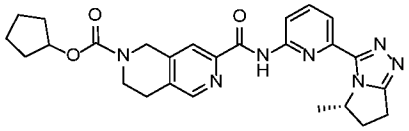
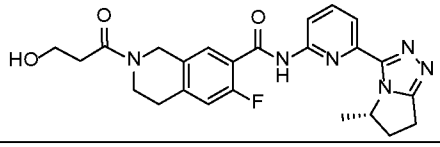
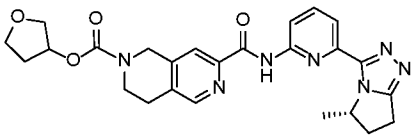
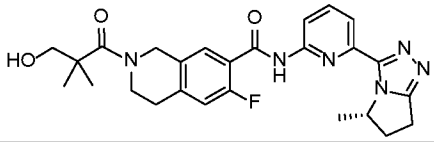
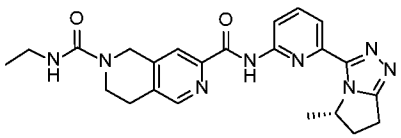
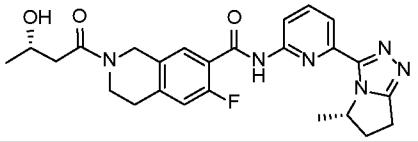
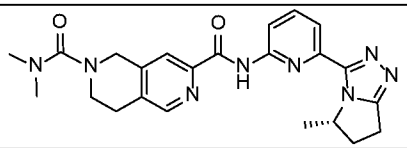
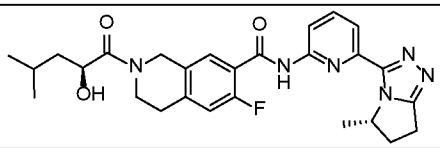
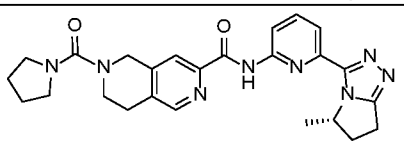
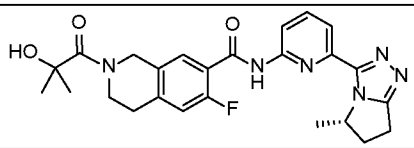
wherein R^3, X^3, and n are as previously defined.

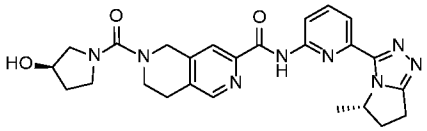
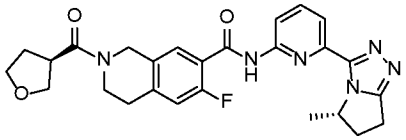
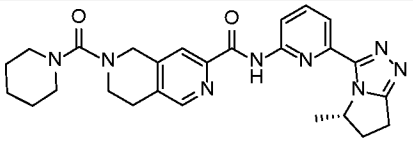
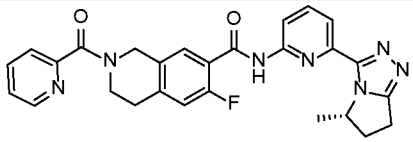
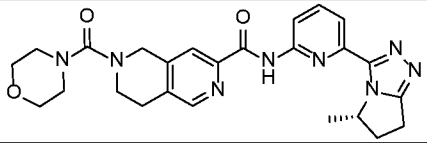
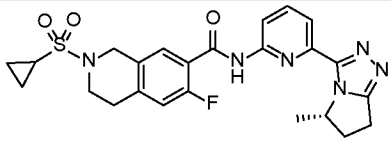
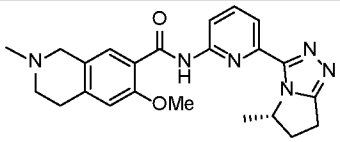
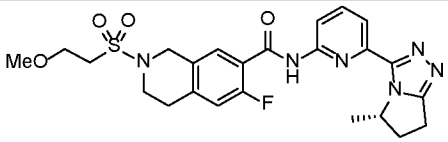
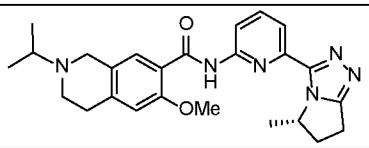
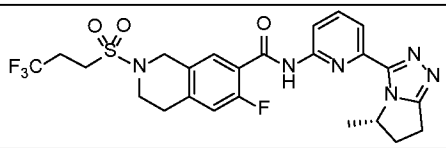
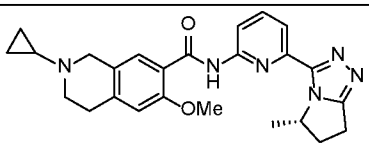
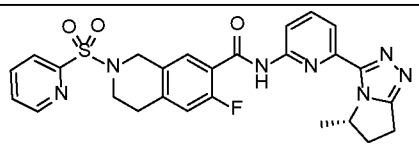
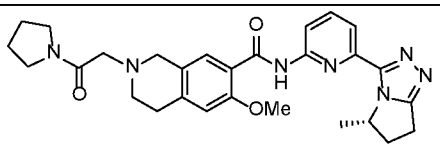
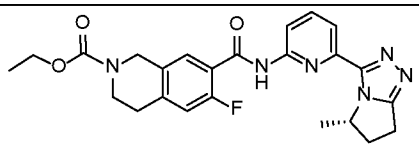
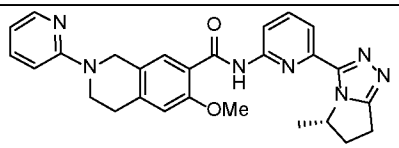
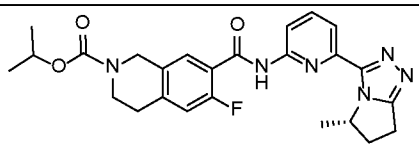
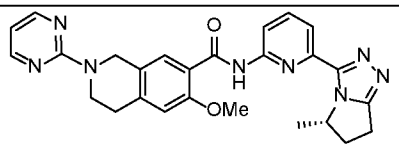
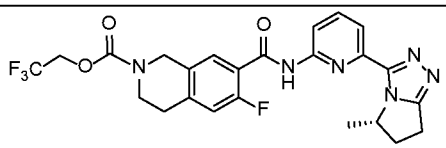
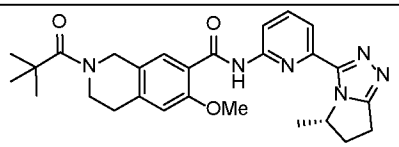
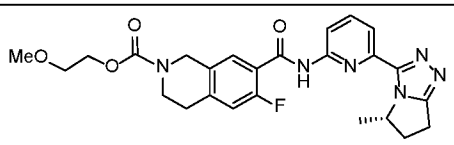
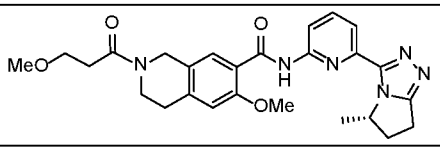
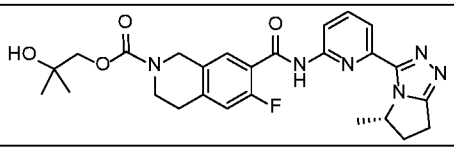
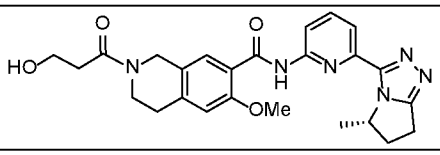
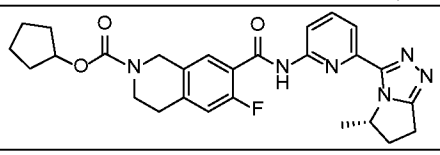
Representative compounds of the invention include, but are not limited to, the following compounds (compound 193 to compound 288 in Table 3) and pharmaceutically acceptable salts thereof.

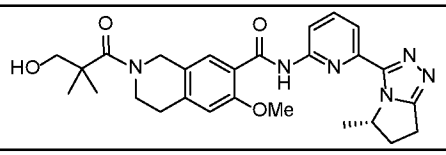
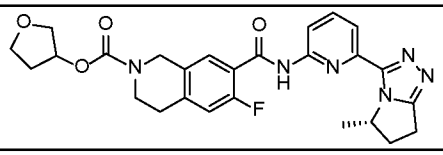
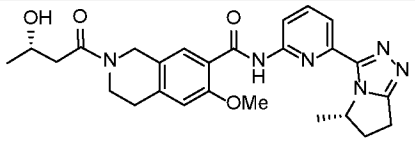
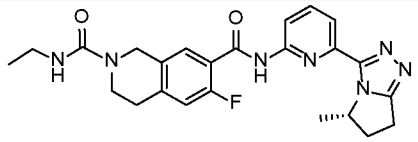
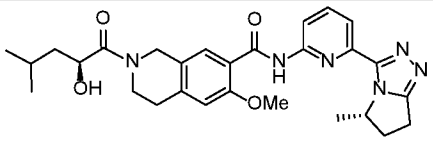
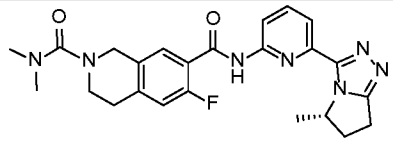
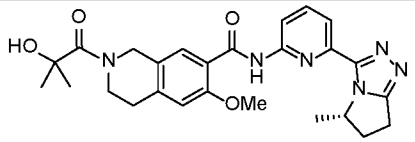
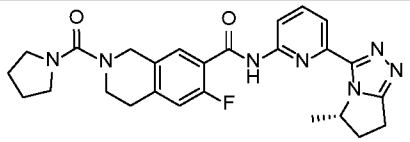
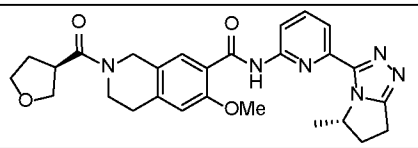
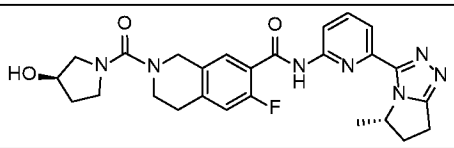
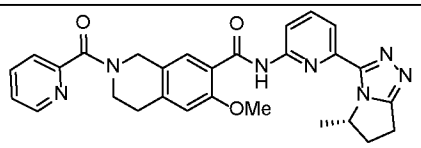
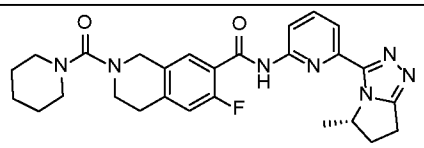
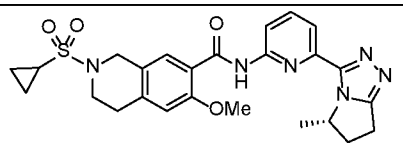
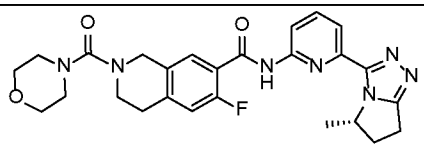
Table 3

Compound	Structure	Compound	Structure
193		241	
194		242	
195		243	
196		244	
197		245	

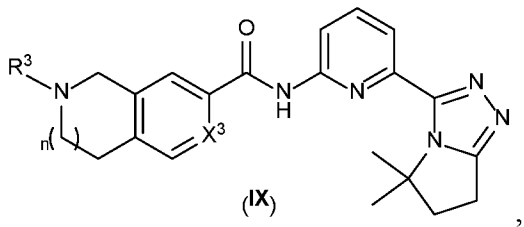
198		246	
199		247	
200		248	
201		249	
202		250	
203		251	
204		252	
205		253	
206		254	
207		255	
208		256	
209		257	

210		258	
211		259	
212		260	
213		261	
214		262	
215		263	
216		264	
217		265	
218		266	
219		267	
220		268	
221		269	

222		270	
223		271	
224		272	
225		273	
226		274	
227		275	
228		276	
229		277	
230		278	
231		279	
232		280	
233		281	

234		282	
235		283	
236		284	
237		285	
238		286	
239		287	
240		288	

In certain embodiments, the compound of Formula I is represented by Formula IX or a pharmaceutically acceptable salt or ester thereof:

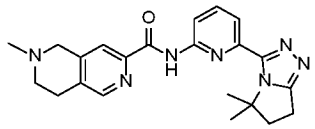
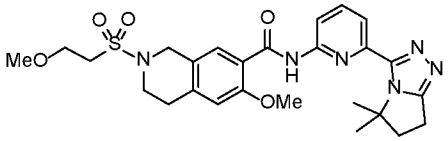
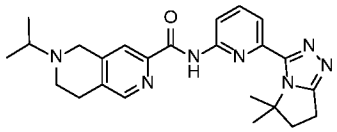
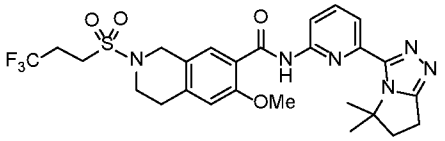
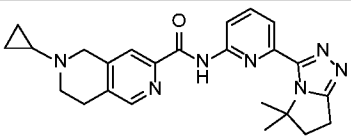
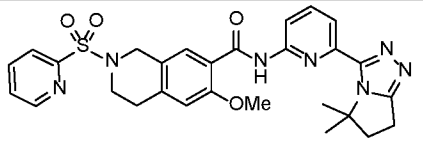
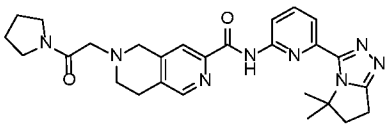
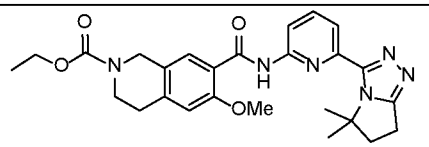
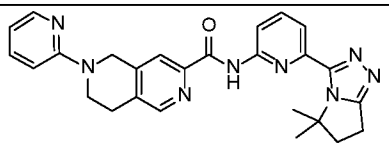
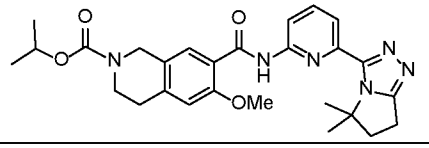
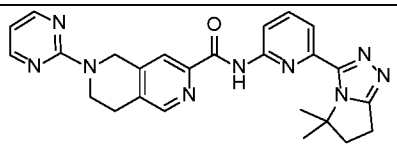
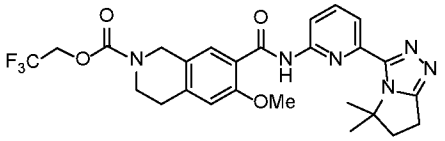
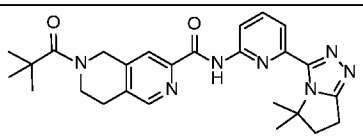
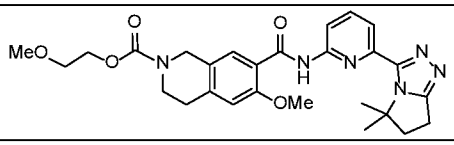
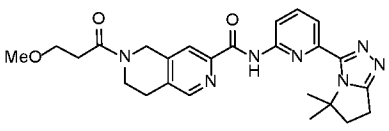
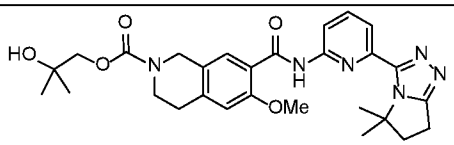
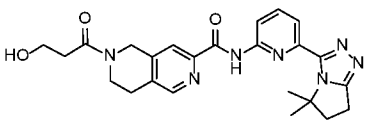
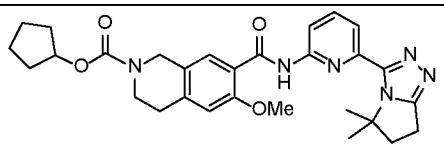
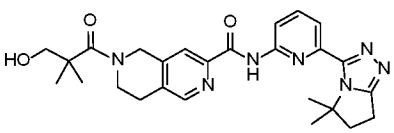
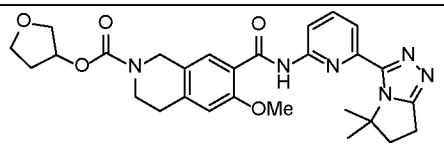
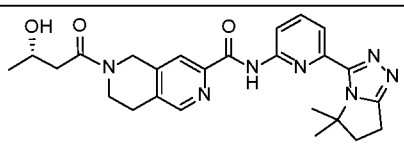
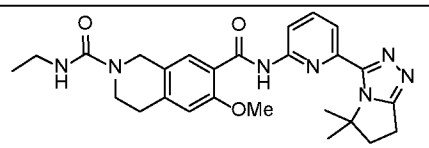
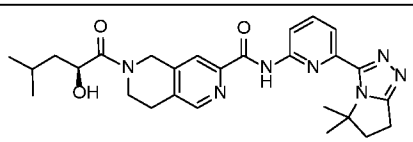
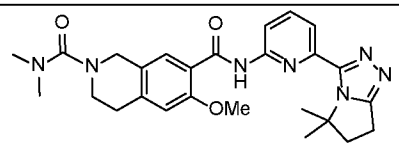


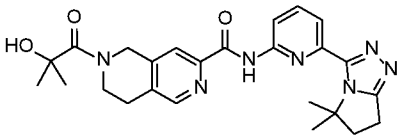
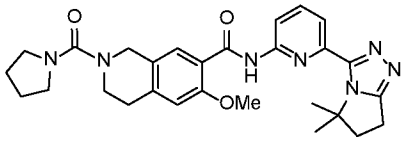
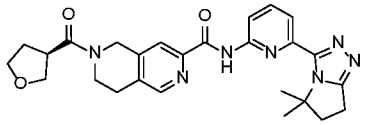
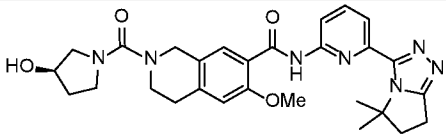
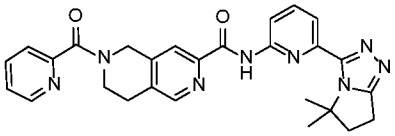
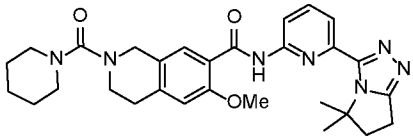
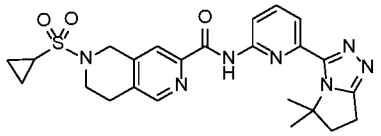
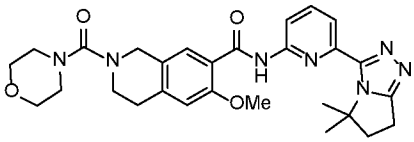
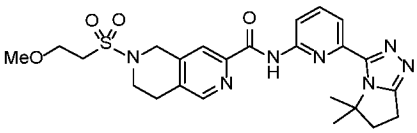
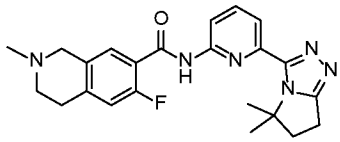
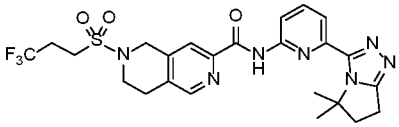
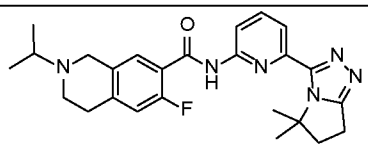
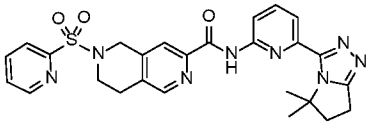
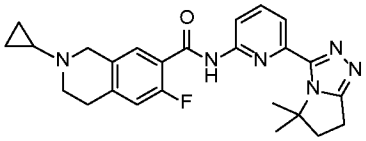
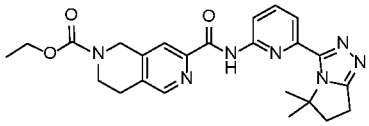
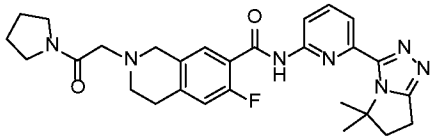
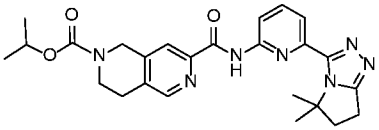
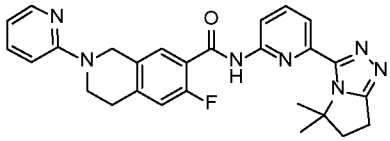
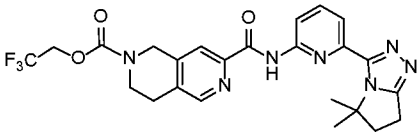
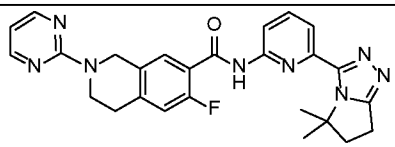
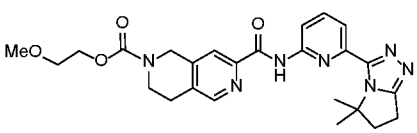
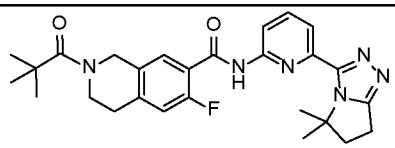
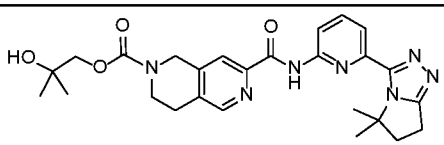
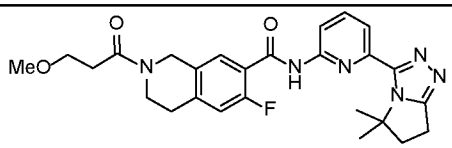
(IX)

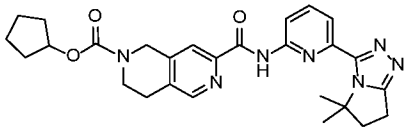
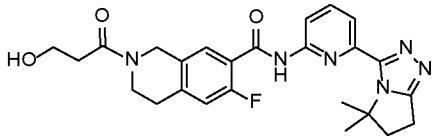
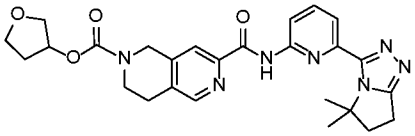
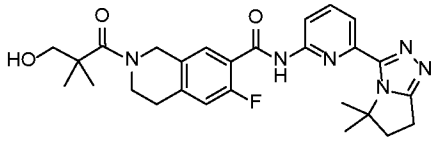
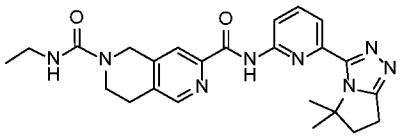
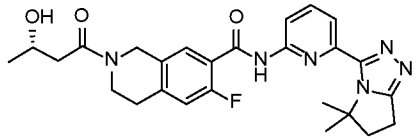
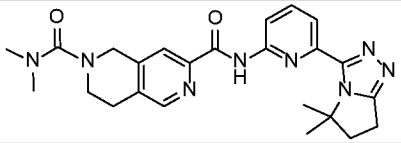
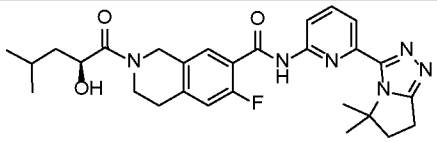
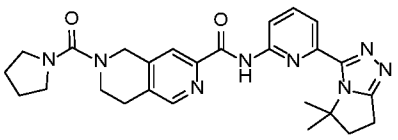
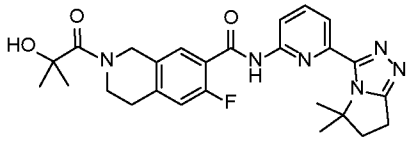
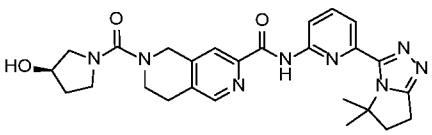
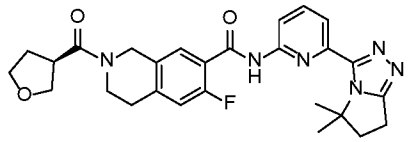
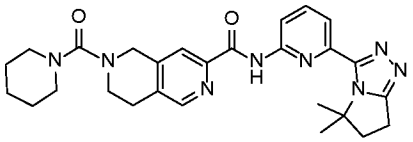
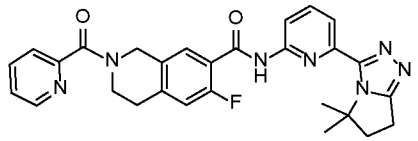
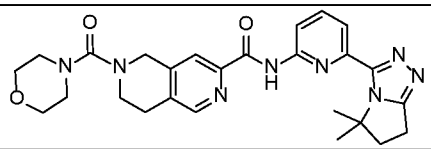
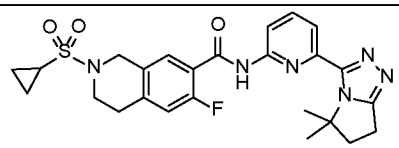
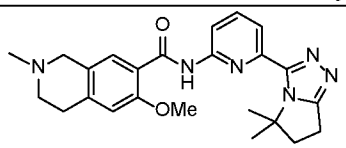
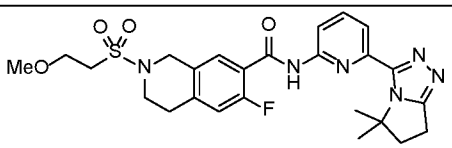
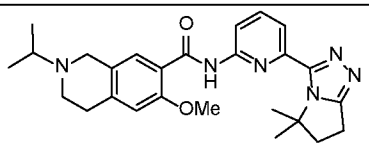
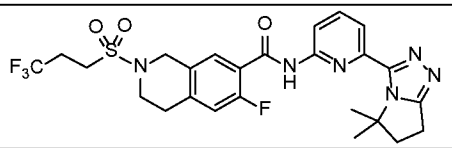
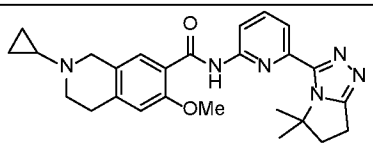
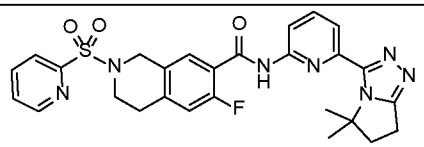
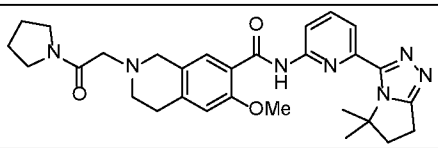
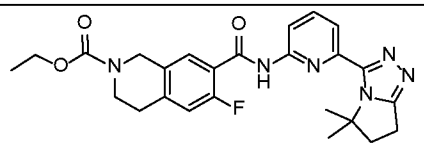
wherein R^3, X^3, and n are as previously defined.

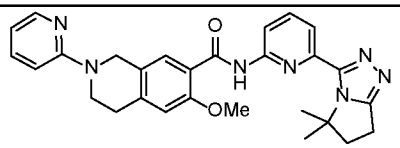
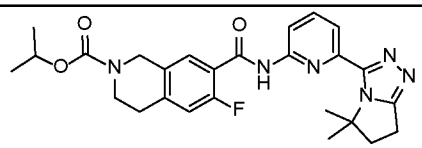
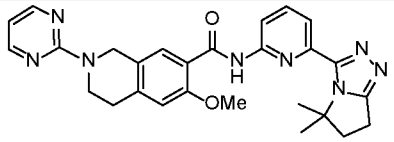
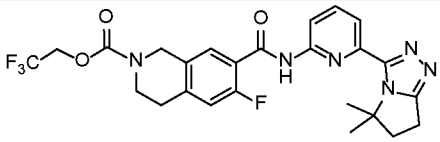
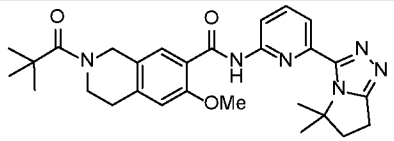
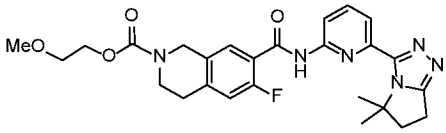
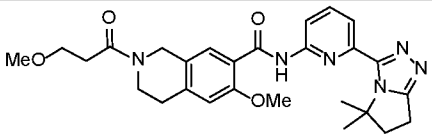
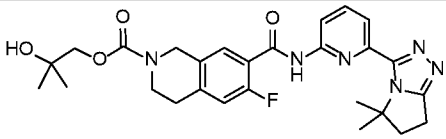
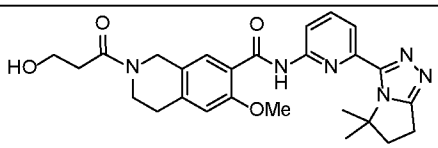
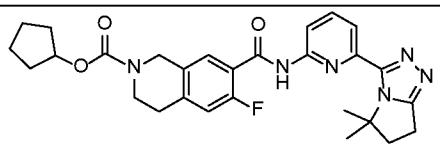
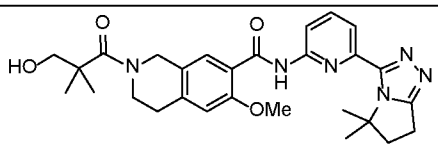
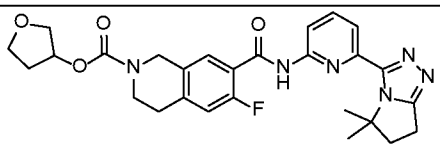
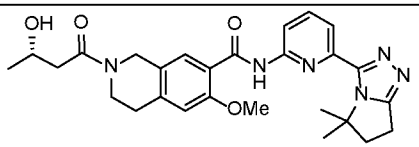
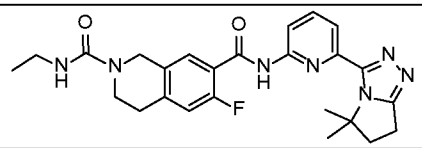
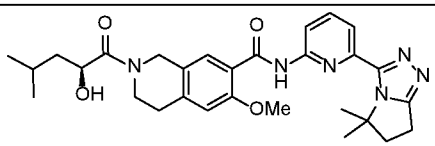
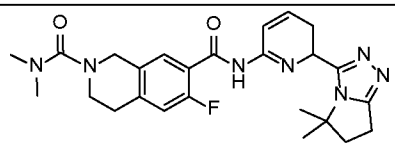
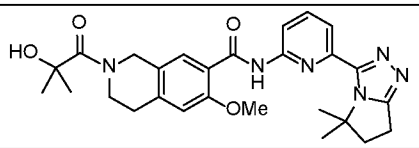
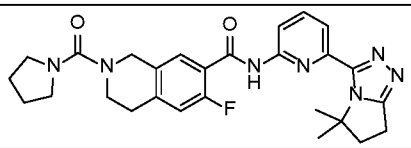
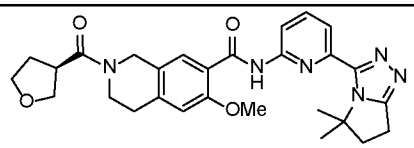
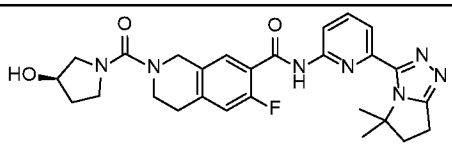
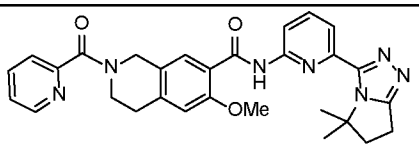
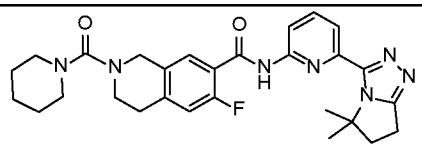
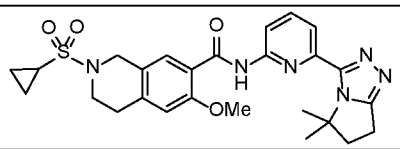
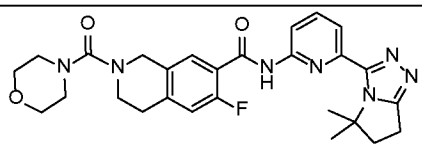
Representative compounds of the invention include, but are not limited to, the following compounds (compound 289 to compound 384 in Table 4), and pharmaceutically acceptable salts thereof.

Table 4

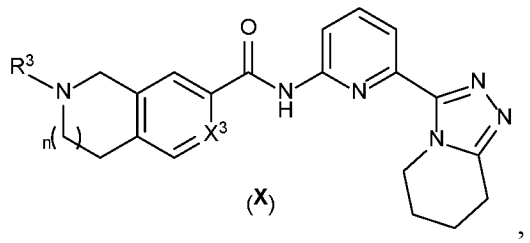
Compound	Structure	Compound	Structure
289		337	
290		338	
291		339	
292		340	
293		341	
294		342	
295		343	
296		344	
297		345	
298		346	
299		347	
300		348	

301		349	
302		350	
303		351	
304		352	
305		353	
306		354	
307		355	
308		356	
309		357	
310		358	
311		359	
312		360	

313		361	
314		362	
315		363	
316		364	
317		365	
318		366	
319		367	
320		368	
321		369	
322		370	
323		371	
324		372	

325		373	
326		374	
327		375	
328		376	
329		377	
330		378	
331		379	
332		380	
333		381	
334		382	
335		383	
336		384	

In certain embodiments, the compound of Formula I is represented by Formula X or a pharmaceutically acceptable salt or ester thereof:



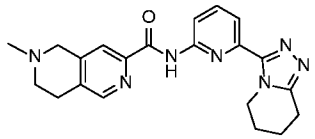
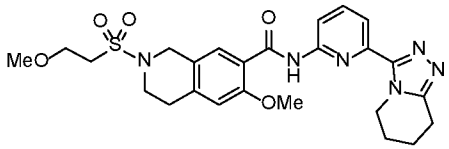
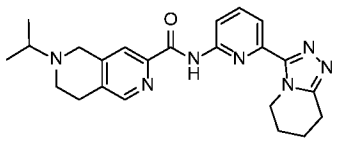
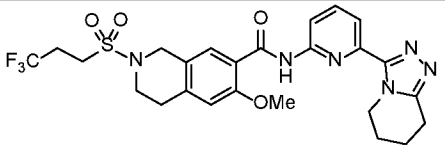
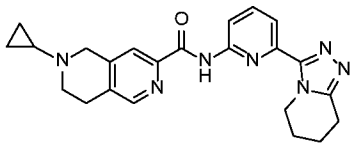
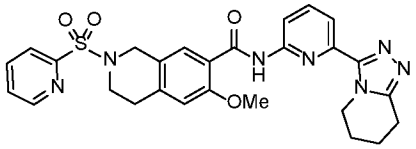
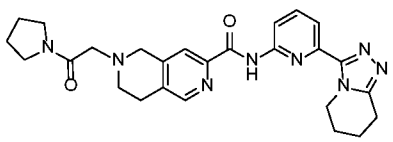
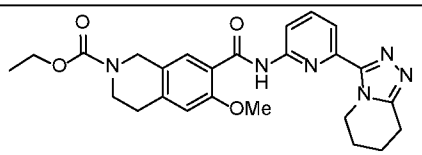
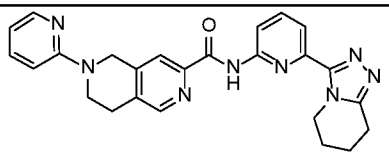
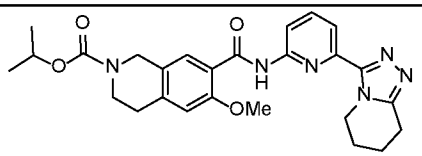
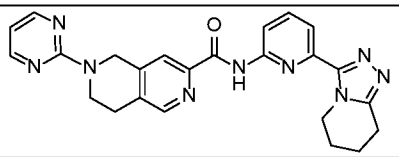
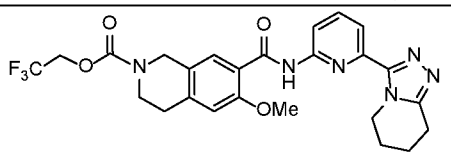
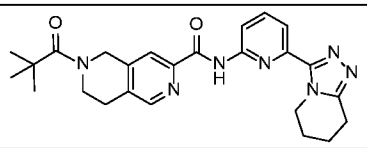
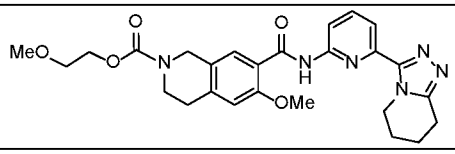
(X)

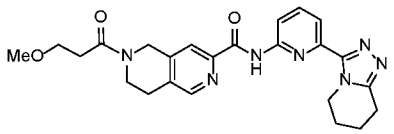
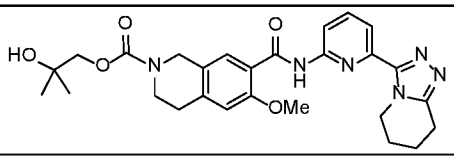
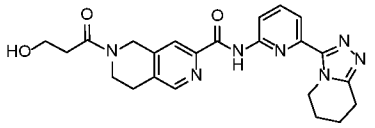
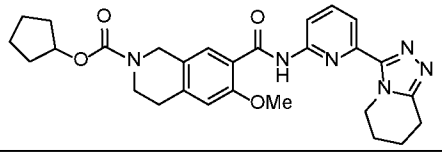
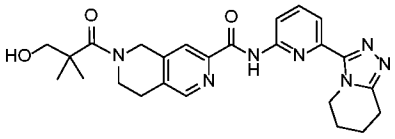
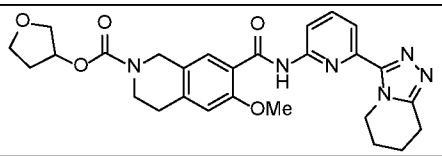
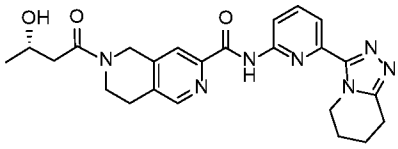
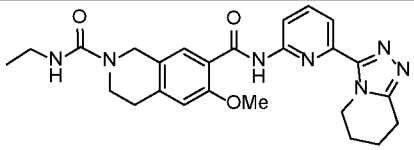
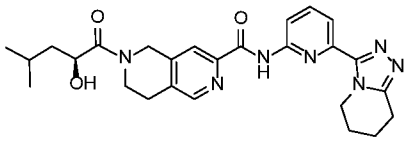
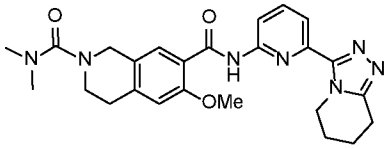
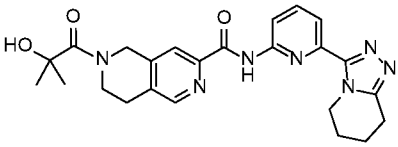
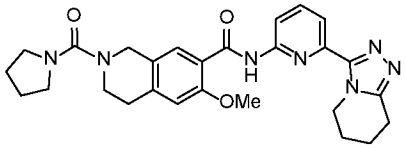
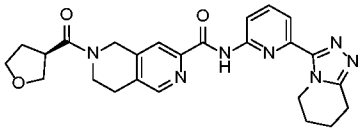
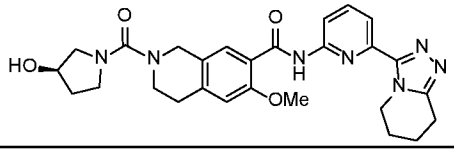
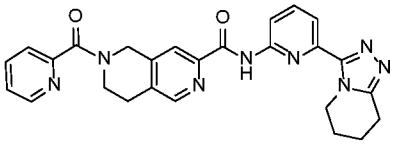
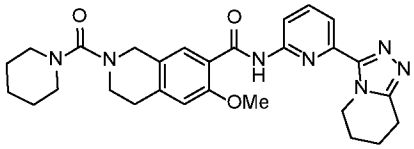
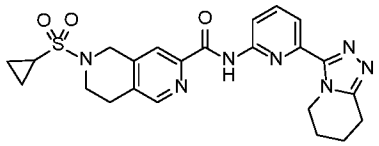
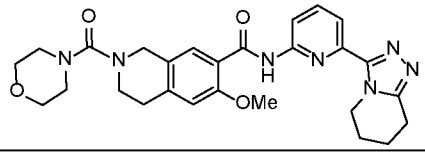
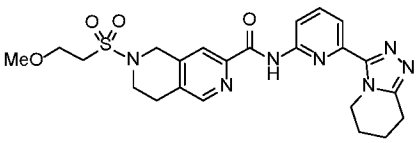
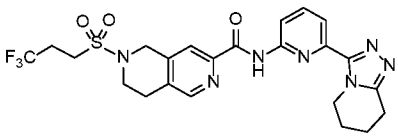
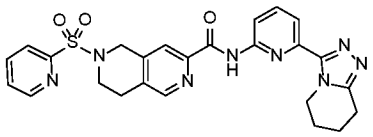
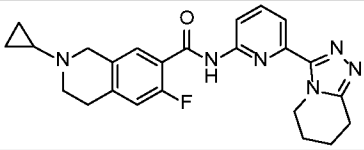
,

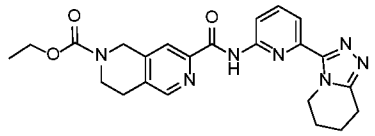
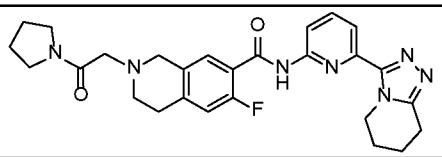
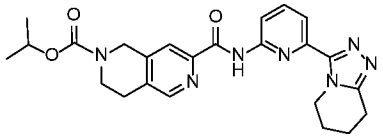
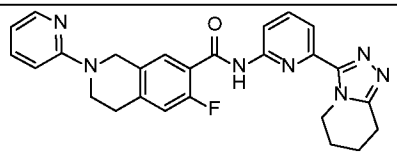
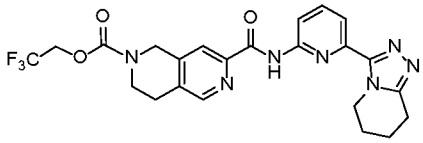
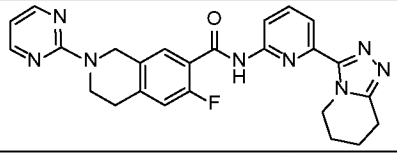
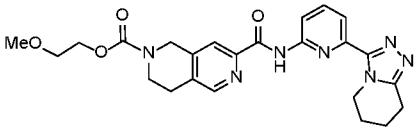
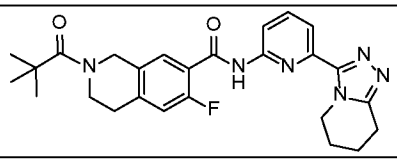
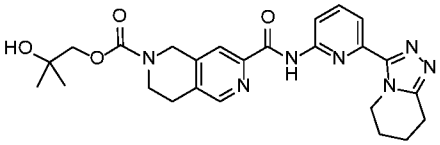
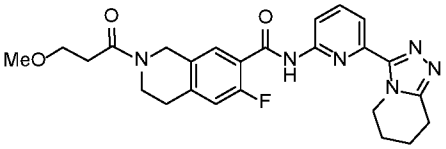
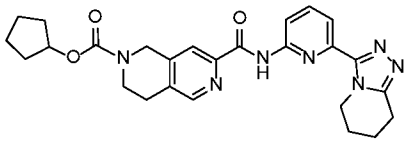
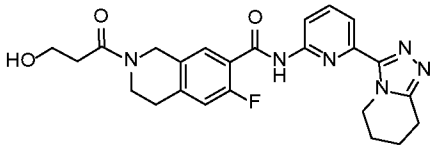
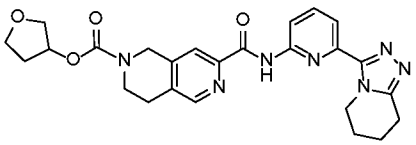
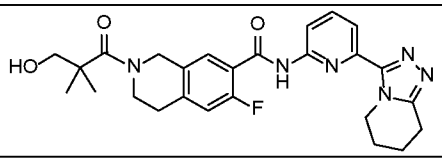
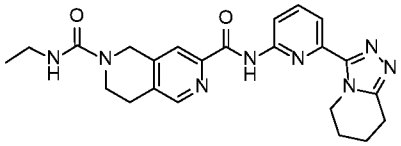
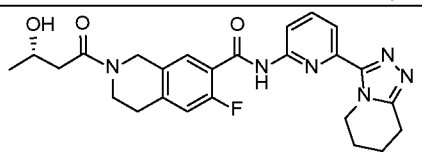
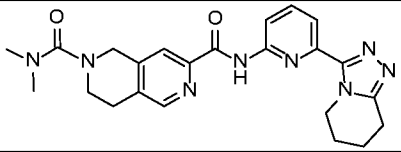
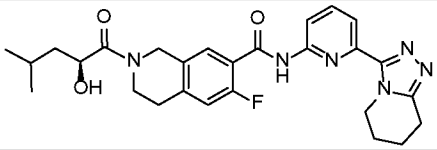
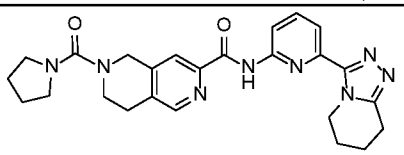
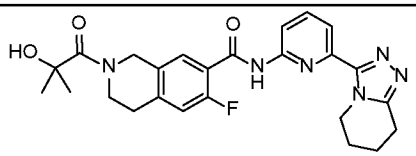
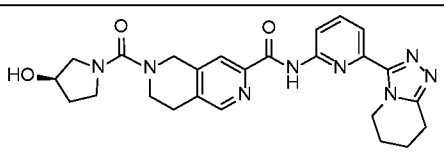
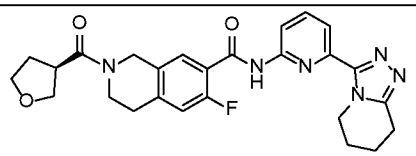
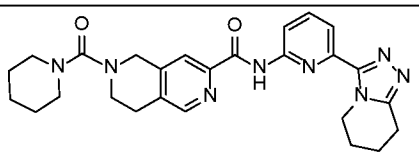
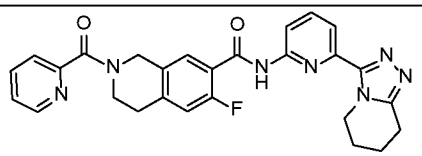
wherein R^3, X^3, and n are as previously defined.

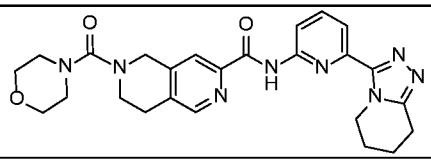
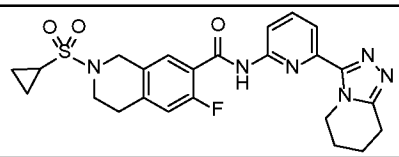
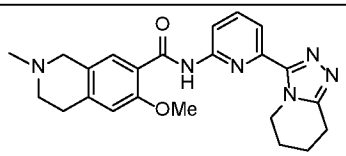
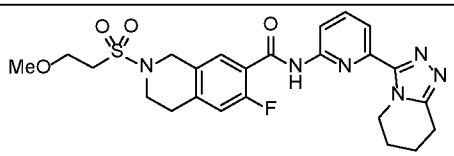
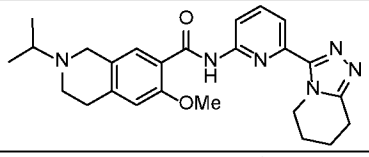
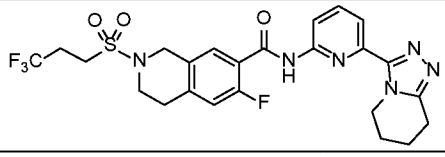
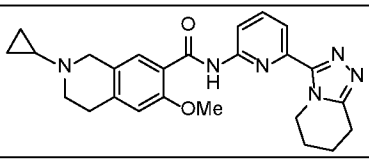
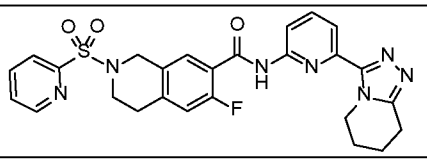
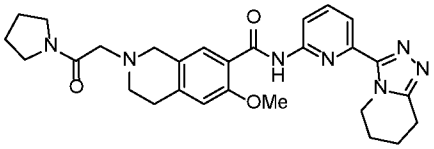
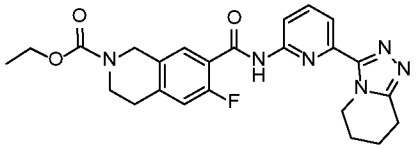
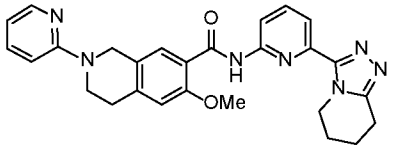
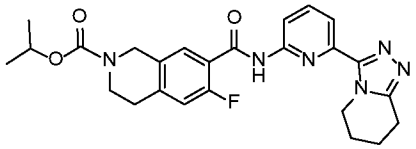
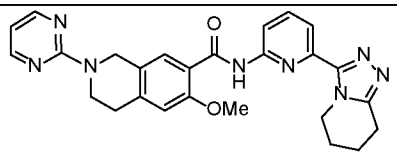
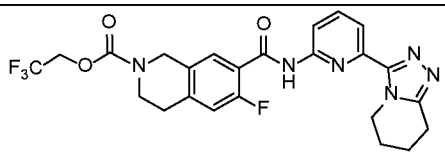
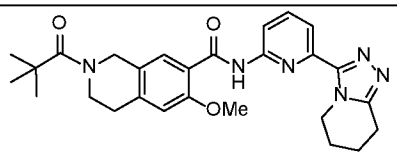
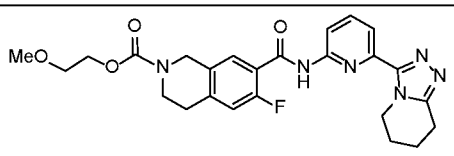
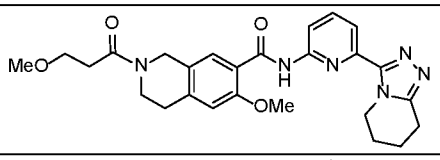
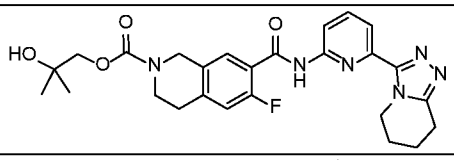
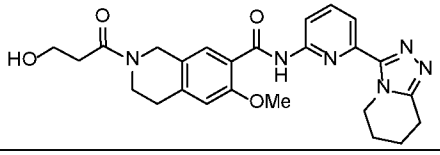
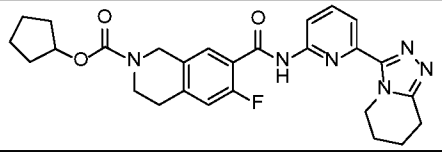
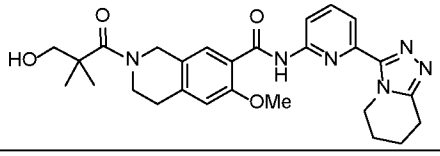
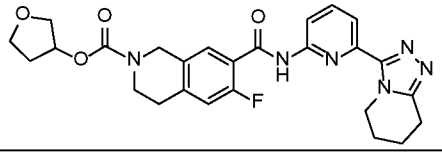
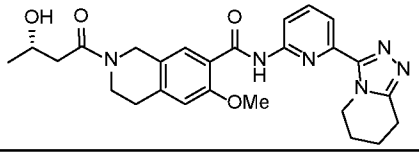
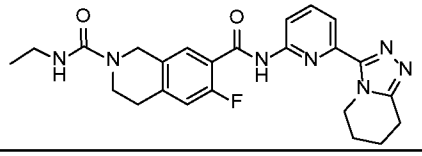
Representative compounds of the invention include, but are not limited to, the following compounds (compound 385 to compound 480 in Table 5) and pharmaceutically acceptable salts thereof.

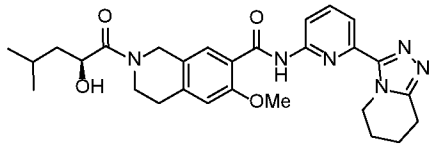
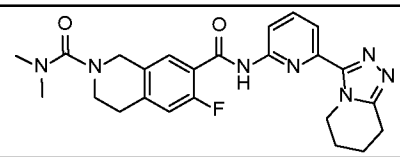
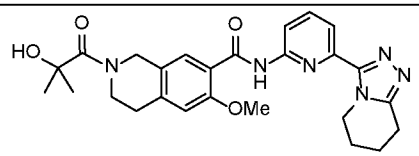
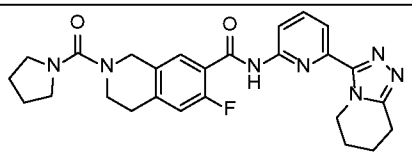
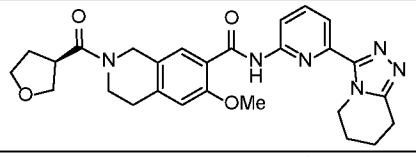
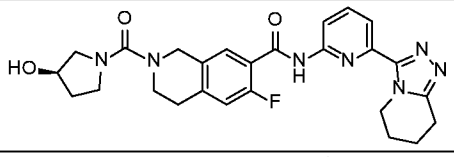
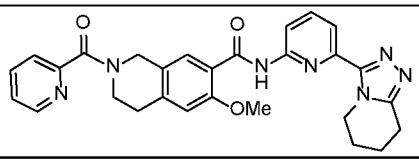
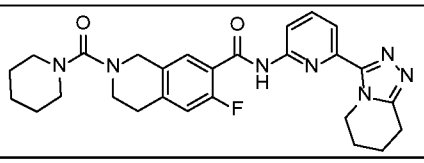
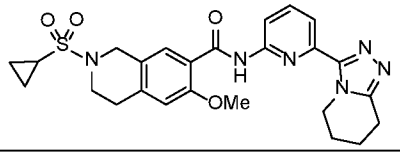
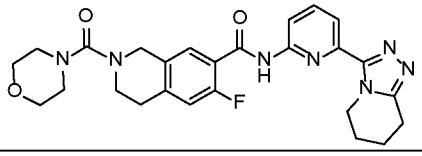
Table 5

Compound	Structure	Compound	Structure
385		433	
386		434	
387		435	
388		436	
389		437	
390		438	
391		439	

392		440	
393		441	
394		442	
395		443	
396		444	
397		445	
398		446	
399		447	
400		448	
401		449	
402		450	
403		451	

404		452	
405		453	
406		454	
407		455	
408		456	
409		457	
410		458	
411		459	
412		460	
413		461	
414		462	
415		463	

416		464	
417		465	
418		466	
419		467	
420		468	
421		469	
422		470	
423		471	
424		472	
425		473	
426		474	
427		475	

428		476	
429		477	
430		478	
431		479	
432		480	

In certain embodiments, the present invention provides a method for the 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 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, reperfusion/ischemia in stroke, cardiac hypertrophy, respiratory diseases, heart attacks, myocardial ischemia.

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

In certain embodiments, the chronic kidney disease is polycystic kidney disease, pyelonephritis, kidney fibrosis and glomerulonephritis.

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, -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. 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_6-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 refer to a non-aromatic ring or a bi- or tri-cyclic group fused, bridged or spiro system, where (i) the ring system contains at least one heteroatom independently selected from oxygen, sulfur and nitrogen, (ii) the 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.

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 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 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:

AcOH for acetic acid;

AIBN for azobisisobutyronitrile;

ASK1 for apoptosis signal-regulating kinase 1;

ATP for adenosine triphosphate;

Boc for *tert*-butyloxycarbonyl;

Boc_2O for di-tert-butyl dicarbonate;

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

Cbz for benzyloxycarbonyl;

Cbz-Cl for benzyl chloroformate;

CDI for carbonyldiimidazole;

DCC for *N,N'*-dicyclohexylcarbodiimide;

1,2-DCE for 1,2-dichloroethane;

DCM for dichloromethane;

DIPEA or Hunig's base or *i*-Pr_2NEt for *N,N*-diisopropylethylamine;

DMA for *N,N*-dimethylacetamide;

DMAP for *N,N*-dimethylaminopyridine;

DMF for *N,N*-dimethyl formamide;

dppp for 1,3-bis(diphenylphosphino)propane;

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

EGTA for ethylene glycol-bis(2-aminoethylether)-*N,N,N',N'*-tetraacetic acid;

ESI for electrospray ionization;

Et_3N or TEA for triethylamine;

EtOAc for ethyl acetate;

Ghosez's Reagent for 1-chloro-*N,N*,2-trimethyl-1-propenylamine;

h, hr, or hrs for hours;

HATU for 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate;

HEPES for 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid, N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid);

IC_{50} for half maximal inhibitory concentration;

KO*t*-Bu for potassium *tert*-butoxide;

LC-MS for liquid chromatography-mass spectrometry;

MeCN or ACN for acetonitrile;

min or mins for minutes;

MTBE or TBME for methyl *tert*-butyl ether;

m/z for mass-to-charge ratio;

NaO*t*-Bu for sodium *tert*-butoxide;

NMP for 1-methyl-2-pyrrolidinone;

NMR for nuclear magnetic resonance spectroscopy;
Pd/C for palladium on carbon;
PhMe or tol for toluene;
-OTBS for tert-butyldimethylsiloxy;
-OTf or triflate for trifluoromethanesulfonate;
PyAOP for 7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate;
PyBOP for benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate;
rt for room temperature;
STK3 for serine/threonine-protein kinase 3;
Tf_2O for trifluoromethanesulfonic anhydride;
TFA for trifluoroacetic acid;
THF for tetrahydrofuran;
TR-FRET for time-resolved fluorescence energy transfer.

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, compounds of Formula (**Ie**) are prepared from the compound of Formula (1-1) wherein X^3 and n are as previously defined. X^4 is Br, Cl, I, or OTf. Thus, the compound of Formula (1-1) is reacted with a suitable N-functionalizing reagent to afford a compound of Formula (1-2), wherein R^{15} is a suitable nitrogen protecting group, such as, but not limited to Boc or Cbz. If R^{15} is Cbz, a compound of Formula (1-1) is reacted with Cbz-Cl to afford a compound of Formula (1-2) using a suitable base such as, but not limited to, Et_3N, DIPEA, DMAP, or pyridine. The reaction solvent can be, but is not limited to, THF or DCM. The reaction temperature is from -20°C to 40 °C. If R^{15} is Boc, a compound of Formula (1-1) is reacted with Boc_2O to afford a compound of Formula (1-2) using a suitable

base such as, but not limited to, Et_3N, DIPEA, DMAP, or pyridine. The reaction solvent can be, but is not limited to, THF or DCM. The reaction temperature is from -20 °C to 40 °C. The compound of Formula (1-2) is converted to a compound of Formula (1-3), wherein R^{14} is an alkyl group, such as, but not limited to, methyl, ethyl, propyl, tert-butyl, and isopropyl. Thus, the compound of Formula (1-2) is reacted with a suitable metallating reagent, such as, but not limited to, isopropylmagnesium chloride, followed by reacting the resultant intermediate with carbon dioxide to afford a compound of Formula (1-3). The reaction solvent can be, but is not limited to, THF. The reaction temperature is from -80 °C to 25 °C. Alternatively, the compound of Formula (1-2) is reacted with a suitable palladium catalyst, a suitable ligand, a suitable base, a suitable alcohol, and carbon monoxide to afford a compound of Formula (1-3). The palladium catalyst can be, but is not limited to, palladium(II) acetate, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), or tetrakis(triphenylphosphine) palladium(0). The ligand, can be, but is not limited to, 1,3-bis(diphenylphosphino)propane, or 1,4-bis(diphenylphosphino)butane. The base can be, but is not limited to, Et_3N, DIPEA, K_2CO_3, Na_2CO_3, or Cs_2CO_3. The alcohol can be, but is not limited to, methanol, ethanol, 2-propanol, n-propanol, or tert-butanol. The reaction solvent can be, but is not limited to, DMF, NMP, or DMA. The reaction temperature is from 25 °C to 150 °C. The compound of Formula (1-3) is hydrolyzed to afford a compound of Formula (1-4) using a suitable hydroxide source such as, but not limited to, NaOH or LiOH. Alternatively, if R^{14} is tert-butyl, then the compound of Formula (1-3) is reacted with a suitable acid to afford a compound of Formula (1-4). The acid can be, but is not limited to, hydrochloric acid or TFA. The compound of Formula (1-4) is reacted with a suitable chlorinating reagent such as, but not limited to, oxalyl chloride in combination with a catalytic quantity of DMF, thionyl chloride, or Ghosez's reagent to afford a compound of Formula (1-5). The reaction solvent can be, but is not limited to, THF or DCM. The reaction temperature is from -20 °C to 40 °C. The compound of Formula (1-5) is reacted with a compound of Formula (1-6), wherein X^1, X^2, R^1 and R^2 are as previously defined, to afford a compound of Formula (1-6) using a suitable base such as, but not limited to, Et_3N, DMAP, pyridine, or DIPEA. The reaction solvent can be, but is not limited to, THF, DCM, pyridine and toluene. The reaction temperature is from -20 °C to 40 °C. Alternatively, the compound of Formula (1-4) is reacted with a compound of Formula (1-6) to afford a compound of Formula (1-7) using a suitable coupling reagent such as, but not limited to, BOP-Cl, CDI, DCC, EDC, HATU, PyAOP or PyBOP in the presence of a suitable base such as, but not limited to, Et_3N or DIPEA. The reaction solvent can be, but is

not limited to, THF, DCM and DMF. The reaction temperature is from -20 °C to 40 °C. Alternatively, the compound of Formula (1-3) is reacted with a compound of Formula (1-6) in the presence of trimethylaluminum to afford a compound of Formula (1-7). The reaction solvent can be, but is not limited to, DCM or PhMe. The reaction temperature is from 0 °C to 100 °C. Alternatively, the compound of Formula (1-2) can be reacted with a compound of Formula (1-6) and carbon monoxide in the presence of a suitable palladium catalyst, a suitable ligand and a suitable base to afford a compound of Formula (1-7). The palladium catalyst can be, but is not limited to, palladium(II) acetate, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), or tetrakis(triphenylphosphine) palladium(0). The ligand, can be, but is not limited to, 1,3-bis(diphenylphosphino)propane, or 1,4-bis(diphenylphosphino)butane. The base can be, but is not limited to, Et_3N, DIPEA, K_2CO_3, Na_2CO_3, or Cs_2CO_3. The reaction solvent can be, but is not limited to, DMF, NMP, or DMA. The reaction temperature is from 25 °C to 150 °C. If R^{15} is Cbz, the compound of Formula (1-7) is reacted with palladium on carbon in the presence of hydrogen gas to afford a compound of Formula (1-8). The reaction solvent can be, but is not limited to, MeOH, EtOH, EtOAc, and THF. If R^{15} is Boc, the compound of Formula (1-7) is reacted with a suitable acid, such as, but not limited to, hydrochloric acid or TFA to afford a compound of Formula (1-8). The reaction solvent can be, but is not limited to, MeOH, EtOH, EtOAc, THF, and 1,4-dioxane. Compounds of Formula (1-8) are reacted with a suitable combination of reagents to afford compounds of Formula (**Ie**). The reagent combinations may be, but are not limited to:

1) An aldehyde in combination with a suitable reducing agent, such as, but not limited to, $NaBH_4$, $NaBH(OAc)_3$, or $NaBH_3CN$. The reaction solvent can be, but is not limited to, DCM, 1,2-DCE, or THF.
2) A ketone in combination with a suitable reducing agent, such as, but not limited to, $NaBH_4$, $NaBH(OAc)_3$, or $NaBH_3CN$. The reaction solvent can be, but is not limited to, DCM, 1,2-DCE, or THF.
3) An alkyl halide, alkyl mesylate, or alkyl tosylate in combination with a suitable base such as, but not limited to, NaH, NaO*t*-Bu, KO*t*-Bu, Et_3N, or DIPEA. The reaction solvent can be, but is not limited to, DCM or THF.
4) An aryl-, heteroaryl-, or alkenyl-halide, or an aryl- or heteroaryl-, or alkenyl-triflate in combination with a suitable base, palladium(0) catalyst, ligand, and solvent. The base can be, but is not limited to, NaO*t*-Bu or KO*t*-Bu. The palladium(0) catalyst can be, but is not limited to, $Pd(PPh_3)_4$ or $Pd_2(dba)_3$. The ligand can be, but is not limited to,

P(*o*-tolyl)$_3$ or (2-biphenyl)di-*tert*-butylphosphine. The solvent can be, but is not limited to, toluene or THF.

5) An acyl chloride in the presence of a suitable base such as, but not limited to, Et_3N, DIPEA, or DMAP. The reaction solvent can be, but is not limited to, DCM or THF.

6) A chloroformate in the presence of a suitable base such as, but not limited to, Et_3N, DIPEA, or DMAP. The reaction solvent can be, but is not limited to, DCM or THF.

7) A sulfonyl chloride in the presence of a suitable base such as, but not limited to, Et_3N, DIPEA, or DMAP. The reaction solvent can be, but is not limited to, DCM or THF.

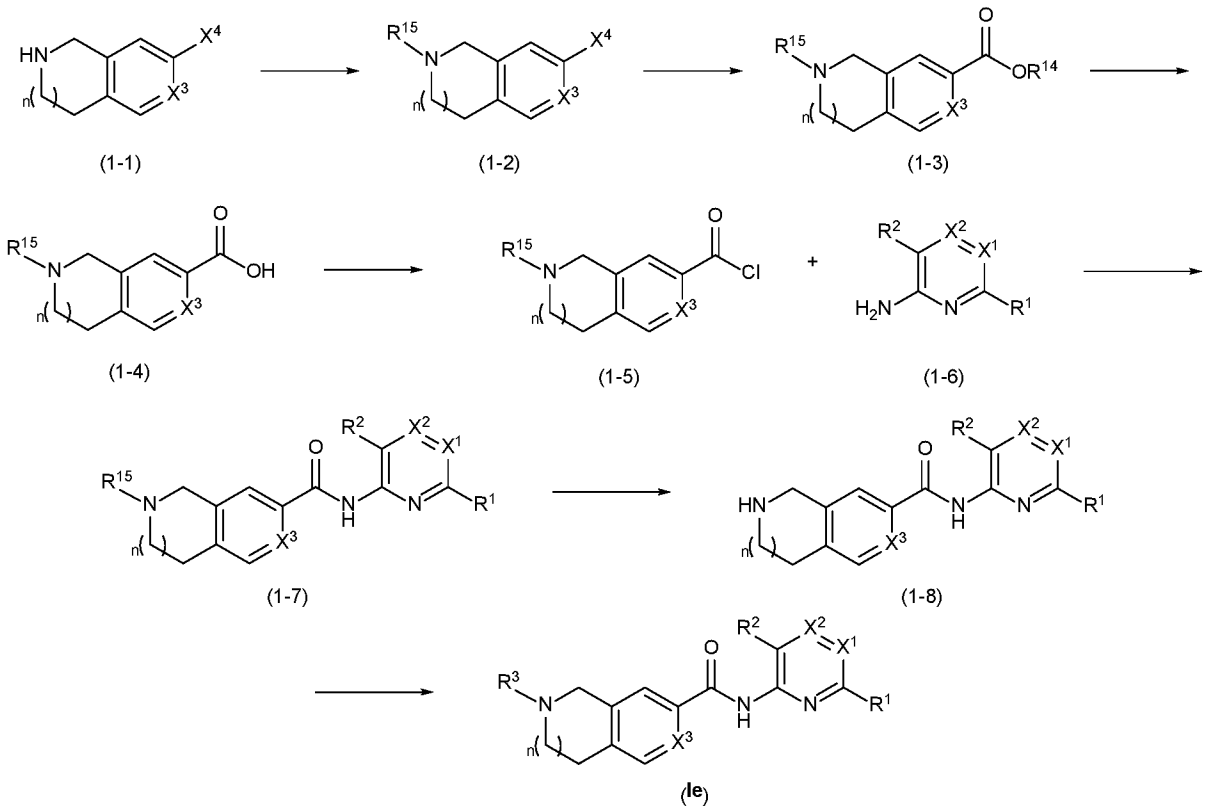
8) An isocyanate in the presence of a suitable base such as, but not limited to, Et_3N, DIPEA, or DMAP. The reaction solvent can be, but is not limited to, DCM or THF.

9) A primary or secondary amine in the presence of a suitable activating reagent such as, but not limited to, phosgene, triphosgene, or CDI. The reaction solvent can be, but is not limited to, DCM or THF.

10) A carboxylic acid in the presence of a suitable coupling reagent, and base. The coupling reagent can be, but is not limited to, BOP-Cl, CDI, DCC, EDC, HATU, PyAOP or PyBOP. The base can be, but is not limited to, Et_3N, DIPEA, or pyridine.

11) An aryl or heteroaryl halide in the presence of a suitable base, such as, but not limited to, Cs_2CO_3, K_2CO_3, Et_3N, DBU, DIPEA, or pyridine. The reaction solvent can be, but is not limited to, DCM, THF, DMF, or NMP.

Scheme 1



As shown in Scheme 2, compounds of Formula (**Ie**) are prepared from the compound of Formula (1-1) wherein X^3 and n are as previously defined. X^4 is Br, Cl, I, or OTf. Thus, the compound of Formula (1-1) is reacted with a suitable N-functionalizing reagent to afford a compound of Formula (1-2), wherein R^{15} is a suitable nitrogen protecting group, such as, but not limited to Boc or Cbz. If R^{15} is Cbz, a compound of Formula (1-1) is reacted with Cbz-Cl to afford a compound of Formula (1-2) using a suitable base such as, but not limited to, Et_3N, DIPEA, DMAP, or pyridine. The reaction solvent can be, but is not limited to, THF or DCM. The reaction temperature is from -20°C to 40 °C. If R^{15} is Boc, a compound of Formula (1-1) is reacted with Boc_2O to afford a compound of Formula (1-2) using a suitable base such as, but not limited to, Et_3N, DIPEA, DMAP, or pyridine. The reaction solvent can be, but is not limited to, THF or DCM. The reaction temperature is from -20 °C to 40 °C. The compound of Formula (1-2) is converted to a compound of Formula (2-1), wherein R^{16}, R^{17}, and R^{18} are hydrogen, substituted or unsubstituted $-C_1$-C_8 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted $-C_3$-C_8 cycloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted 3- to 8- membered heterocycloalkyl, substituted or unsubstituted heteroarylalkyl, or R^{16} and R^{17} are taken together to form an optionally substituted cycloalkyl or heterocycloalkyl, or R^{17} and R^{18} are

taken together to form an optionally substituted cycloalkyl or heterocycloalkyl. Thus, the compound of Formula (1-2) is reacted with a suitable boronic ester or boronic acid in the presence of a suitable palladium catalyst, a suitable ligand, and a suitable base to afford a compound of Formula (2-1). The boronic ester or boronic acid can be, but is not limited to, vinylboronic acid pinacol ester or trans-2-(phenyl)vinylboronic acid pinacol ester. The palladium catalyst can be, but is not limited to, palladium(II) acetate, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), or tetrakis(triphenylphosphine) palladium(0). The ligand, can be, but is not limited to, 1,3-bis(diphenylphosphino)propane, PCy_3HBF_4, PCy_3, or PPh_3. The base can be, but is not limited to, Et_3N, DIPEA, K_2CO_3, Na_2CO_3, Cs_2CO_3, or K_3PO_4. The reaction solvent can be, but is not limited to, DMF, NMP, DMA, H_2O, or 1,4-dioxane. The reaction temperature is from 25 °C to 150 °C. Alternatively, the compound of Formula (1-2) is reacted with a suitable organotin reagent in the presence of a suitable palladium catalyst and a suitable ligand to afford a compound of Formula (2-1). The organotin reagent can be, but is not limited to, tributyl(vinyl)tin. The palladium catalyst can be, but is not limited to, tetrakis(triphenylphosphine) palladium(0), palladium(II) acetate, or tris(dibenzylideneacetone)dipalladium(0). The ligand can be, but is not limited to, triphenylphosphine, tri-tert-butylphosphine, tri(ortho-tolyl)phosphine, or 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl. The reaction solvent can be, but is not limited to, THF, 1,4-dioxane, or toluene. The reaction temperature is from 25 °C to 150 °C. The compound of Formula (2-1) is reacted with a suitable oxidant in the presence of a suitable base to afford a compound of Formula (2-2). The oxidant can be, but is not limited to osmium tetroxide, or a combination of osmium tetroxide and sodium periodate. The base can be, but is not limited to, 2,6-lutidine. The reaction solvent can be, but is not limited to, 1,4-dioxane, H_2O or a combination of these. The reaction temperature is from 0 °C to 50 °C. Alternatively, the compound of Formula (2-1) is reacted with ozone followed by a suitable reducing agent to afford a compound of Formula (2-2). The reducing agent can be, but is not limited to, dimethylsulfide or triphenylphosphine. The reaction solvent can be, but is not limited to, methanol or dichloromethane. The reaction temperature is from -80 °C to 25 °C. The compound of Formula (2-2) is reacted with a suitable chlorous acid source in the presence of a suitable hypochlorous acid scavenger and a suitable buffer to afford a compound of Formula (1-4). The chlorous acid source can be, but is not limited to, $NaClO_2$. The hypochlorous acid scavenger can be, but is not limited to, 2-methyl-2-butene. The buffer can be, but is not limited to, NaH_2PO_4. The reaction solvent can be, but is not limited to, THF,

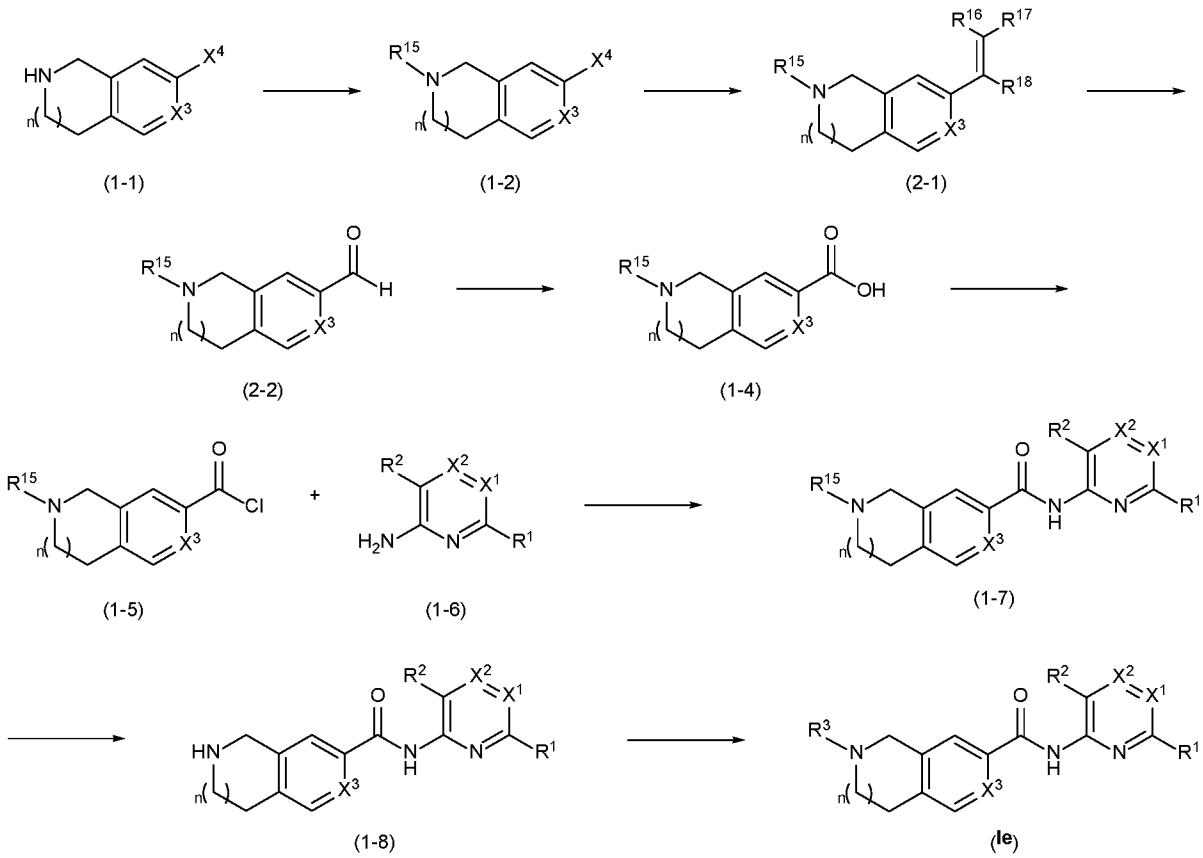
tert-butanol, CH_3CN, H_2O, or a combination of these. The reaction temperature is from 0 °C to 50 °C. Alternatively, the compound of Formula (2-1) is reacted with a catalytic quantity of $RuCl_3$ in the presence of a suitable oxidant to afford a compound of Formula (1-4). The oxidant can be, but is not limited to sodium periodate. The reaction solvent can be, but is not limited to, EtOAc, CCl_4, CH_2Cl_2, CH_3CN, H_2O, or a combination of these. The reaction temperature is from 0 °C to 50 °C. The compound of Formula (1-4) is reacted with a suitable chlorinating reagent such as, but not limited to, oxalyl chloride in combination with a catalytic quantity of DMF, thionyl chloride, or Ghosez's reagent to afford a compound of Formula (1-5). The reaction solvent can be, but is not limited to, THF or DCM. The reaction temperature is from -20 °C to 40 °C. The compound of Formula (1-5) is reacted with a compound of Formula (1-6), wherein X^1, X^2, R^1 and R^2 are as previously defined, to afford a compound of Formula (1-6) using a suitable base such as, but not limited to, Et_3N, DMAP, pyridine, or DIPEA. The reaction solvent can be, but is not limited to, THF, DCM, pyridine and toluene. The reaction temperature is from -20 °C to 40 °C. Alternatively, the compound of Formula (1-4) is reacted with a compound of Formula (1-6) to afford a compound of Formula (1-7) using a suitable coupling reagent such as, but not limited to, BOP-Cl, CDI, DCC, EDC, HATU, PyAOP or PyBOP in the presence of a suitable base such as, but not limited to, Et_3N or DIPEA. The reaction solvent can be, but is not limited to, THF, DCM and DMF. The reaction temperature is from -20 °C to 40 °C. Alternatively, the compound of Formula (1-3) is reacted with a compound of Formula (1-6) in the presence of trimethylaluminum to afford a compound of Formula (1-7). The reaction solvent can be, but is not limited to, DCM or PhMe. The reaction temperature is from 0 °C to 100 °C. Alternatively, the compound of Formula (1-2) can be reacted with a compound of Formula (1-6) and carbon monoxide in the presence of a suitable palladium catalyst, a suitable ligand and a suitable base to afford a compound of Formula (1-7). The palladium catalyst can be, but is not limited to, palladium(II) acetate, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), or tetrakis(triphenylphosphine) palladium(0). The ligand, can be, but is not limited to, 1,3-bis(diphenylphosphino)propane, or 1,4-bis(diphenylphosphino)butane. The base can be, but is not limited to, Et_3N, DIPEA, K_2CO_3, Na_2CO_3, or Cs_2CO_3. The reaction solvent can be, but is not limited to, DMF, NMP, or DMA. The reaction temperature is from 25 °C to 150 °C. If R^{15} is Cbz, the compound of Formula (1-7) is reacted with palladium on carbon in the presence of hydrogen gas to afford a compound of Formula (1-8). The reaction solvent can be, but is not limited to, MeOH, EtOH,

EtOAc, and THF. If R^{15} is Boc, the compound of Formula (1-7) is reacted with a suitable acid, such as, but not limited to, hydrochloric acid or TFA to afford a compound of Formula (1-8). The reaction solvent can be, but is not limited to, MeOH, EtOH, EtOAc, THF, and 1,4-dioxane. Compounds of Formula (1-8) are reacted with a suitable combination of reagents to afford compounds of Formula (**Ie**). The reagent combinations may be, but are not limited to:

1) An aldehyde in combination with a suitable reducing agent, such as, but not limited to, $NaBH_4$, $NaBH(OAc)_3$, or $NaBH_3CN$. The reaction solvent can be, but is not limited to, DCM, 1,2-DCE, or THF.
2) A ketone in combination with a suitable reducing agent, such as, but not limited to, $NaBH_4$, $NaBH(OAc)_3$, or $NaBH_3CN$. The reaction solvent can be, but is not limited to, DCM, 1,2-DCE, or THF.
3) An alkyl halide, alkyl mesylate, or alkyl tosylate in combination with a suitable base such as, but not limited to, NaH, NaO*t*-Bu, KO*t*-Bu, Et_3N, or DIPEA. The reaction solvent can be, but is not limited to, DCM or THF.
4) An aryl-, heteroaryl-, or alkenyl-halide, or an aryl- or heteroaryl-, or alkenyl-triflate in combination with a suitable base, palladium(0) catalyst, ligand, and solvent. The base can be, but is not limited to, NaO*t*-Bu or KO*t*-Bu. The palladium(0) catalyst can be, but is not limited to, $Pd(PPh_3)_4$ or $Pd_2(dba)_3$. The ligand can be, but is not limited to, P(*o*-tolyl)$_3$ or (2-biphenyl)di-*tert*-butylphosphine. The solvent can be, but is not limited to, toluene or THF.
5) An acyl chloride in the presence of a suitable base such as, but not limited to, Et_3N, DIPEA, or DMAP. The reaction solvent can be, but is not limited to, DCM or THF.
6) A chloroformate in the presence of a suitable base such as, but not limited to, Et_3N, DIPEA, or DMAP. The reaction solvent can be, but is not limited to, DCM or THF.
7) A sulfonyl chloride in the presence of a suitable base such as, but not limited to, Et_3N, DIPEA, or DMAP. The reaction solvent can be, but is not limited to, DCM or THF.
8) An isocyanate in the presence of a suitable base such as, but not limited to, Et_3N, DIPEA, or DMAP. The reaction solvent can be, but is not limited to, DCM or THF.
9) A primary or secondary amine in the presence of a suitable activating reagent such as, but not limited to, phosgene, triphosgene, or CDI. The reaction solvent can be, but is not limited to, DCM or THF.
10) A carboxylic acid in the presence of a suitable coupling reagent, and base. The coupling reagent can be, but is not limited to, BOP-Cl, CDI, DCC, EDC, HATU, PyAOP or PyBOP. The base can be, but is not limited to, Et_3N, DIPEA, or pyridine.

11) An aryl or heteroaryl halide in the presence of a suitable base, such as, but not limited to, Cs_2CO_3, K_2CO_3, Et_3N, DBU, DIPEA, or pyridine. The reaction solvent can be, but is not limited to, DCM, THF, DMF, or NMP.

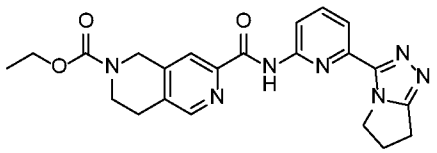
Scheme 2



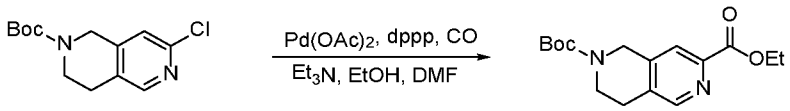
EXAMPLES

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.

Example 1: Synthesis of N-(6-(4-isopropyl-4H-1,2,4-triazol-3-yl)pyridin-2-yl)-6-pivaloyl-5,6,7,8-tetrahydro-2,6-naphthyridine-3-carboxamide.

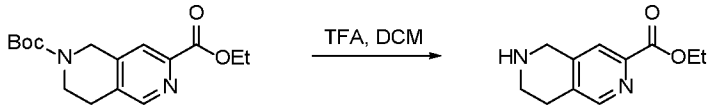


Step 1. Synthesis of ethyl 7-((6-(6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydro-2,6-naphthyridine-2(1H)-carboxylate.



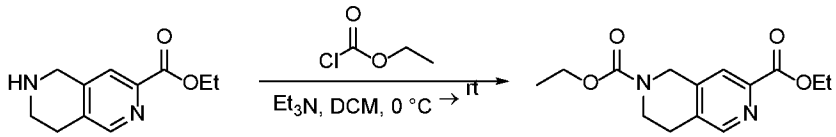
A mixture of *tert*-butyl 7-chloro-3,4-dihydro-2,6-naphthyridine-2(1H)-carboxylate (3.0 g, 11.16 mmol), $Pd(OAc)_2$ (0.251 g, 1.12 mmol), 1,3-bis(diphenylphosphino)propane (0.921 g, 2.23 mmol), and Et_3N (4.67 ml, 33.5 mmol) in DMF (29.8 ml)/EtOH (14.9 ml) were stirred under a balloon of CO at 80 °C overnight. The reaction was quenched with H_2O/brine and diluted with EtOAc. The layers were separated and the organic layer was washed with H_2O/brine (2x). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant brown gum was purified by column chromatography eluting with hexanes/EtOAc (0% EtOAc → 75% EtOAc) to afford 2-(tert-butyl) 7-ethyl 3,4-dihydro-2,6-naphthyridine-2,7(1H)-dicarboxylate (2.17 g, 7.08 mmol, 64 % yield) as a pale yellow oil: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 7.89 (s, 1H), 4.64 (s, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 3.70 (t, *J* = 5.8 Hz, 2H), 2.90 (t, *J* = 5.8 Hz, 2H), 1.50 (s, 9H), 1.44 (t, *J* = 7.1 Hz, 3H).

Step 2. Synthesis of ethyl 5,6,7,8-tetrahydro-2,6-naphthyridine-3-carboxylate.



A solution of 2-(tert-butyl) 7-ethyl 3,4-dihydro-2,6-naphthyridine-2,7(1H)-dicarboxylate (200 mg, 0.7 mmol) in TFA (1.0 mL) and DCM (5.0 mL) was stirred for 1h at rt. The resulting mixture was concentrated under reduced pressure, and the crude product was used in the next step directly without further purification.

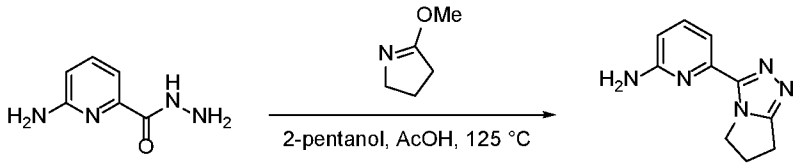
Step 3. Synthesis of diethyl 3,4-dihydro-2,6-naphthyridine-2,7(1H)-dicarboxylate.



Ethyl chloroformate (0.16 mL, 178 mg, 1.6 mmol) was added to a solution of ethyl 5,6,7,8-tetrahydro-2,6-naphthyridine-3-carboxylate (135 mg, 0.7 mmol) and Et_3N (0.46 mL, 331 mg, 3.3 mmol) in DCM (5.0 mL) at 0 °C. The cold bath was removed and the reaction was stirred for 1h at rt. The reaction was concentrated under reduced pressure. The resultant residue was purified by reverse phase flash chromatography eluting with MeCN/H_2O (5%

MeCN → 93% MeCN over 25 minutes) to afford 3,4-dihydro-2,6-naphthyridine-2,7(1H)-dicarboxylate (150 mg, 0.54 mmol, 82%) as a pale yellow oil.

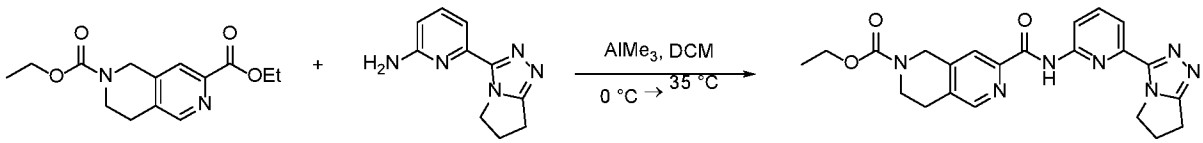
Step 4. Synthesis of 6-(6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine.



A mixture of 6-aminopyridine-2-carbohydrazide (2.4 g, 15.4 mmol), 2-methoxy- 4,5-dihydro-3H-pyrrole (1.7 g, 17.1 mmol) and AcOH (2.0 mL, 34.9 mmol) in 2-pentanol (20.0 mL) was heated at reflux overnight. After cooling to rt, the mixture was basified with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resultant white solid was washed with a acetonitrile and hexanes successively to give 6-(6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine (2.4 g, 11.4 mmol, 77%) as a white solid: LC-MS, ES^+: *m/z* 202.05 $[M+H]^+$; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.65 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 4.42 (t, *J* = 7.2 Hz, 2H), 3.01 (t, *J* = 7.7 Hz, 2H), 2.78 (m, 2H).

Step 5. Synthesis of ethyl 7-((6-(6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydro-2,6-naphthyridine-2(1H)-carboxylate.

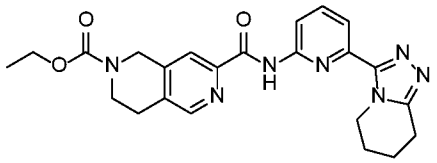
Representative procedure for amide formation with trimethylaluminum.



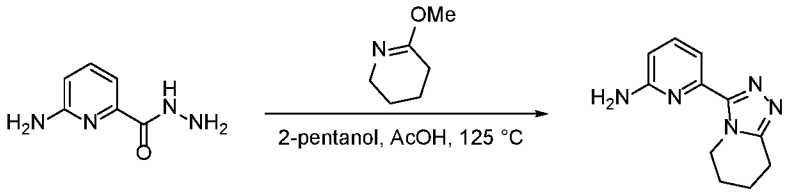
6-(6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine (40 mg, 0.2 mmol) was added to a solution of trimethylaluminum (0.35 mL, 0.7 mmol of a 2.0M solution in PhMe) in CH_2Cl_2 (5.0 mL) at 0 °C. The cold bath was removed and the reaction was stirred for1 h at rt. 3,4-dihydro-2,6-naphthyridine-2,7(1H)-dicarboxylate (50 mg, 0.2 mmol) was added and the reaction was heated at 35 °C overnight. The reaction was cooled to rt and quenched with H_2O and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resultant yellow gum was purified by reverse phase flash chromatography eluting with MeCN/H_2O (0% MeCN → 45% MeCN) to afford ethyl 7-((6-(6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-

2-yl)carbamoyl)-3,4-dihydro-2,6-naphthyridine-2(1H)-carboxylate (16.8 mg, 0.04 mmol, 20 % yield) as an off-white solid.

Example 2: Synthesis of ethyl 7-((6-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydro-2,6-naphthyridine-2(1H)-carboxylate.



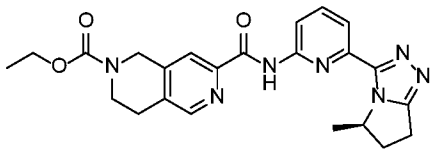
Step 1. Synthesis of 6-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)pyridin-2-amine.



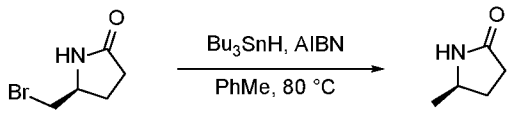
A mixture of 6-aminopyridine-2-carbohydrazide (4.0 g, 26.3 mmol), 6-methoxy-2,3,4,5-tetrahydropyridine (3.6 g, 31.6 mmol) and AcOH (3.5 mL, 61.1 mmol) in 2-pentanol (35.0 mL) was heated at reflux overnight. After cooling to rt, the mixture was basified with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resultant white solid was washed with a acetonitrile and hexanes successively to give 6-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)pyridin-2-amine (4.4 g, 20.4 mmol, 77%) as a white solid: LC-MS, ES^+: *m/z* 216.20 $[M+H]^+$; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.65 – 7.52 (m, 2H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.49 (t, *J* = 6.0 Hz, 2H), 3.07 (t, *J* = 6.4 Hz, 2H), 2.07 – 1.90 (m, 4H).

Example 2 was prepared from 6-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)pyridin-2-amine and 3,4-dihydro-2,6-naphthyridine-2,7(1H)-dicarboxylate according to the representative procedure for amide formation with trimethylaluminum.

Example 3: Synthesis of ethyl (R)-7-((6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydro-2,6-naphthyridine-2(1H)-carboxylate.

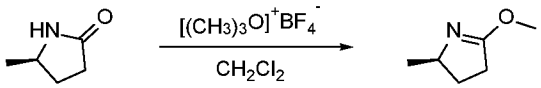


Step 1. Synthesis of (R)-5-methylpyrrolidin-2-one.



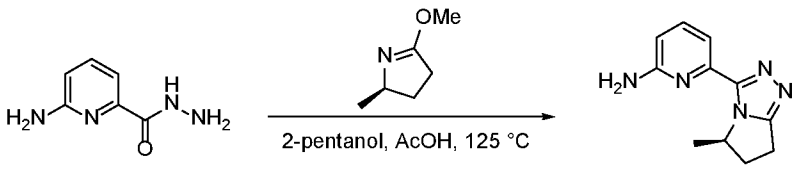
To a solution of (S)-5-(bromomethyl)pyrrolidin-2-one (5.0 g, 28.1 mmol) in toluene (100 mL) was added Bu_3SnH (9.1 mL, 33.7 mmol) and AIBN (1.4 mL, 0.28 mmol) (0.2M in toluene) and the reaction was heated at 80 °C for 5 h. The reaction was cooled to rt and was concentrated under reduced pressure. The resultant pale yellow oil was purified by column chromatography eluting with CH_2Cl_2/MeOH (0% MeOH → 8% MeOH) to give (R)-5-methylpyrrolidin-2-one (2.6 g, 26.2 mmol, 93 % yield) as a colorless oil: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.93 (br s, 1H), 3.78 (h, *J* = 6.4 Hz, 1H), 2.43 – 2.21 (comp, 3H), 1.73 – 1.60 (m, 1H), 1.22 (d, *J* = 6.3 Hz, 3H).

Step 2. Synthesis of (R)-5-methoxy-2-methyl-3,4-dihydro-2H-pyrrole.



Trimethyloxonium tetrafluoroborate (1.3 g, 9.1 mmol) was added portion wise to a solution of (R)-5-methylpyrrolidin-2-one (600 mg, 6.1 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C over 5 min. The reaction was stirred overnight at rt. The reaction was quenched with sat. $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and filtered. AcOH (2.0 mL) was added to the filtrate, and the mixture was concentrated under reduced pressure. The crude product (600 mg) was taken on to the next step without purification.

Step 3. Synthesis of (R)-6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine.

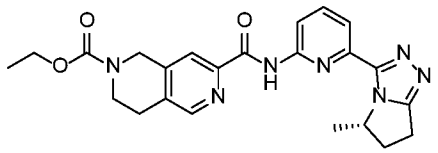


A mixture of 6-aminopyridine-2-carbohydrazide (450 mg, 2.96 mmol), 6-methoxy-2,3,4,5-tetrahydropyridine (600 mg, 5.30 mmol) and AcOH (1.0 mL, 17.5 mmol) in 2-pentanol (10.0 mL) was heated at reflux overnight. After cooling to rt, the mixture was basified with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resultant white solid was washed with a acetonitrile and hexanes successively to give (R)-6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine (300 mg, 1.39

mmol, 47%) as a white solid: LC-MS, ES^+: *m/z* 216.15 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.65 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.57 – 7.50 (m, 1H), 6.51 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.08 – 4.96 (m, 1H), 3.14 – 2.90 (comp, 3H), 2.44 – 2.32 (m, 1H), 1.48 (d, *J* = 6.5 Hz, 3H).

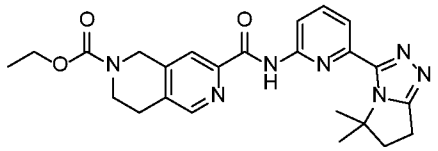
Example 3 was prepared from (R)-6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine and 3,4-dihydro-2,6-naphthyridine-2,7(1H)-dicarboxylate according to the representative procedure for amide formation with trimethylaluminum.

Example 4: Synthesis of ethyl (S)-7-((6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydro-2,6-naphthyridine-2(1H)-carboxylate.

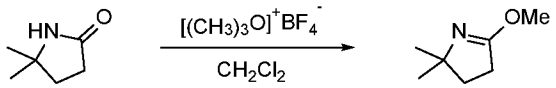


Example 4 was prepared from (R)-5-(bromomethyl)pyrrolidin-2-one using the sequence of reactions outlined for the preparation of (R)-7-((6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydro-2,6-naphthyridine-2(1H)-carboxylate.

Example 5: Synthesis of ethyl 7-((6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydro-2,6-naphthyridine-2(1H)-carboxylate.



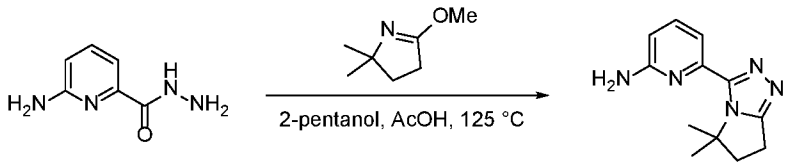
Step 1. Synthesis of 5-methoxy-2,2-dimethyl-3,4-dihydro-2H-pyrrole.



Trimethyloxonium tetrafluoroborate (19.6 g, 132.5 mmol) was added portion wise to a solution of 5,5-dimethylpyrrolidin-2-one (10.0 g, 89.2 mmol) in CH_2Cl_2 (100.0 mL) at 0 °C over 5 min. The reaction was stirred overnight at rt. The reaction was quenched with sat. $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and filtered. AcOH (8.0 mL) was added to the filtrate, and the

mixture was concentrated under reduced pressure. The crude product (11.0 g) was taken on to the next step without purification.

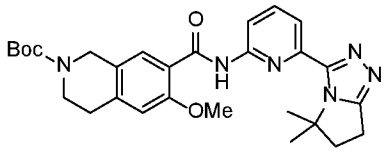
Step 2. Synthesis of 6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine.



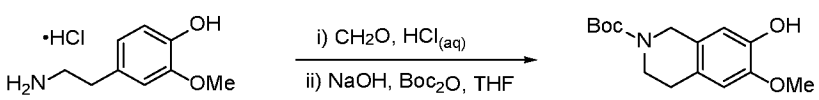
A mixture of 6-aminopyridine-2-carbohydrazide (8.4 g, 55.2 mmol), 5-methoxy-2,2-dimethyl-3,4-dihydro-2H-pyrrole (11.0 g, 86.5 mmol) and AcOH (16.3 mL, 285.5 mmol) in 2-pentanol (40.0 mL) was heated at reflux overnight. After cooling to rt, the mixture was basified with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resultant white solid was washed with a acetonitrile and hexanes successively to give 6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine (4.2 g, 18.3 mmol, 33%) as a white solid: LC-MS, ES^+: *m/z* 230.15 $[M+H]^+$; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.64 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 6.55 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.3 (brs, 2H), 3.05 (t, *J* = 7.6 Hz, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.77 (s, 6H).

Example 5 was prepared from 6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine and 3,4-dihydro-2,6-naphthyridine-2,7(1H)-dicarboxylate according to the representative procedure for amide formation with trimethylaluminum.

Example 6: Synthesis of tert-butyl 7-((6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate.



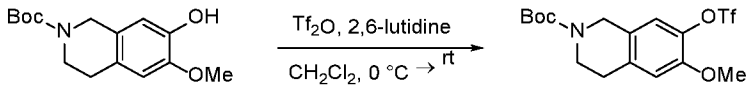
Step 1: Synthesis of tert-butyl 7-hydroxy-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate.



Formaldehyde (2.6 mL, 34.4 mmol of a 36% aqueous solution) was added to a solution of 4-(2-aminoethyl)-2-methoxyphenol, hydrochloride (1.0 g, 4.9 mmol) in 1M

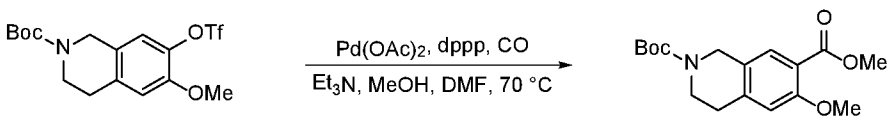
$HCl_{(aq)}$ (4.9 mL) and the reaction was stirred at 50 °C for 6 h. The reaction was cooled to 0 °C and made basic with 50% aqueous NaOH (0.31 mL, 5.9 mmol). A solution of Boc_2O (5.7 mL, 24.55 mmol) in THF (4.9 mL) was added dropwise at 0 °C. The cold bath was removed, and the reaction was stirred at rt for 17 h. The reaction was quenched with H_2O and diluted with MTBE (30 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 x 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant orange oil was purified by column chromatography eluting with hexanes/EtOAc (0% EtOAc → 40% EtOAc) to afford tert-butyl 7-hydroxy-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (570 mg, 2.04 mmol, 41.6 % yield) as a colorless gum: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.65 (s, 1H), 6.60 (s, 1H), 5.48 (s, 1H), 4.45 (s, 2H), 3.86 (s, 3H), 3.61 (t, *J* = 5.9 Hz, 2H), 2.74 (t, *J* = 5.9 Hz, 2H), 1.48 (s, 9H).

Step 2: Synthesis of tert-butyl 6-methoxy-7-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate.



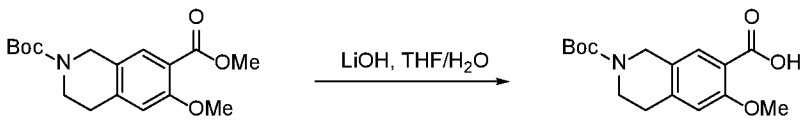
Trifluoromethanesulfonic anhydride (61.2 mL, 61.2 mmol, of a 1.0M solution in CH_2Cl_2) was added dropwise to a solution of tert-butyl 7-hydroxy-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (11.4 g, 40.8 mmol) and 2,6-lutidine (14.3 mL, 13.1 g, 122 mmol) in CH_2Cl_2 (204 mL) at 0 °C. The cold bath was removed and the reaction was stirred at rt overnight. The reaction was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (150 mL x 2) and brine (150 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant yellow gum was purified by column chromatography eluting with hexanes/EtOAc (0% EtOAc → 40% EtOAc) to afford tert-butyl 6-methoxy-7-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate (12.5 g, 30.4 mmol, 75% yield) as a colorless solid: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.95 (s, 1H), 6.78 (s, 1H), 4.50 (s, 2H), 3.89 (s, 3H), 3.64 (t, *J* = 5.8 Hz, 3H), 2.82 (t, *J* = 5.9 Hz, 2H), 1.49 (s, 9H).

Step 3: Synthesis of 2-(tert-butyl) 7-methyl 6-methoxy-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate.



A mixture of 6-methoxy-7-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate (6.0 g, 14.6 mmol), $Pd(OAc)_2$ (0.327 g, 1.46 mmol), 1,3-bis(diphenylphosphino)propane (0.602 g, 1.46 mmol), and Et_3N (6.10 mL, 43.8 mmol) in DMF (58.3 ml)/MeOH (38.9 ml) were stirred under a balloon of CO at 70 °C for 5 h. The reaction was quenched with H_2O/brine (200 m) and diluted with EtOAc (200 mL) and the layers were separated. The organic layer was washed with water/brine (2 x 100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant brown oil was purified by column chromatography eluting with hexanes/EtOAc (0% EtOAc → 40% EtOAc) to afford 2-(tert-butyl) 7-methyl 6-methoxy-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate (4.3 g, 13.38 mmol, 92 % yield) as a colorless solid: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (s, 1H), 6.72 (s, 1H), 4.51 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.63 (t, *J* = 6.1 Hz, 2H), 2.84 (t, *J* = 6.1 Hz, 2H), 1.48 (s, 9H).

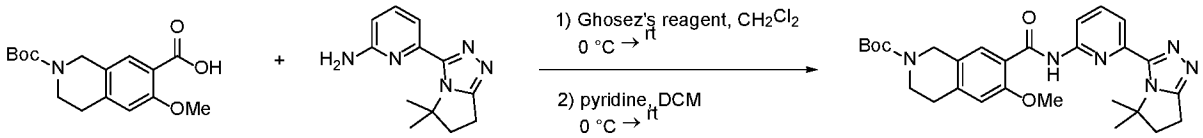
Step 4: Synthesis of 2-(tert-butoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid.



$LiOH•H_2O$ (1.8 g, 43.6 mmol) was added to a solution of 2-(tert-butyl) 7-methyl 6-methoxy-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate (2.8 g, 8.7 mmol) in THF (25 mL)/H_2O (8 mL) and the reaction was heated at 50 °C for 2 h. The reaction was cooled to rt then acidified with 10% citric acid (50 mL) and diluted with CH_2Cl_2 (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 2-(tert-butoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (2.68 g, 8.7 mmol, 100 % yield) as a colorless amorphous solid: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.67 (br s, 1H), 7.94 (s, 1H), 6.81 (s, 1H), 4.55 (s, 2H), 4.06 (s, 3H), 3.66 (t, *J* = 5.8 Hz, 2H), 2.88 (t, *J* = 5.8 Hz, 2H), 1.49 (s, 9H).

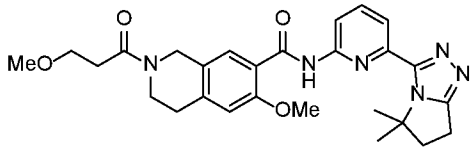
Step 5: Synthesis of tert-butyl 7-((6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate.

Representative procedure for amide formation with Ghosez's reagent.



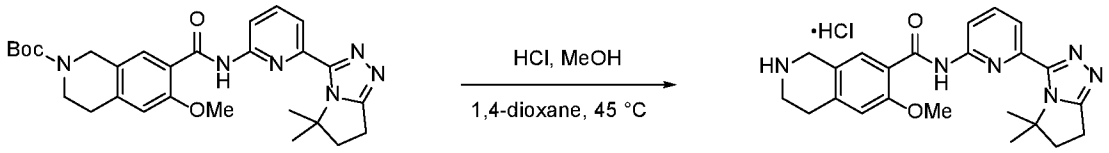
Ghosez's Reagent (0.83 mL, 6.25 mmol) was added dropwise to a solution of 2-(tert-butoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (800 mg, 2.60 mmol) in CH_2Cl_2 (7.0 mL) at 0 °C. The cold bath was removed and the reaction was stirred at rt for 1 h. The reaction was concentrated under reduced pressure and the resultant acid chloride was dissolved in CH_2Cl_2 (7.0 mL) and cooled to 0 °C. 6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine (597 mg, 2.60 mmol) was added, followed by pyridine (0.84 mL, 0.82 g, 10.41 mmol). The reaction was stirred overnight, slowly warming to rt. The reaction was quenched with sat. $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the organic layer was washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant pale yellow gum was purified by column chromatography eluting with CH_2Cl_2/MeOH (0% MeOH → 5% MeOH) to afford tert-butyl 7-((6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (993 mg, 1.92 mmol, 74 % yield) as a pale yellow solid.

Example 7: Synthesis of N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-6-methoxy-2-(3-methoxypropanoyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide.



Step 1: Synthesis of N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide, hydrochloride.

Representative procedure for Boc deprotection.

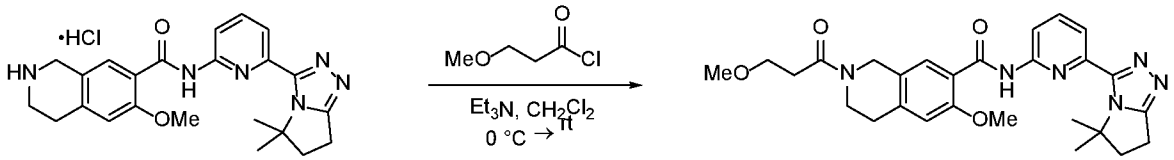


4M HCl in dioxane (4.7 mL) was added to a solution of tert-butyl 7-((6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (989 mg, 1.91 mmol) in MeOH (9.4

mL) and the reaction was stirred for 20 min at 45 °C. The reaction was concentrated under reduced pressure to afford crude N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide, hydrochloride (937 mg, 1.91 mmol, 100% yield) as a tan solid: LC-MS, ES^+: *m/z* 419.22 $[M+H]^+$.

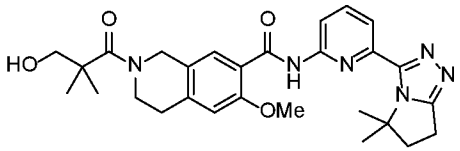
Step 2: Synthesis of N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-6-methoxy-2-(3-methoxypropanoyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide.

Representative procedure for amide formation using acid chlorides.



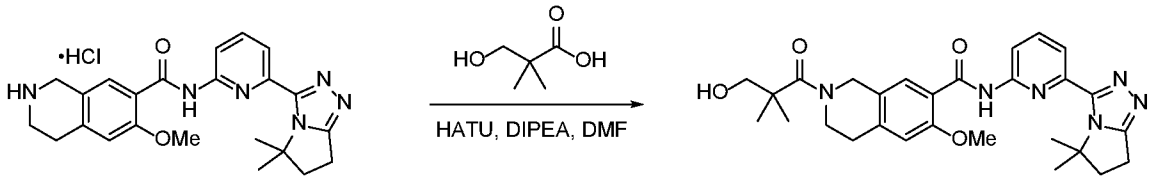
3-methoxypropanoyl chloride (15 µl, 15 mg, 0.12 mmol) was added dropwise to a solution of N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide, hydrochloride (50 mg, 0.10 mmol) and Et_3N (71 µL, 52 mg, 0.51 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. The cold bath was removed and the reaction was stirred 1 h at rt. The reaction was quenched with sat. $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant yellow gum was purified by column chromatography eluting with CH_2Cl_2/MeOH (0% MeOH → 7% MeOH) to afford N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-6-methoxy-2-(3-methoxypropanoyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (20.8 mg, 0.041 mmol, 41 % yield) as a colorless amorphous solid.

Example 8: Synthesis of N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-2-(3-hydroxy-2,2-dimethylpropanoyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide.



Step 1: Synthesis of N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-2-(3-hydroxy-2,2-dimethylpropanoyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide.

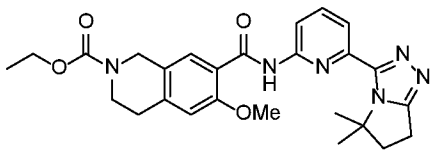
Representative procedure for HATU coupling.



HATU (58.0 mg, 0.153 mmol) was added to a solution of 3-hydroxy-2,2-dimethylpropanoic acid (12.0 mg, 0.102 mmol) in DMF (0.42 mL) and the reaction was stirred for 5 min at rt. N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide, hydrochloride (50 mg, 0.102 mmol) was added, followed by DIPEA (89 µL, 65.8 mg, 0.509 mmol), and the reaction was stirred for 2 h at rt. The reaction was quenched with sat. $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant white solid was purified by column chromatography eluting with CH_2Cl_2/MeOH (0% MeOH → 7% MeOH) to afford N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-2-(3-hydroxy-2,2-dimethylpropanoyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide (45.7 mg, 0.088 mmol, 87 % yield) as a colorless amorphous solid.

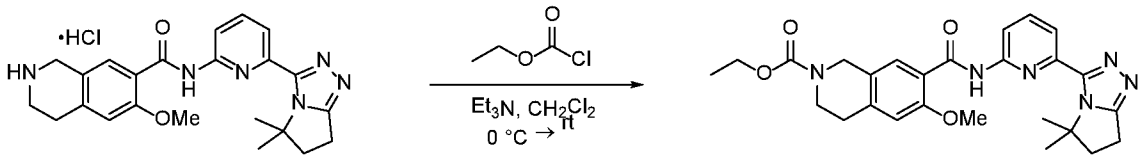
(S)-N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-2-(3-hydroxybutanoyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide, (S)-N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-2-(2-hydroxy-4-methylpentanoyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide, and N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-2-(2-hydroxy-2-methylpropanoyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide were prepared from N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide, hydrochloride according to the representative procedure for HATU coupling.

Example 9: Synthesis of ethyl 7-((6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate.



Step 1: Synthesis of ethyl 7-((6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate.

Representative procedure for carbamate formation.



Ethyl chloroformate (12 μl, 13 mg, 0.12 mmol) was added dropwise to a solution of N-(6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxamide, hydrochloride (50 mg, 0.10 mmol) and Et_3N (71 μL, 52 mg, 0.51 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. The cold bath was removed and the reaction was stirred 1 h at rt. The reaction was quenched with sat. $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant yellow gum was purified by column chromatography eluting with CH_2Cl_2/MeOH (0% MeOH → 7% MeOH) to afford ethyl 7-((6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (15.7 mg, 0.032 mmol, 27 % yield) as a colorless amorphous solid.

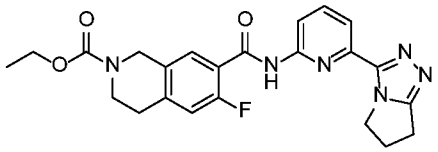
Ethyl 6-methoxy-7-((6-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate was prepared in analogous fashion to example 9, starting from 2-(tert-butoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid and 6-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)pyridin-2-amine.

Ethyl (R)-6-methoxy-7-((6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate was prepared in analogous fashion to example 9, starting from 2-(tert-butoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid and (R)-6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine.

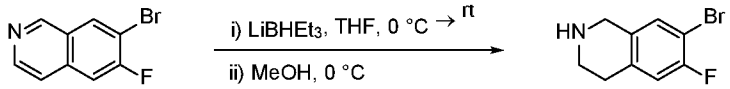
Ethyl (S)-6-methoxy-7-((6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate was prepared in analogous fashion to example 9, starting from 2-(tert-butoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid and (S)-6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine.

Ethyl 7-((6-(6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate was prepared in analogous fashion to example 9, starting from 2-(tert-butoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid and 6-(6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine.

Example 10: Synthesis of ethyl 7-((6-(6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate.

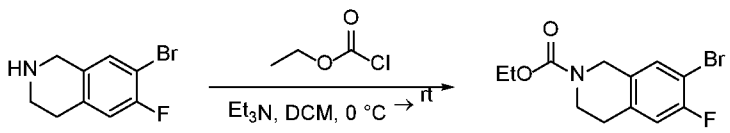


Step 1. Synthesis of 7-bromo-6-fluoro-1,2,3,4-tetrahydroisoquinoline.



Lithium triethylborohydride (74.0 mL, 74.0 mmol of a 1.0M solution in THF) was added dropwise to a solution of 7-bromo-6-fluoroisoquinoline (7.6 g, 33.6 mmol) in THF (210 mL) at 0 °C. The cold bath was removed, and the reaction was stirred at rt overnight. The reaction was cooled to 0 °C and quenched dropwise with MeOH until gas evolution ceased. The mixture was diluted with 1M HCl and MTBE. The layers were separated and the organic layer was extracted with 1M HCl (2x). The combined aqueous layers were washed with MTBE (3x). The aqueous layer was made basic (pH 14) with 50% NaOH, then extracted (5 x 100 mL) with DCM. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford crude 7-bromo-6-fluoro-1,2,3,4-tetrahydroisoquinoline (6.4 g) as a yellow oil: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 (d, *J* = 6.9 Hz, 1H), 6.85 (d, *J* = 9.3 Hz, 1H), 3.94 (s, 2H), 3.10 (t, *J* = 6.1 Hz, 2H), 2.73 (t, *J* = 6.0 Hz, 2H).

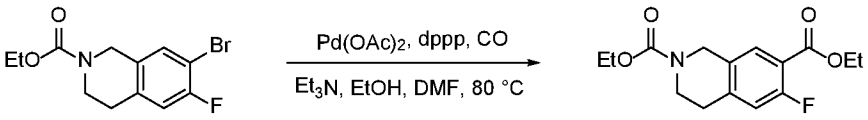
Step 2. Synthesis of ethyl 7-bromo-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate.



Ethyl chloroformate (1.1 mL, 1.25 g, 11.5 mmol) was added to a solution of 7-bromo-6- fluoro-1,2,3,4-tetrahydroisoquinoline (2.2 g, 9.6 mmol) and Et_3N (2.6 mL, 1.9 g, 19.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The cold bath was removed and the reaction stirred for 2 h at rt. The reaction was quenched with H_2O and the layers were separated. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to

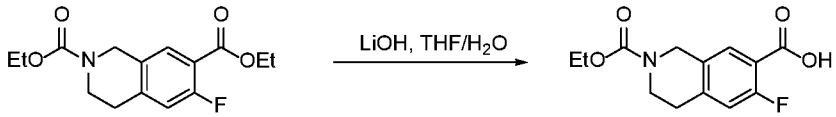
afford ethyl 7-bromo-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.5 g, 5.08 mmol, 52.9%) as a yellow oil which was used in the next step without further purification: LC-MS, ES^+: *m/z* 301.90 $[M+H]^+$.

Step 3. Synthesis of diethyl 6-fluoro-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate.



A mixture of ethyl 7-bromo-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.5 g, 5.0 mmol), $Pd(OAc)_2$ (113 mg, 0.5 mmol), 1,3-bis(diphenylphosphino)propane (412 mg, 1.0 mmol), and Et_3N (1.38 mL, 1.0 g, 10.0 mmol) in DMF (20.0 mL)/EtOH (7.0 mL) were stirred under a balloon of CO at 80 °C for 24 h. The reaction was cooled to rt, quenched with H_2O (30 mL), and diluted with EtOAc (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resultant residue was purified by column chromatography eluting with hexanes/EtOAc (0% EtOAc → 20% EtOAc) to afford diethyl 6-fluoro-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate (0.9 g, 3.05 mmol, 61 % yield) as a yellow oil: LC-MS, ES^+: *m/z* 296.10 $[M+H]^+$.

Step 4. Synthesis of 2-(ethoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid.



diethyl 6-fluoro-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate (0.9 g, 3.0 mmol) was added to a solution of LiOH (1.4 g, 60 mmol) in THF (15.0 mL)/H_2O (15.0 mL) and the reaction was stirred overnight at rt. The pH was adjusted to ~4 with 1M $HCl_{(aq)}$. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 2-(ethoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (600 mg, 2.25 mmol, 75%) as a yellow oil: LC-MS, ES^+: *m/z* 268.00 $[M+H]^+$.

Example 10 was prepared from 2-(ethoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid and 6-(6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine according to the representative procedure for amide formation with Ghosez's reagent.

Ethyl 6-fluoro-7-((6-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate was prepared from 2-

(ethoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid and 6-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)pyridin-2-amine according to the representative procedure for amide formation with Ghosez's reagent.

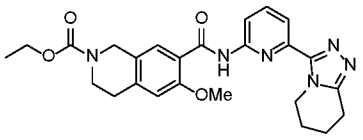
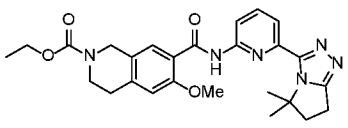
Ethyl 7-((6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-6-fluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate was prepared from 2-(ethoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid and 6-(5,5-dimethyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine according to the representative procedure for amide formation with Ghosez's reagent.

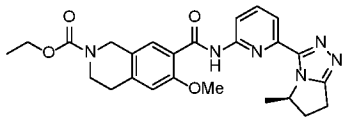
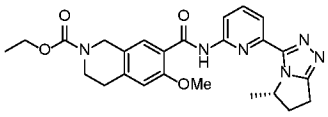
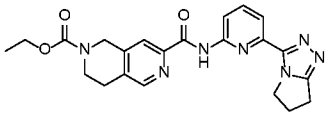
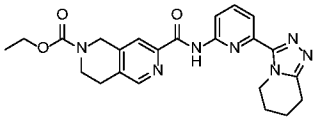
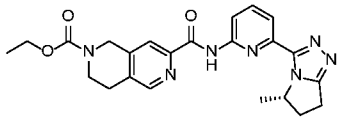
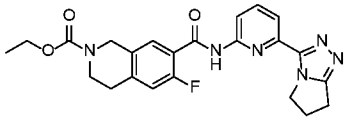
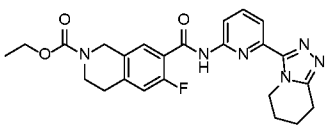
Ethyl (R)-6-fluoro-7-((6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate was prepared from 2-(ethoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid and (R)-6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine according to the representative procedure for amide formation with Ghosez's reagent.

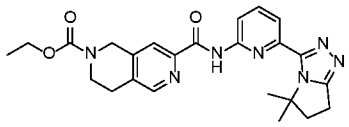
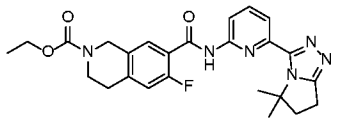
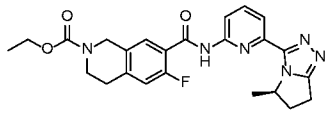
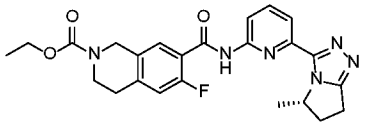
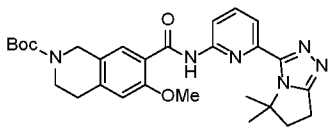
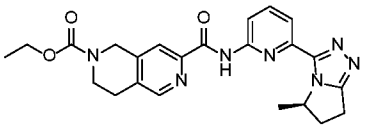
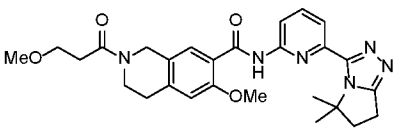
Ethyl (S)-6-fluoro-7-((6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate was prepared from 2-(ethoxycarbonyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid and (S)-6-(5-methyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-3-yl)pyridin-2-amine according to the representative procedure for amide formation with Ghosez's reagent.

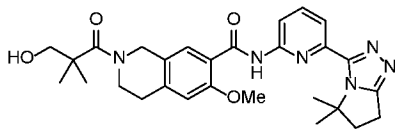
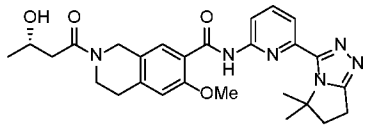
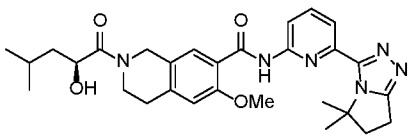
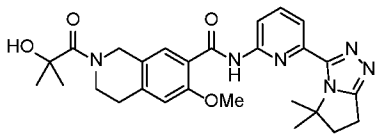
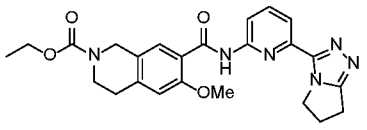
Characterization data for examples are shown in Table 6.

Table 6

Example	Structure	LC-MS $[M+H]^+$ unless otherwise noted	^{1}H-NMR
1		477	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.00 (t, J = 8.0 Hz, 1H), 7.87 (dd, J = 7.8, 0.9 Hz, 1H), 7.68 (s, 1H), 7.08 (s, 1H), 4.56 (s, 2H), 4.49 (t, J = 6.0 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.96 (s, 3H), 3.62 (t, J = 6.0 Hz, 2H), 2.93(t, J = 6.4 Hz, 2H), 2.88 (t, J = 6.0 Hz, 2H), 2.06 – 1.80 (m, 4H), 1.22 (t, J = 7.1 Hz, 3H).
2		491	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 8.37 (d, J = 8.2 Hz, 1H), 8.04 (t, J = 8.0 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.87 (s, 1H), 7.16 (s, 1H), 4.57 (s, 2H), 4.10 (q, J = 7.1 Hz, 2H), 4.04 (s, 3H), 3.63 (t, J = 5.9 Hz, 2H), 3.06 (t, J = 7.5 Hz, 2H), 2.89 (t, J = 5.9 Hz, 2H), 2.64 (t, J = 7.5 Hz, 2H), 1.79 (s, 6H), 1.22 (t, J = 7.1 Hz, 3H).

3		477	^{1}H NMR (400 MHz, Chloroform-d) δ 10.37 (s, 1H), 8.47 (d, *J* = 8.2 Hz, 1H), 8.10 - 8.08 (m, 2H), 7.89 (t, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 5.09 (m, 1H), 4.67 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.08 (s, 3H), 3.75 (t, *J* = 7.1 Hz, 2H), 3.18 - 3.09 (m, 3H), 2.94 (t, *J* = 5.8 Hz, 2H), 2.48 (m, 1H), 1.60 (s, 3H),1.33 (t, *J* = 7.1 Hz, 3H).
4		477	^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.37 (s, 1H), 8.46 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 2H), 7.88 (t, *J* = 8.0 Hz, 1H), 6.84 (s, 1H), 5.07 (m, 1H), 4.67 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.08 (s, 3H), 3.75 (t, *J* = 6.0 Hz, 2H), 3.15 - 3.08 (m, 3H), 2.93 (t, *J* = 5.9 Hz, 2H), 2.48 (m, 1H), 1.64 (d, *J* = 6.4 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).
5		434	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.54 (s, 1H), 8. 50 (d, *J* = 8.0 Hz, 1H), 8.12 – 8.03 (m, 2H), 7.97 (d, *J* = 7.6 Hz, 1H), 4.79 (s, 2H), 4.70 (t, *J* = 7.2 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.81 (t, *J* = 5.7 Hz, 2H), 3.19 (t, *J* = 7.7 Hz, 2H), 3.02 – 2.92 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 3H).
6		448	^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.39 (s, 1H), 8.49 – 8.43 (m, 2H), 8.10 - 8.07 (m, 2H), 7.91 (t, *J* = 7.9 Hz, 1H), 4.77 (s, 2H), 4.60 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.81 (t, *J* = 5.8 Hz, 2H), 3.13 (s, 2H), 2.98 (t, *J* = 5.6 Hz, 2H), 2.11 (m, 2H), 2.01 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).
7		448	^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.43 (s, 1H), 8.54 – 8.45 (m, 2H), 8.16 - 8.08 (m, 2H), 7.95 (t, *J* = 7.9 Hz, 1H), 5.39 – 5.23 (m, 4H), 4.78 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.82 (t, *J* = 5.7 Hz, 2H), 3.25 (s, 2H), 3.15 (s, 1H), 2.99 (t, *J* = 5.7 Hz, 2H), 2.54 (m, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).
8		451	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.07 (d, *J* = 15.9 Hz, 1H), 8.39 (d, *J* = 8.2 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.90 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 12.6 Hz, 1H), 4.70 (s, 2H), 4.46 (t, *J* = 7.2 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.75 (t, *J* = 6.1 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H), 2.85 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).
9		465	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.06 (d, *J* = 15.4 Hz, 1H), 8.42 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 12.6 Hz, 1H), 4.70 (s, 2H), 4.54 (t, *J* = 5.9 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.75 (t, *J* = 5.9 Hz, 2H), 3.50 (m, 2H), 3.15 (t, *J* = 6.3 Hz, 2H), 2.94 (t, *J* = 6.0 Hz, 2H), 2.09 (m, 2H), 2.01 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

10		462	^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.48 (s, 1H), 8.48 (d, *J* = 6.8 Hz, 2H), 8.10 (d, *J* = 8.3 Hz, 2H), 7.93 (t, *J* = 7.9 Hz, 1H), 4.78 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.81 (t, *J* = 5.7 Hz, 2H), 3.16 (s, 2H), 2.98 (t, *J* = 5.7 Hz, 2H), 2.69 (s, 2H), 1.86 (s, 6H), 1.34 (t, *J* = 7.1 Hz, 3H).
11		479	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.17 (d, *J* = 17.3 Hz, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 12.9 Hz, 1H), 4.71 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.76 (t, *J* = 5.9 Hz, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 2.94 (t, *J* = 5.8 Hz, 2H), 2.68 (t, *J* = 7.2 Hz, 2H), 1.82 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 4H).
12		465	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.10 (d, *J* = 16.6 Hz, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.91 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 12.7 Hz, 1H), 5.06 (m, 1H), 4.71 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.76 (t, *J* = 5.2 Hz, 2H), 3.13 (s, 0H), 3.05 (t, *J* = 10.0 Hz, 3H), 2.94 (t, *J* = 5.9 Hz, 2H), 2.46 (d, *J* = 10.5 Hz, 1H), 1.58 (d, *J* = 6.2 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).
13		465	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.10 (d, *J* = 16.5 Hz, 1H), 8.39 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.90 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 12.8 Hz, 1H), 5.05 (m, 1H), 4.70 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.75 (t, *J* = 5.9 Hz, 2H), 3.09 – 2.99 (m, 3H), 2.94 (t, *J* = 5.6 Hz, 2H), 2.45 (m, 1H), 1.57 (d, *J* = 6.4 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).
14		519	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 8.33 (dd, *J* = 8.3, 0.9 Hz, 1H), 8.01 (t, *J* = 8.0 Hz, 1H), 7.89 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.86 (s, 1H), 7.14 (s, 1H), 4.52 (s, 2H), 4.03 (s, 3H), 3.57 (t, *J* = 5.8 Hz, 2H), 2.98 (dd, *J* = 8.1, 7.0 Hz, 2H), 2.87 (t, *J* = 5.9 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.76 (s, 6H), 1.43 (s, 9H).
15		448	^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.41 (s, 1H), 8.47 – 8.45 (m, 2H), 8.13 – 8.11 (m, 2H), 7.93 (t, *J* = 7.9 Hz, 1H), 5.20 (m, 1H), 4.78 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.82 (t, *J* = 5.6 Hz, 2H), 3.17 – 3.08 (m, 3H), 2.99 (t, *J* = 6.0 Hz, 2H), 2.48 (m, 1H), 1.59 (d, *J* = 6.3 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).
16		505	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (d, *J* = 4.7 Hz, 1H), 8.38 – 8.30 (m, 1H), 8.01 (td, *J* = 7.9, 1.8 Hz, 1H), 7.92 (d, *J* = 11.7 Hz, 1H), 7.88 (d, *J* = 4.6 Hz, 1H), 7.16 (d, *J* = 2.9 Hz, 1H), 4.71 (s, 1H), 4.62 (s, 1H), 4.04 (d, *J* = 1.5 Hz, 3H), 3.69 (dt, *J* = 9.1, 5.9 Hz, 2H), 3.58 (td, *J* = 6.5, 3.0 Hz, 2H), 3.22 (d, *J* = 6.5 Hz, 3H), 3.02 – 2.91 (comp, 3H), 2.85 (t, *J* = 6.0 Hz, 1H), 2.68

			(dt, J = 8.0, 4.0 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 1.76 (s, 6H).
17		519	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 8.33 (dd, J = 8.3, 0.9 Hz, 1H), 8.01 (t, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.89 (dd, J = 7.7, 0.9 Hz, 1H), 7.14 (s, 1H), 4.72 (s, 2H), 4.58 (t, J = 5.8 Hz, 1H), 4.03 (s, 3H), 3.79 (t, J = 5.9 Hz, 2H), 3.47 (d, J = 5.9 Hz, 2H), 2.98 (dd, J = 8.1, 7.0 Hz, 2H), 2.89 (t, J = 5.9 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 1.76 (s, 6H), 1.19 (s, 6H).
18		505	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (d, J = 4.3 Hz, 1H), 8.38 – 8.30 (m, 1H), 8.01 (td, J = 8.0, 2.1 Hz, 1H), 7.94 – 7.89 (m, 1H), 7.89 – 7.85 (m, 1H), 7.16 (d, J = 3.4 Hz, 1H), 4.80 – 4.56 (comp, 3H), 4.07-3.99 (comp, 4H), 3.76-3.65 (m, 2H), 3.03 – 2.90 (comp, 3H), 2.85 (t, J = 6.0 Hz, 1H), 2.64-2.54 (comp, 3H), 2.41 (ddd, J = 15.0, 9.6, 5.4 Hz, 1H), 1.76 (s, 6H), 1.11 (dd, J = 8.2, 6.2 Hz, 3H).
19		533	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (d, J = 3.1 Hz, 1H), 8.33 (dd, J = 8.3, 0.9 Hz, 1H), 8.00 (t, J = 8.0 Hz, 1H), 7.90 (t, J = 1.5 Hz, 1H), 7.88 (s, 1H), 7.16 (s, 1H), 4.88 (dd, J = 45.6, 7.2 Hz, 1H), 4.81 – 4.52 (m, 2H), 4.48-4.38 (m, 1H), 4.04 (s, 3H), 3.82-3.60 (comp, 2H), 3.01-2.93 (comp, 3H), 2.87 (t, J = 6.0 Hz, 1H), 2.61 (t, J = 7.5 Hz, 2H), 1.84-1.71 (m, 1 H), 1.76 (s, 6H), 1.57 – 1.20 (comp, 2H), 0.97 – 0.82 (m, 6H).
20		505	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 8.33 (dd, J = 8.3, 0.9 Hz, 1H), 8.01 (t, J = 8.0 Hz, 1H), 7.89 (dd, J = 7.7, 0.9 Hz, 1H), 7.86 (s, 1H), 7.14 (s, 1H), 5.50 (s, 1H), 5.24-4.99 (m, 1H), 4.74-4.54 (m, 1H), 4.22-4.08 (m, 1H), 4.04 (s, 3H), 3.85-3.61 (m, 1H), 2.98 (dd, J = 8.1, 7.0 Hz, 2H), 2.91 (br s, 2H), 2.61 (t, J = 7.5 Hz, 2H), 1.76 (s, 6H), 1.34 (s, 6H).
21		463	^{1}H NMR (400 MHz, Methanol-d_4) δ 8.39 (d, J = 8.2 Hz, 1H), 7.99 (t, J = 7.9 Hz, 1H), 7.91 (d, J = 4.7 Hz, 2H), 7.08 (s, 1H), 4.64 (s, 2H), 4.57 (t, J = 7.2 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.10 (s, 3H), 3.74 (s, 2H), 3.05 (m, 2H), 2.98 – 2.86 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H).

ASSAY

HTRF® KinEASE™ Assay

ASK1 was purchased from Thermofisher (Catalogue # PV4011), ATP was purchased from Sigma (Catalogue # A7699), HTRF® KinEASE™ Assay System was obtained from Cisbio (Bedford, Mass). ½ Area plate was purchased from Perkin Elmer (Catalogue # #6005560). HTRF® KinEASE™-STK is a generic method for measuring serine/threonine

kinase activities using a 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 μM) and a fixed amount of ATP and peptide substrates. The test compound, 1μM STK3 peptide substrate, and 5 μM of ASK1 kinase are incubated with kinase reaction buffer containing 50 mM HEPES Ph 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, and 1 mM EGTA for 30 minutes. 100 μM 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 an 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 evaluated for the compounds of Formula (**I**). The results are shown in Table 7. Example numbers correspond to those in Table 6. IC_{50} ranges are as follows: A = IC_{50} < 1.25 nM; B = 1.25 nM < IC_{50} < 10 nM; C = 10 nM < IC_{50} < 100 nM; D = 100 nM < IC_{50} < 1 μM; E = IC_{50} > 1 μM.

Table 7

Example	IC50 (nM)
1	C
2	A
3	A
4	B
5	C
6	E
7	C
8	D
9	E
10	B
11	B
12	B
13	C
14	B
15	B
16	A
17	A
18	A
19	A
20	A
21	B

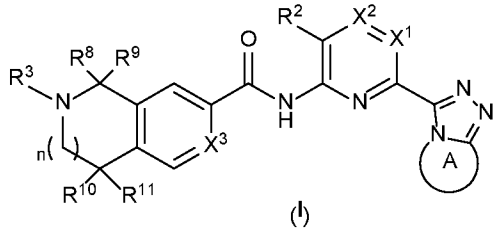
While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended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

5

CLAIMS

WHAT IS CLAIMED:

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



(I)

wherein:

one of X^1 and X^2 is $C(R^6)$, and the other is $C(R^6)$ or N;

X^3 is $C(R^7)$ or N, wherein R^7 is selected from the group consisting of hydrogen, optionally substituted $-C_1$-C_8 alkyl, optionally substituted $-C_1$-C_8 alkoxy and halo;

A is optionally substituted heterocycloalkyl or optionally substituted heteroaryl which is fused with 1,2,4-triazolyl;

R^2 and R^6 are each independently selected from the group consisting of:

1) Hydrogen;
2) Halogen;
3) $-NO_2$;
4) Cyano;
5) Substituted or unsubstituted $-C_1$-C_8 alkyl;
6) Substituted or unsubstituted $-C_2$-C_8 alkenyl;
7) Substituted or unsubstituted $-C_2$-C_8 alkynyl;
8) Substituted or unsubstituted $-C_3$-C_8 cycloalkyl;
9) Substituted or unsubstituted aryl;
10) Substituted or unsubstituted arylalkyl;
11) Substituted or unsubstituted 3- to 8- membered heterocycloalkyl;
12) Substituted or unsubstituted heteroaryl;
13) Substituted or unsubstituted heteroarylalkyl;
14) $-N(R^4)(R^5)$;
15) $-S(O)_2N(R^4)(R^5)$;
16) $-N(R^4)C(O)R^5$; and
17) $-N(R^4)S(O)_2R^5$;

R^3 is selected from the group consisting of:

1) Hydrogen;

2) Substituted or unsubstituted $-C_1$-C_8 alkyl;

3) Substituted or unsubstituted $-C_2$-C_8 alkenyl;

4) Substituted or unsubstituted $-C_2$-C_8 alkynyl;

5) Substituted or unsubstituted $-C_3$-C_8 cycloalkyl;

6) Substituted or unsubstituted aryl;

7) Substituted or unsubstituted arylalkyl;

8) Substituted or unsubstituted 3- to 8- membered heterocycloalkyl;

9) Substituted or unsubstituted heteroaryl;

10) Substituted or unsubstituted heteroarylalkyl;

11) $-C(O)R^4$;

12) $-C(O)OR^4$;

13) $-C(O)N(R^4)(R^5)$; and

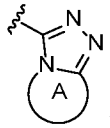
14) $-SO_2R^4$;

R^4 and R^5 are independently hydrogen, $-C_1$-C_8 alkyl, $-C_1$-C_8 alkenyl, $-C_1$-C_8 alkynyl, $-C_3$-C_8 cycloalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroarylalkyl, wherein the $-C_1$-C_8 alkyl, $-C_1$-C_8 alkenyl, $-C_1$-C_8 alkynyl, $-C_3$-C_8 cycloalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroarylalkyl is optionally substituted with 1-3 substituents independently selected from halo, alkyl, oxo, $-C_3$-C_8 cycloalkyl, alkylamino, dialkylamino, alkyl-C(O)-NH-, aryl-C(O)NH-, heteroaryl-C(O)NH-, heterocycloalkyl, heteroceycloalkyl-C(O)-, -OH, $-CN$, alkoxy, $-CF_3$, aryl, and heteroaryl; alternatively R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocycloalkyl;

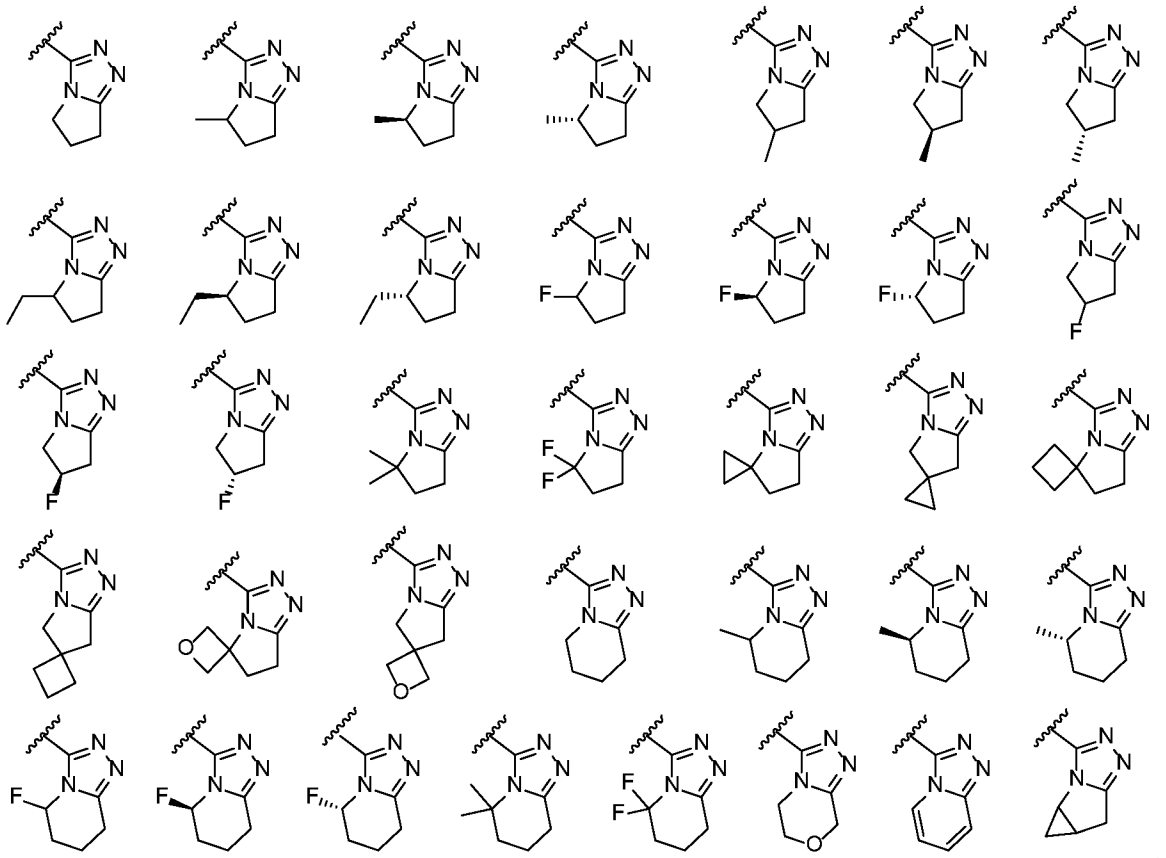
R^8 and R^9 are each independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted $-C_1$-C_8 alkyl; alternatively, R^8 and R^9 are taken together with the carbon atom to which they are attached to form C(O), spiro$-C_3$-C_8 cycloalkyl, or spiro-3- to 8- membered heterocycloalkyl;

R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, halo, and optionally substituted $-C_1$-C_8 alkyl; and

n is 0, 1 or 2.

2. The compound of claim 1, wherein 

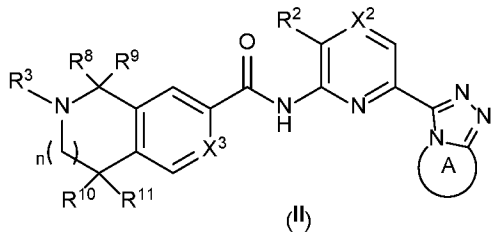
is selected from the groups below:



,

wherein each of the above shown groups is optionally substituted.

3. The compound of claim 1, represented by Formula II or a pharmaceutically acceptable salt thereof:

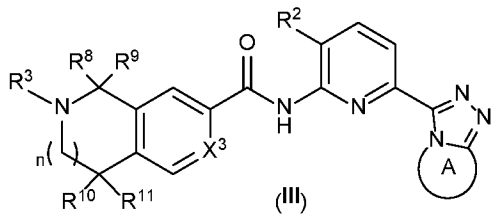


(II)

,

wherein A, R^2, R^3, R^8, R^9, R^{10}, R^{11}, X^2, X^3 and n are as defined in claim 1.

4. The compound of claim 1, represented by Formula III or a pharmaceutically acceptable salt thereof:

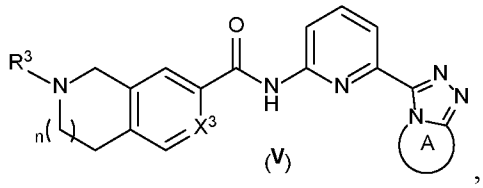


(III)

,

wherein A, R^2, R^3, R^8, R^9, R^{10}, R^{11}, X^3 and n are as defined in claim 1.

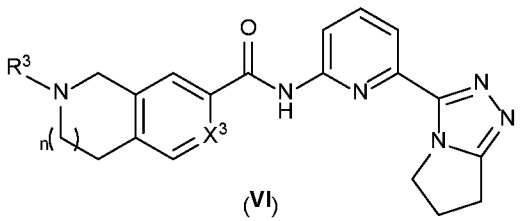
5. The compound of claim 1, represented by Formula V or a pharmaceutically acceptable salt thereof:



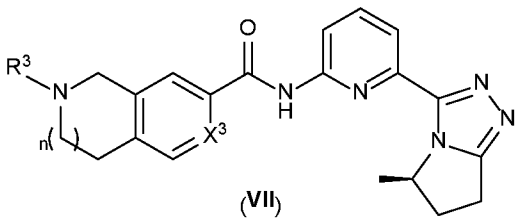
(V)

wherein A, R^3, X^3, and n are as defined in claim 1.

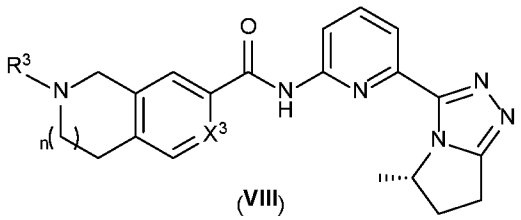
6. The compound of claim 1, which is selected from compounds of Formula VI, Formula VII, Formula VIII, Formula IX, Formula X, or pharmaceutically acceptable salt thereof:



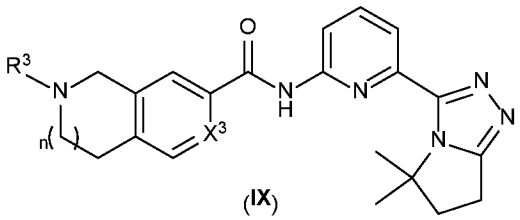
(VI)



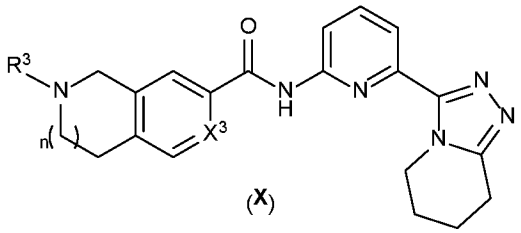
(VII)



(VIII)



(IX)

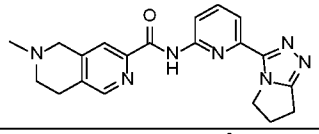
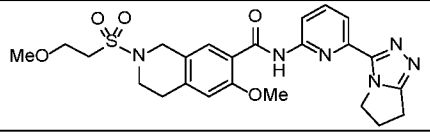
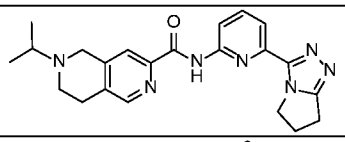
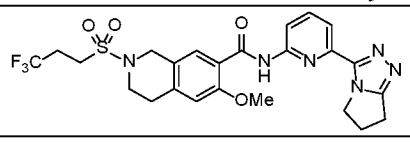
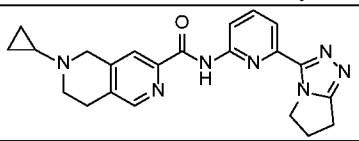
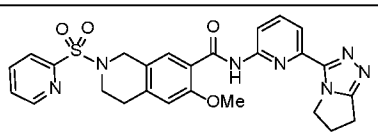
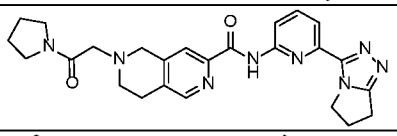
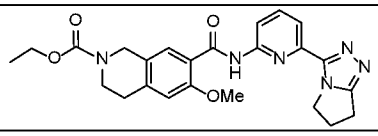
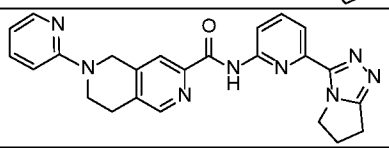
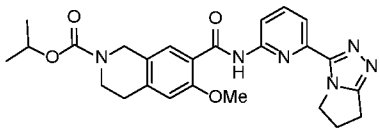
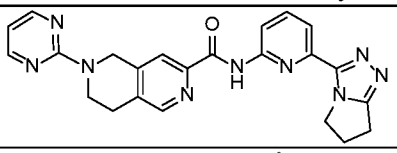
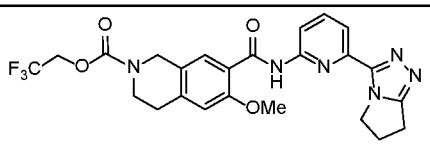
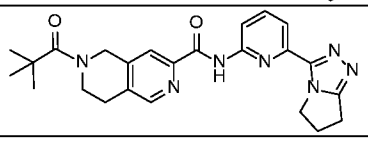
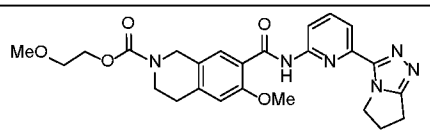
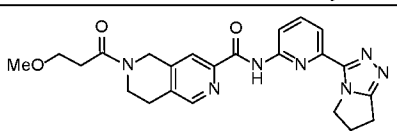
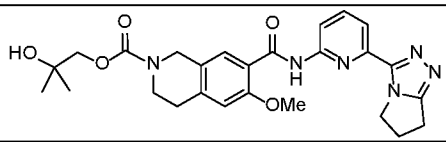
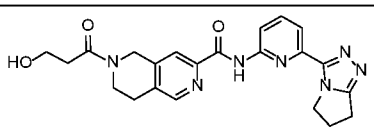
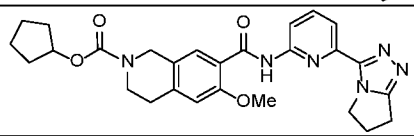
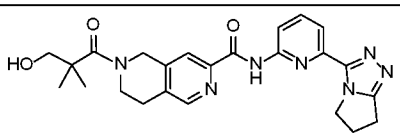
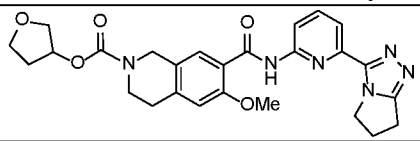
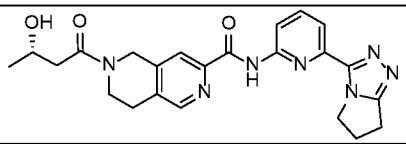
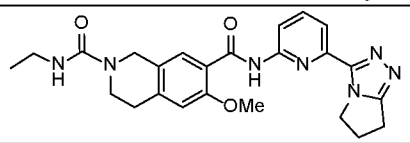
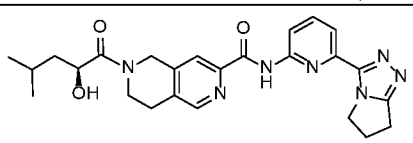
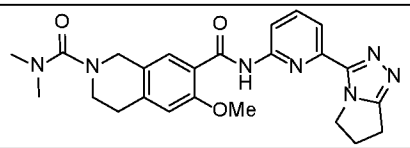
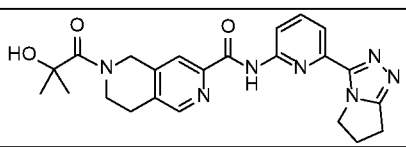
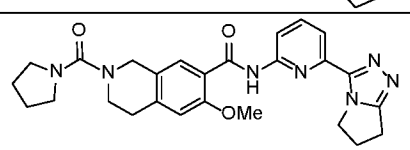


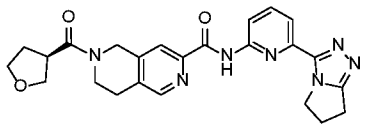
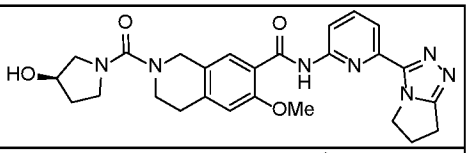
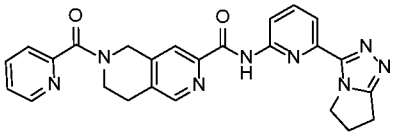
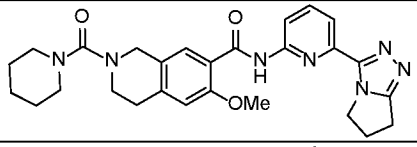
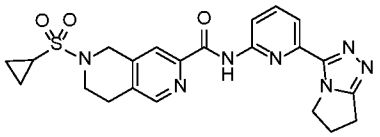
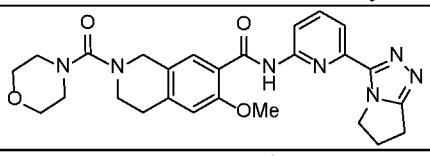
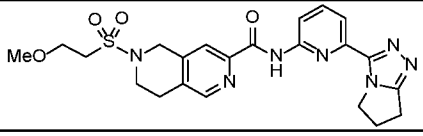
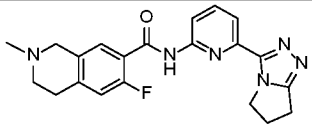
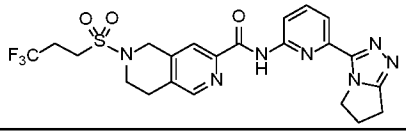
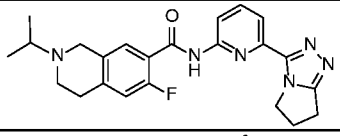
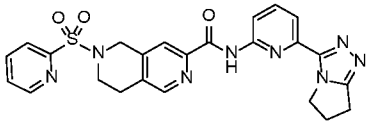
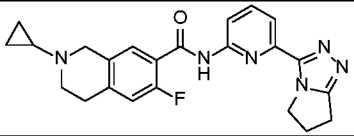
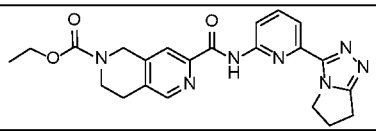
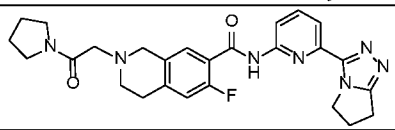
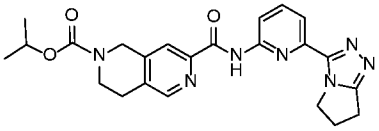
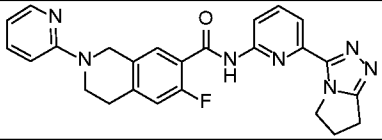
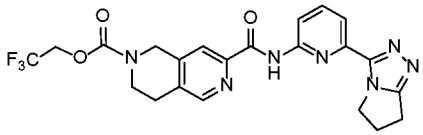
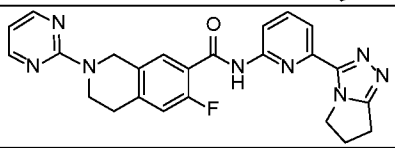
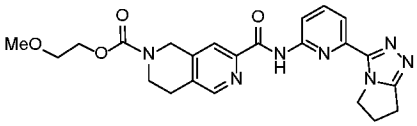
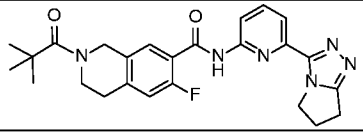
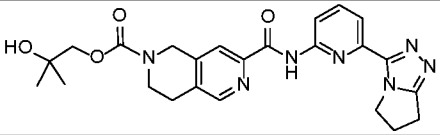
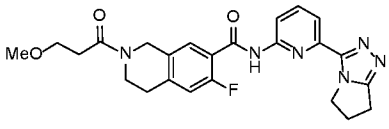
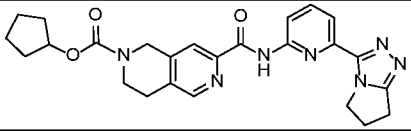
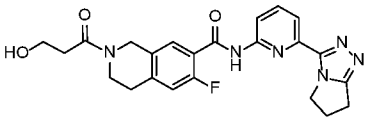
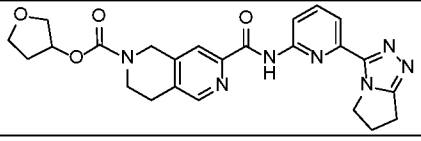
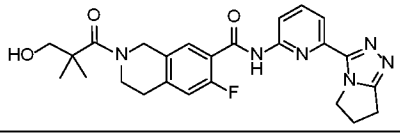
(X)

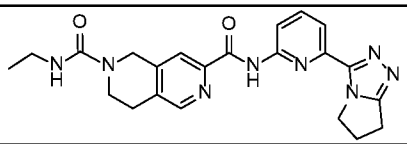
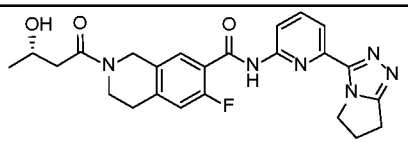
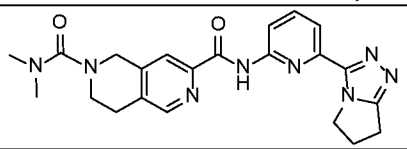
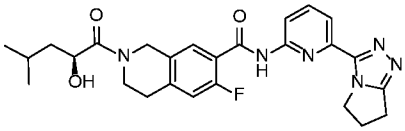
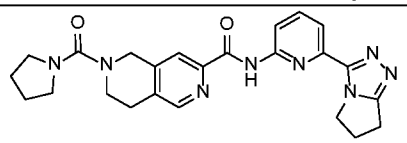
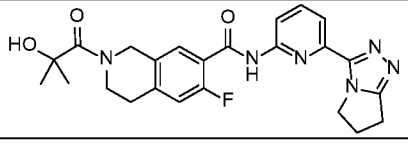
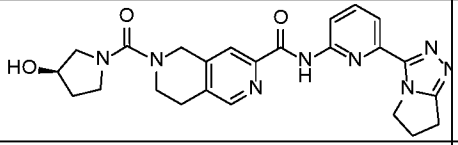
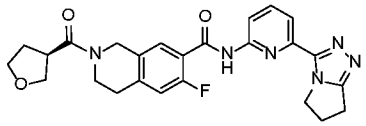
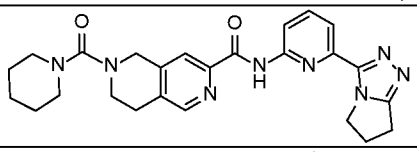
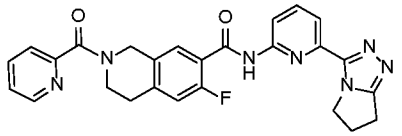
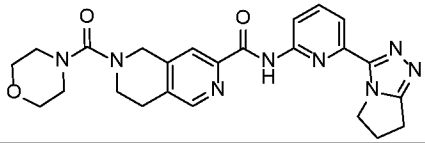
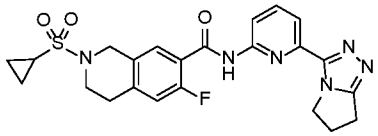
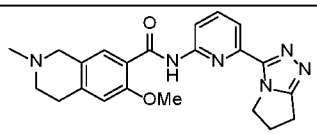
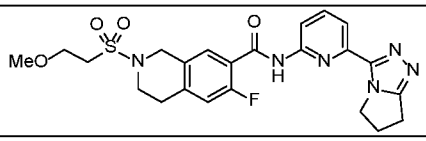
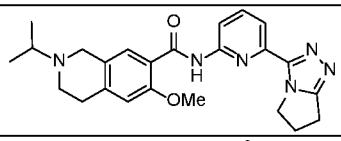
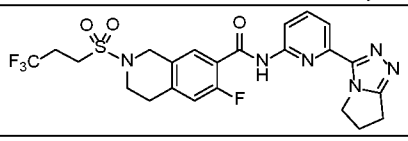
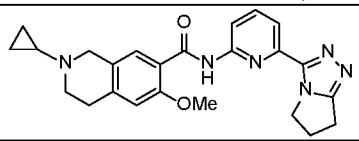
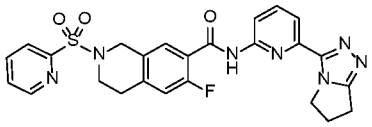
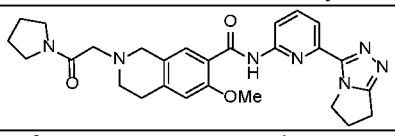
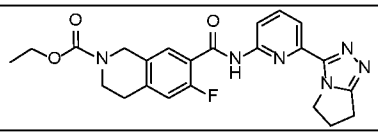
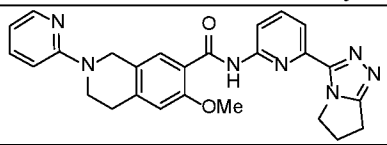
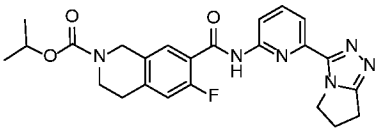
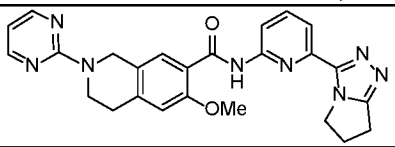
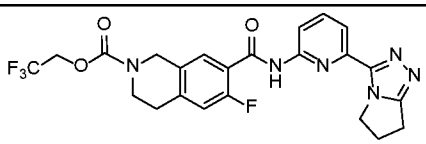
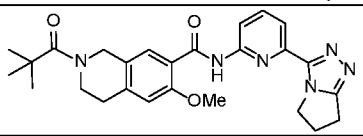
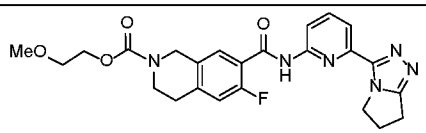
wherein X^3, R^3, and n are as defined in claim 1.

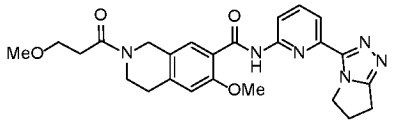
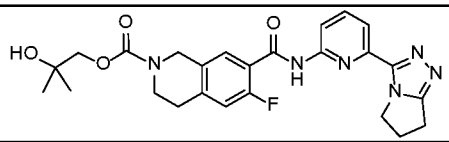
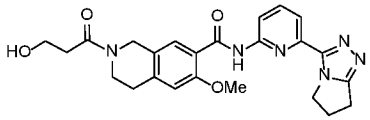
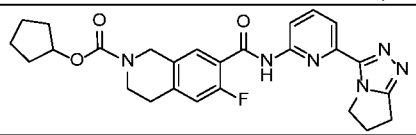
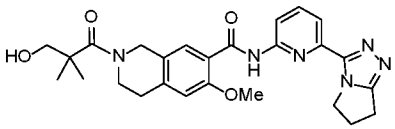
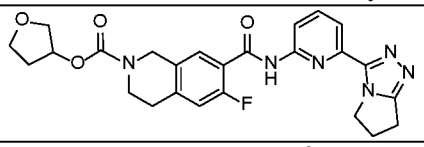
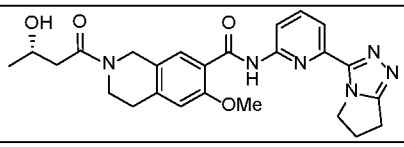
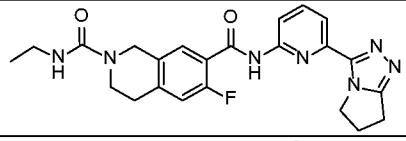
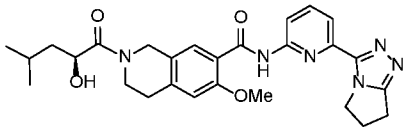
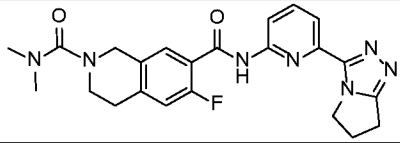
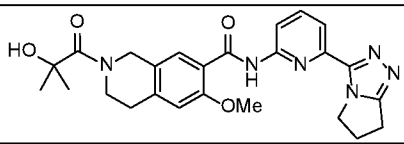
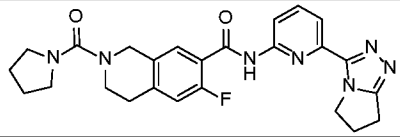
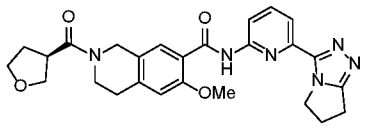
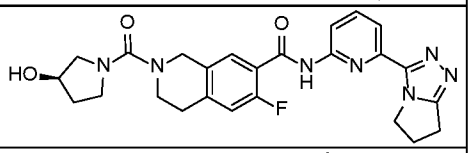
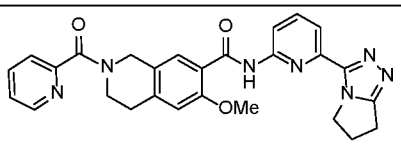
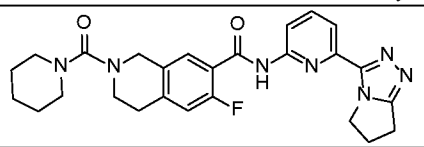
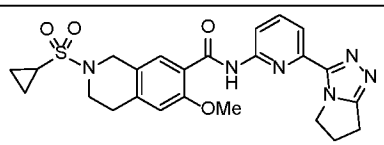
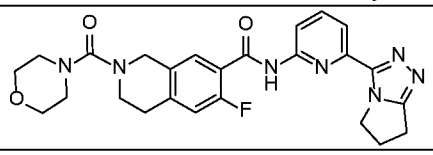
7. The compound of claim 1, which is selected from the compounds set forth in Table 1, or a pharmaceutically acceptable salt thereof:

Table 1

compound	Structure	compound	Structure
1		49	
2		50	
3		51	
4		52	
5		53	
6		54	
7		55	
8		56	
9		57	
10		58	
11		59	
12		60	
13		61	

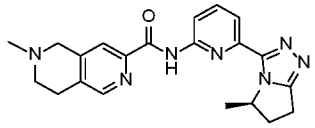
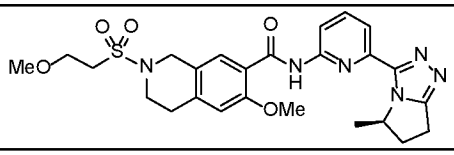
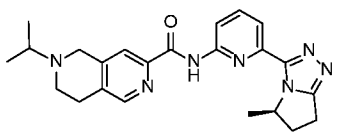
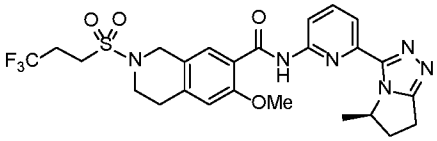
14		62	
15		63	
16		64	
17		65	
18		66	
19		67	
20		68	
21		69	
22		70	
23		71	
24		72	
25		73	
26		74	

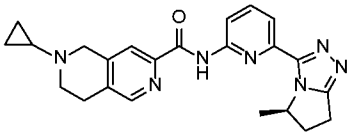
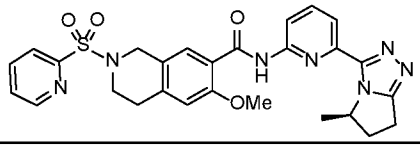
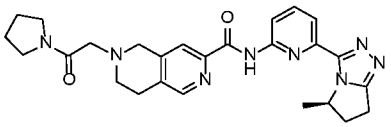
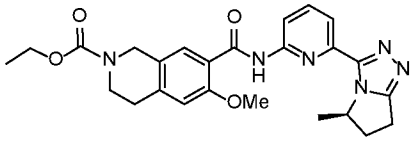
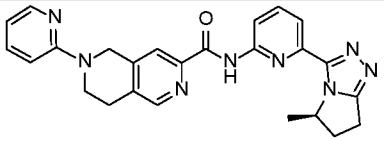
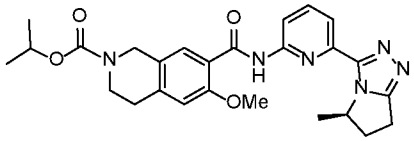
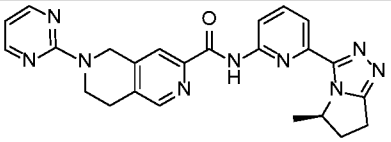
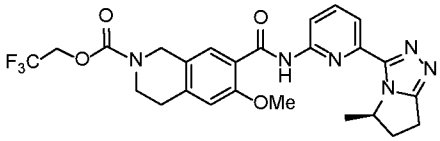
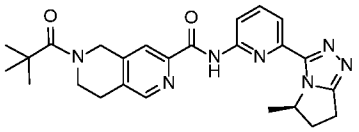
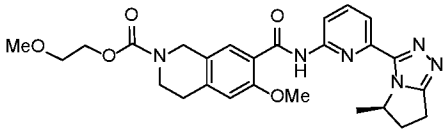
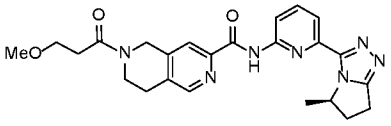
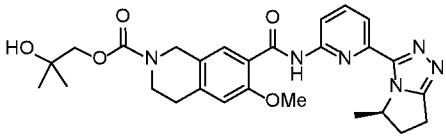
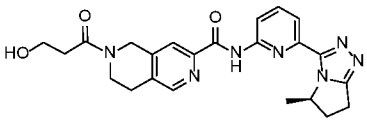
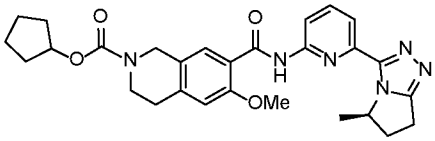
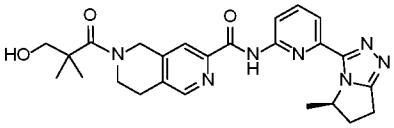
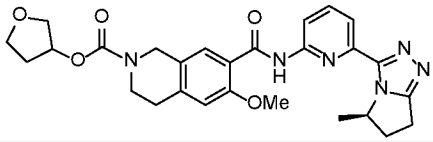
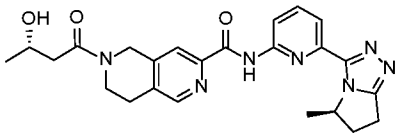
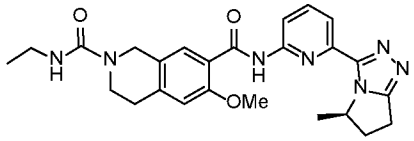
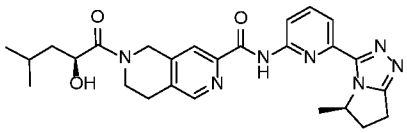
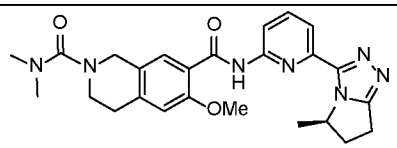
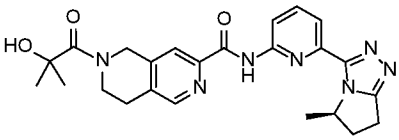
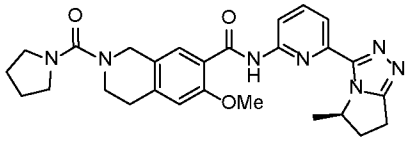
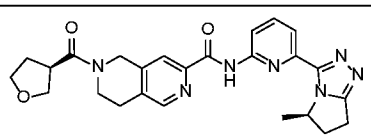
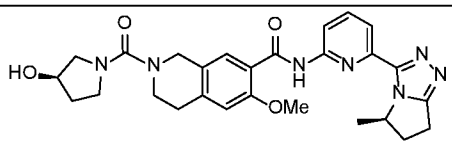
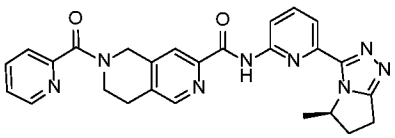
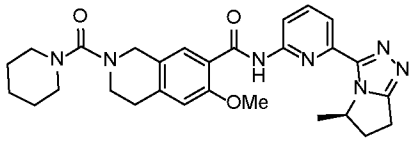
27		75	
28		76	
29		77	
30		78	
31		79	
32		80	
33		81	
34		82	
35		83	
36		84	
37		85	
38		86	
39		87	

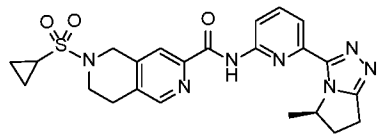
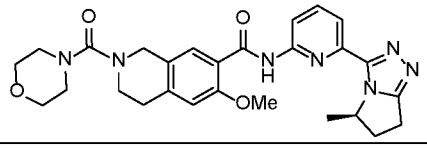
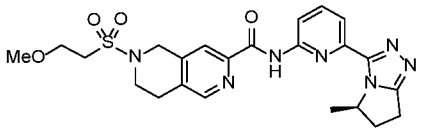
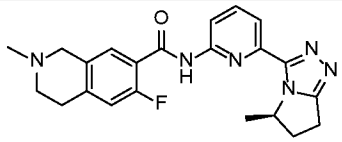
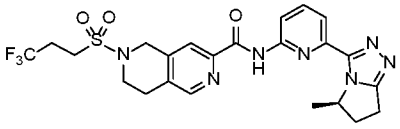
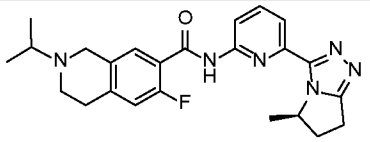
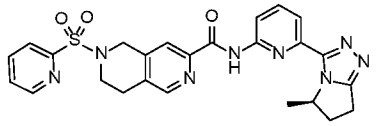
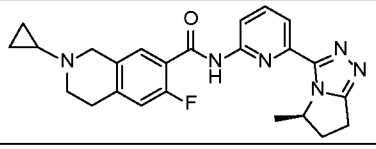
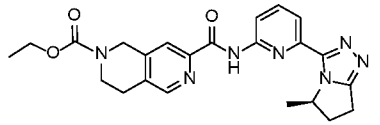
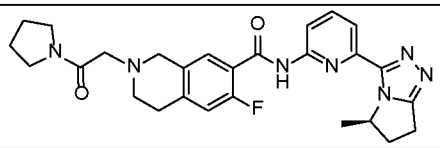
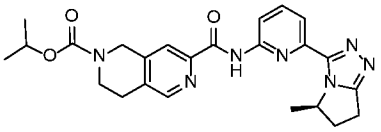
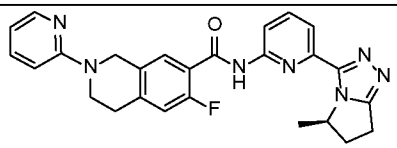
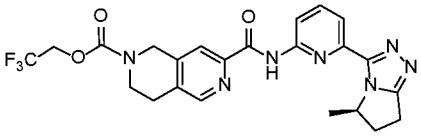
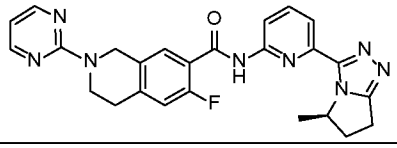
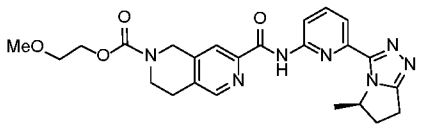
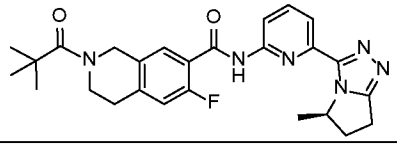
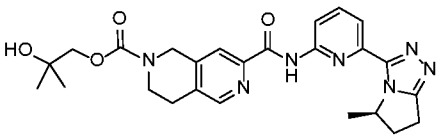
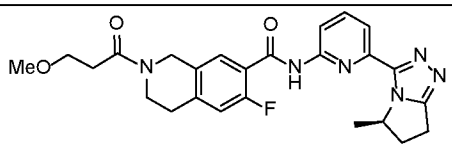
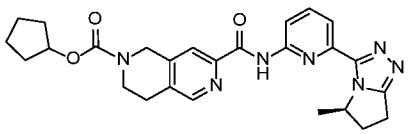
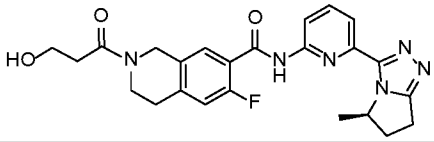
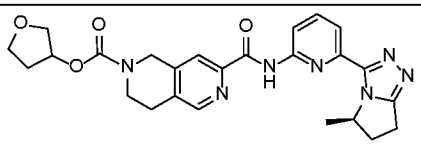
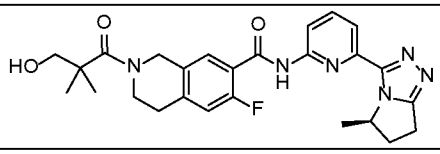
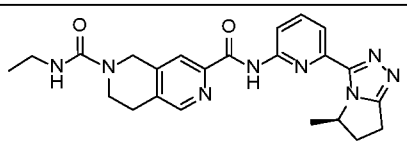
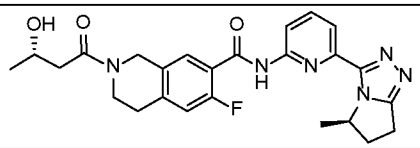
40		88	
41		89	
42		90	
43		91	
44		92	
45		93	
46		94	
47		95	
48		96	

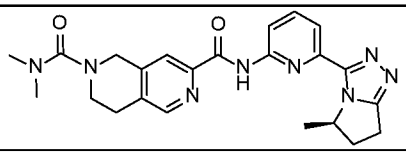
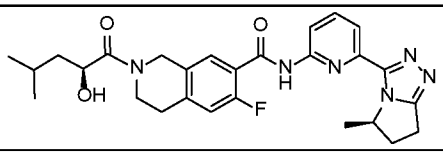
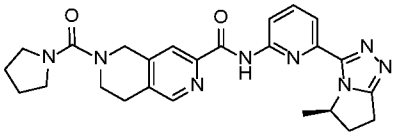
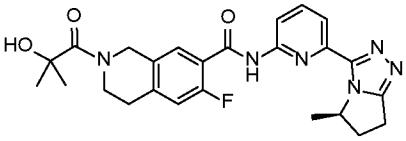
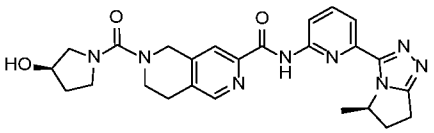
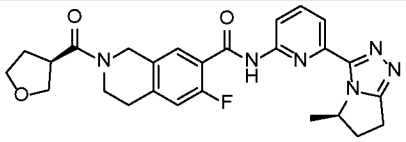
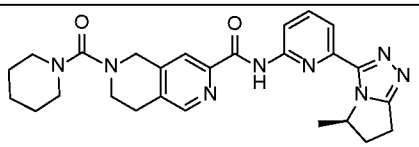
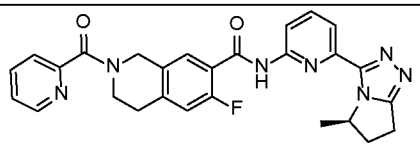
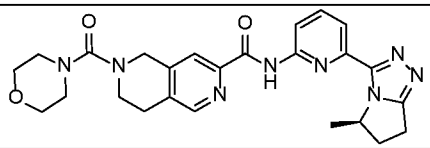
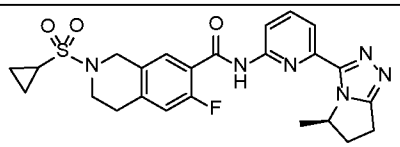
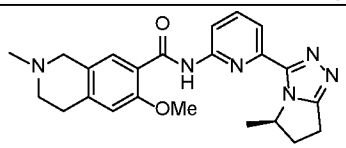
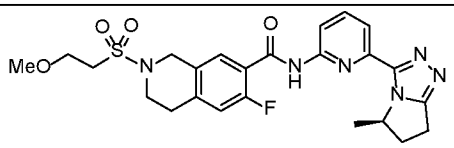
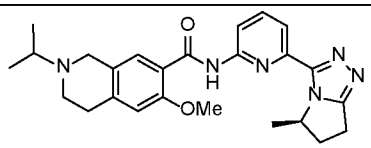
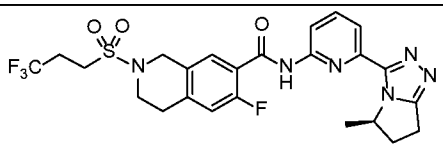
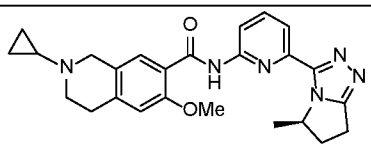
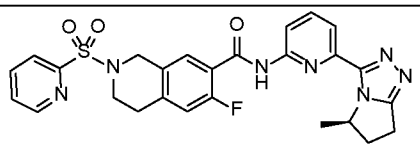
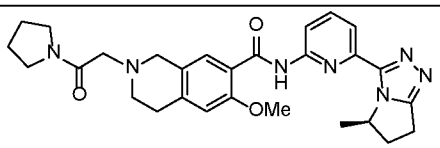
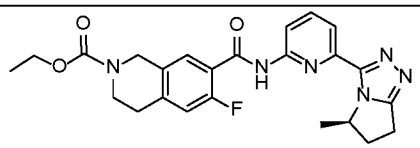
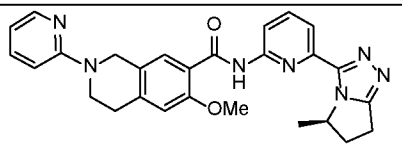
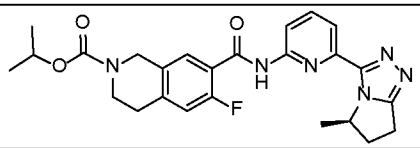
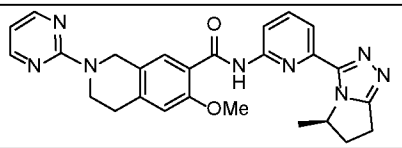
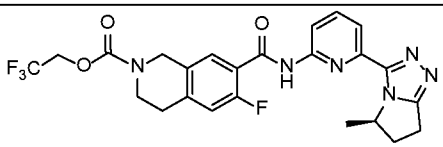
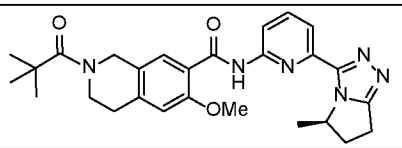
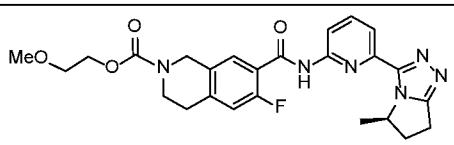
8. The compound of claim 1, which is selected from the compounds set forth in Table 2, or a pharmaceutically acceptable salt thereof:

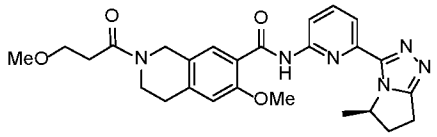
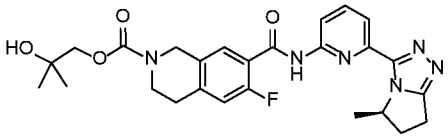
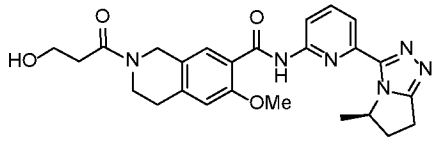
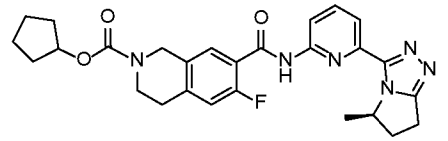
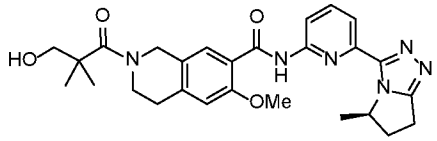
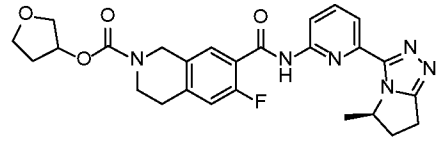
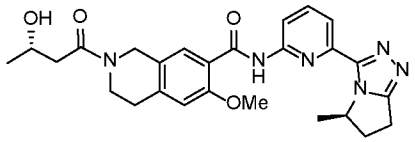
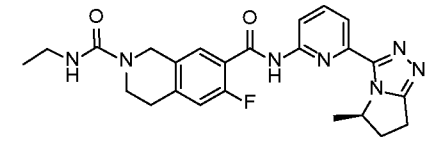
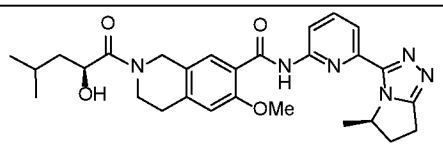
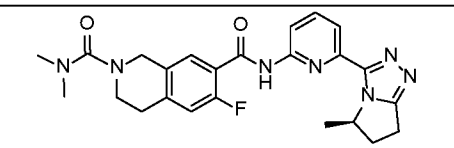
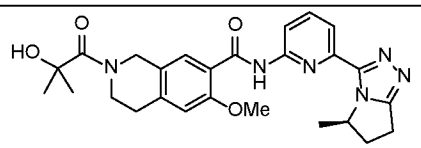
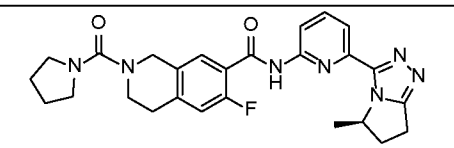
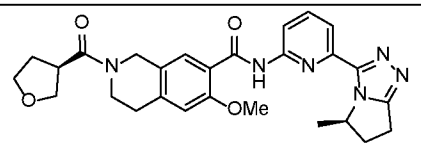
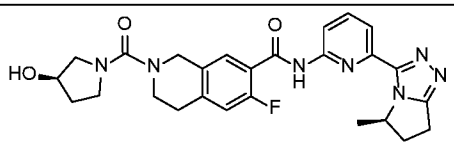
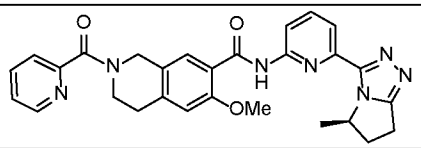
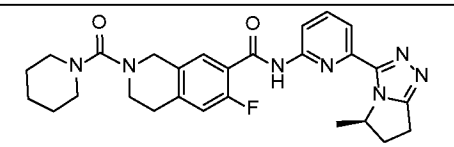
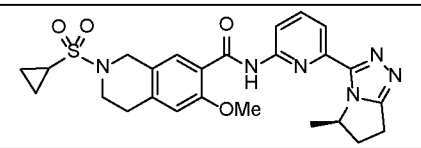
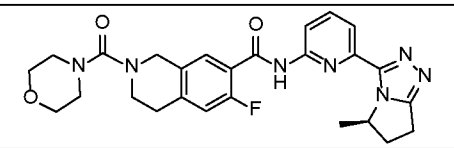
Table 2

compound	Structure	compound	Structure
97		145	
98		146	

99		147	
100		148	
101		149	
102		150	
103		151	
104		152	
105		153	
106		154	
107		155	
108		156	
109		157	
110		158	
111		159	

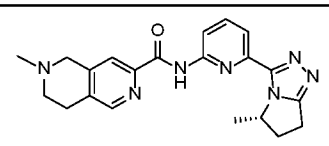
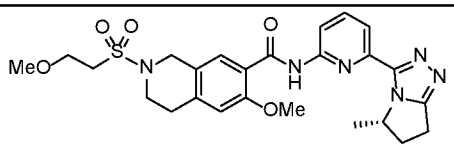
112		160	
113		161	
114		162	
115		163	
116		164	
117		165	
118		166	
119		167	
120		168	
121		169	
122		170	
123		171	

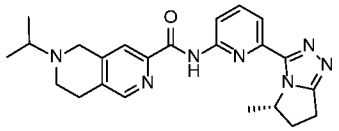
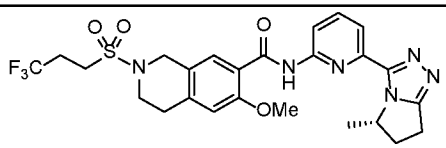
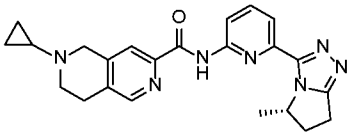
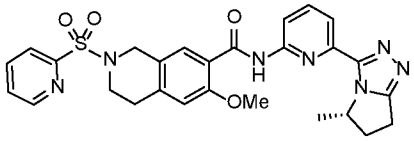
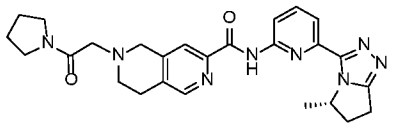
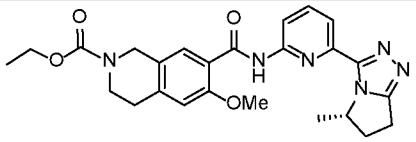
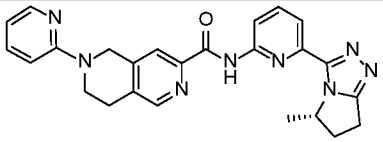
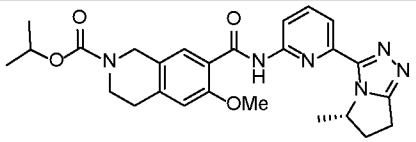
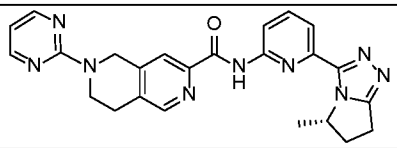
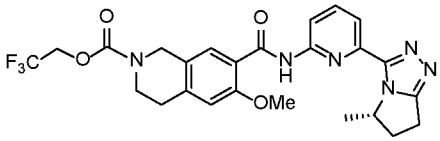
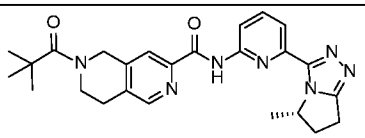
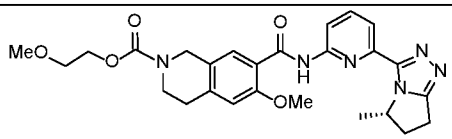
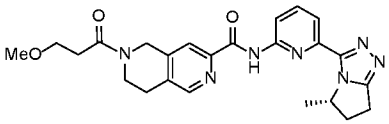
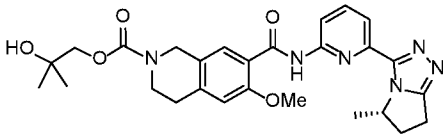
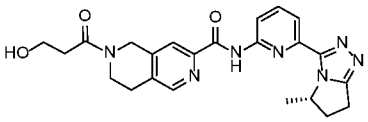
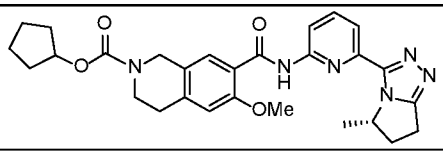
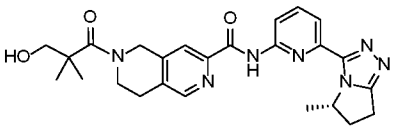
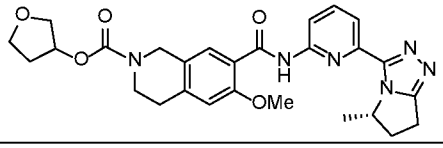
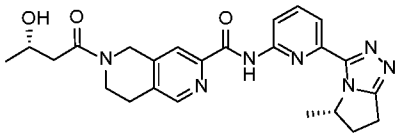
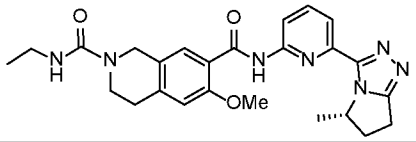
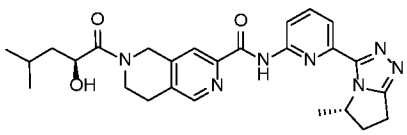
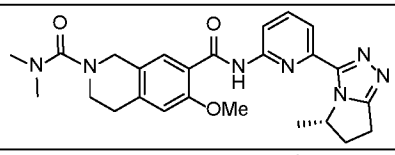
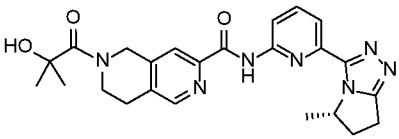
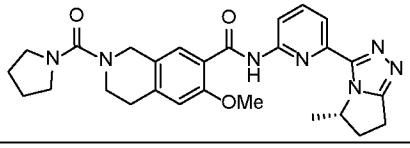
124		172	
125		173	
126		174	
127		175	
128		176	
129		177	
130		178	
131		179	
132		180	
133		181	
134		182	
135		183	

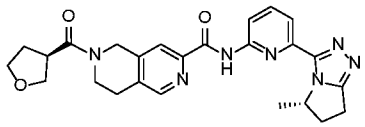
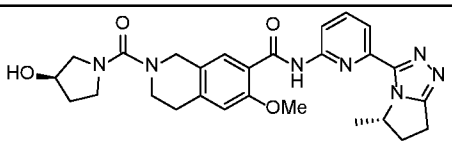
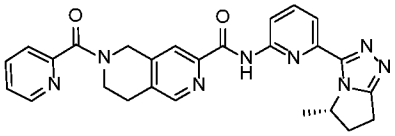
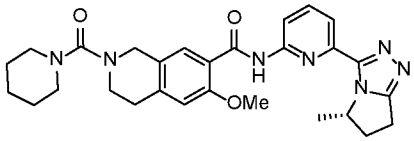
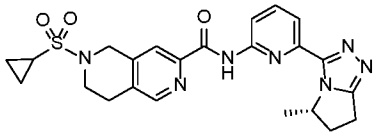
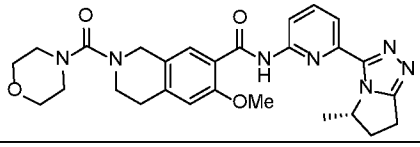
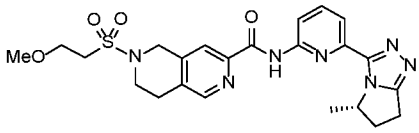
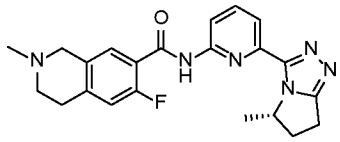
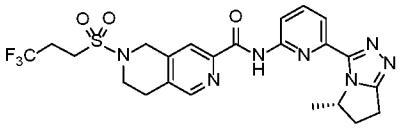
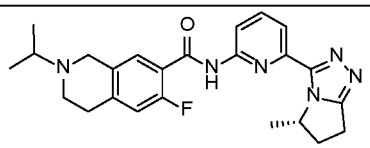
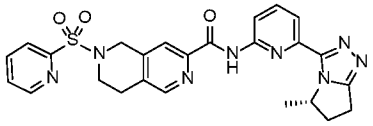
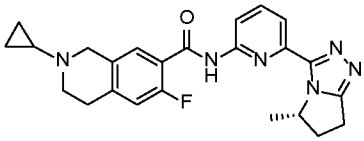
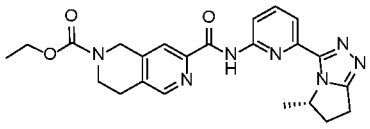
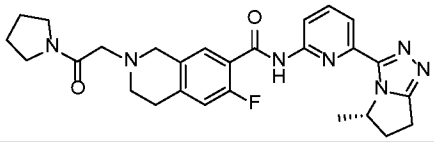
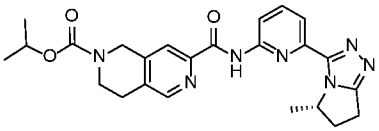
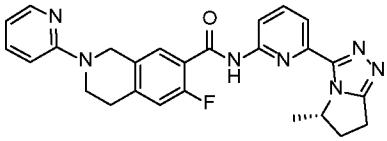
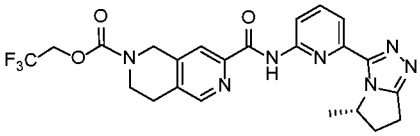
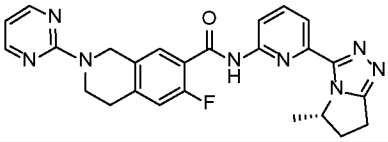
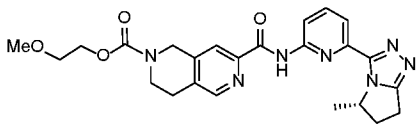
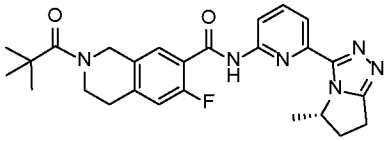
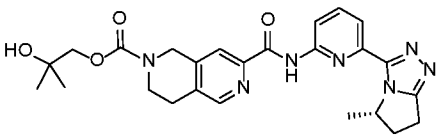
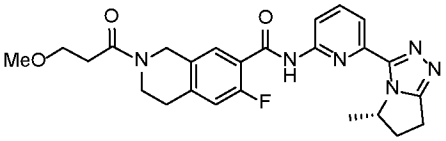
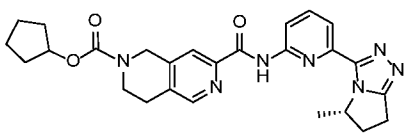
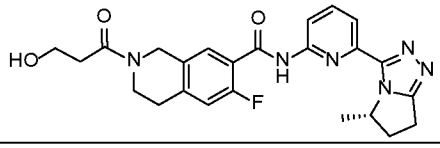
136		184	
137		185	
138		186	
139		187	
140		188	
141		189	
142		190	
143		191	
144		192	

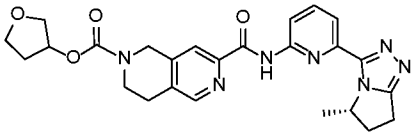
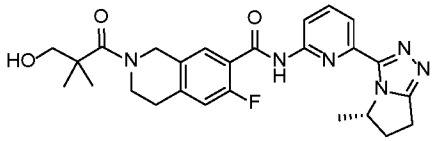
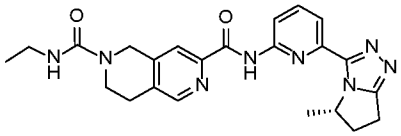
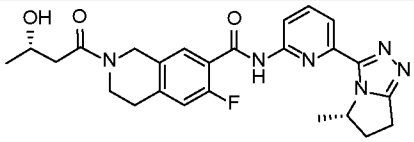
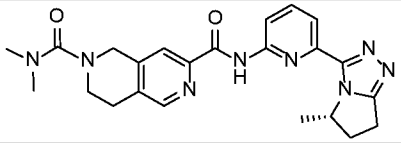
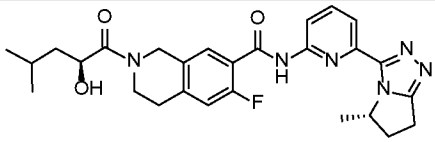
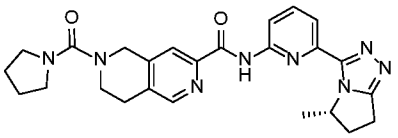
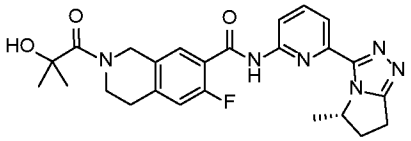
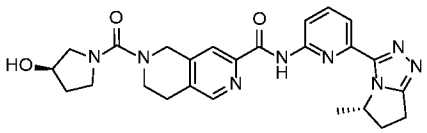
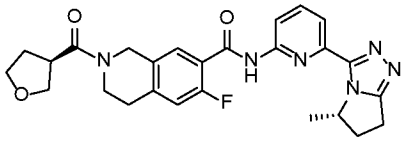
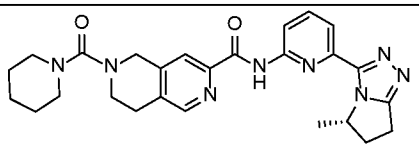
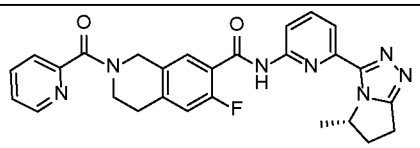
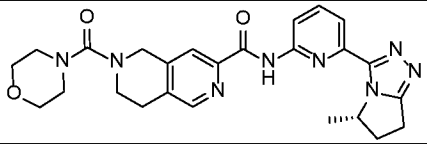
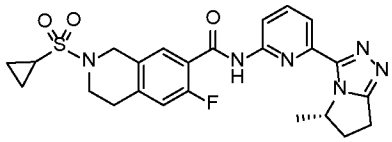
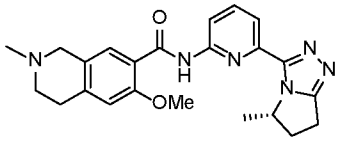
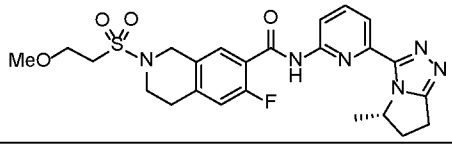
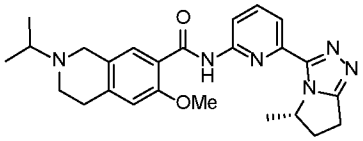
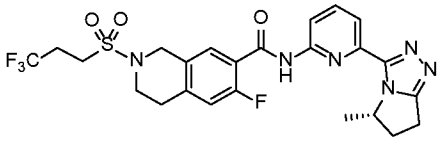
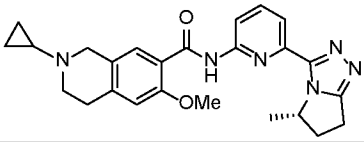
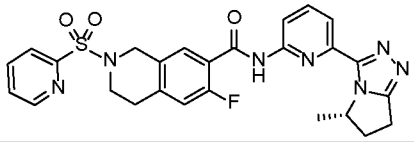
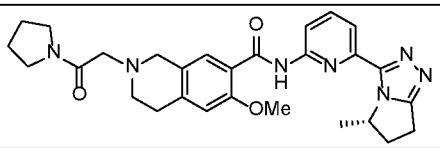
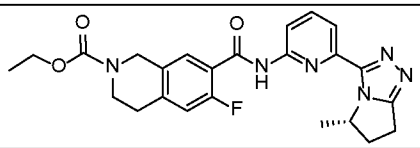
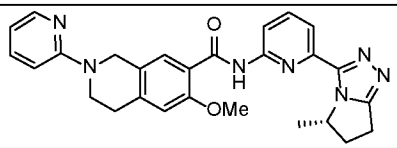
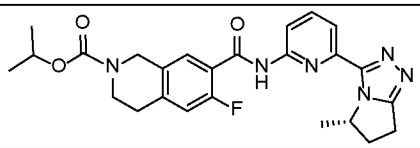
9. The compound of claim 1, selected from the compounds set forth in Table 3, or a pharmaceutically acceptable salt thereof:

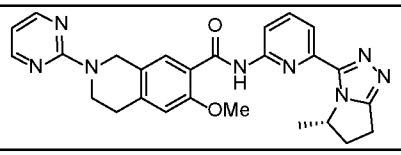
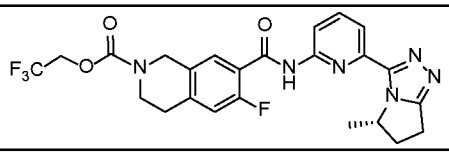
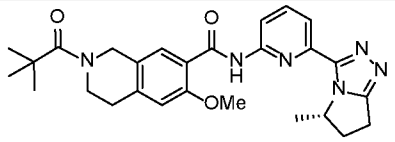
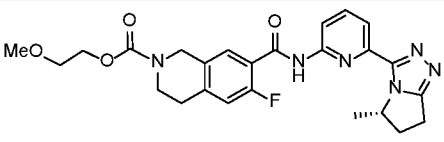
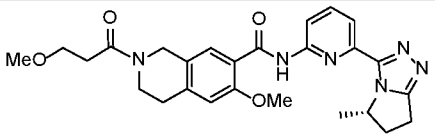
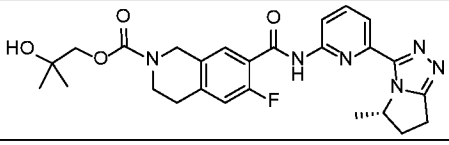
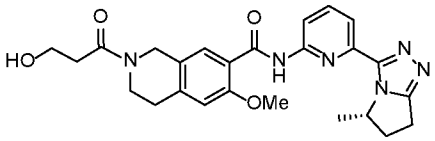
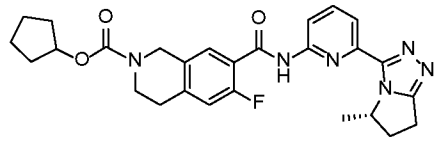
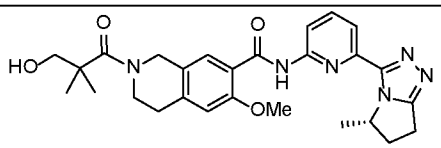
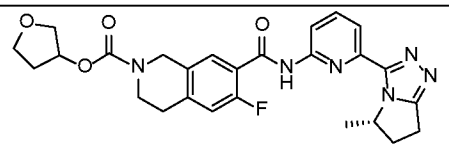
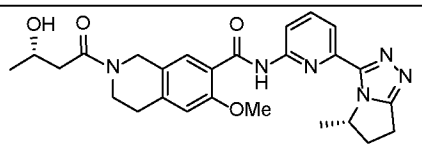
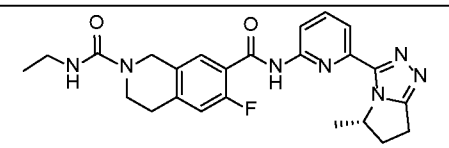
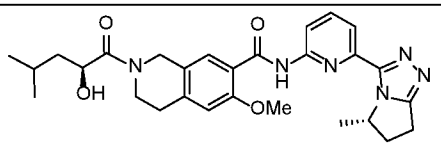
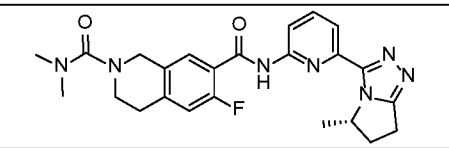
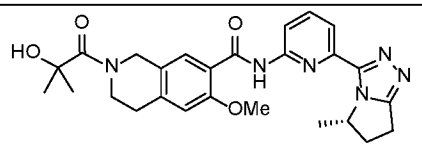
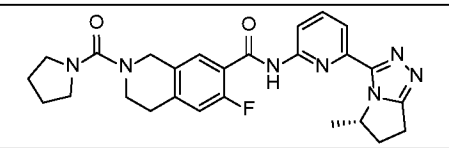
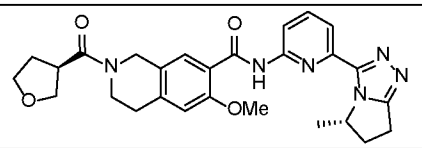
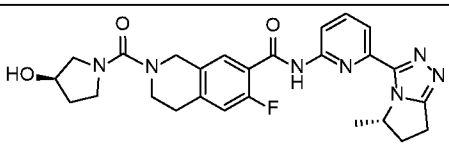
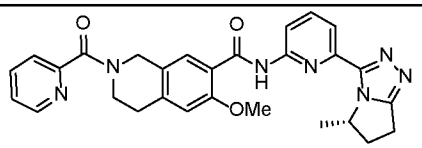
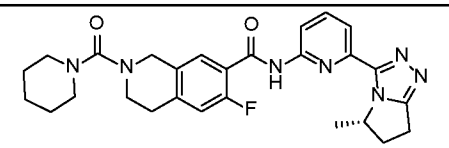
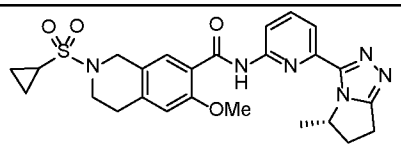
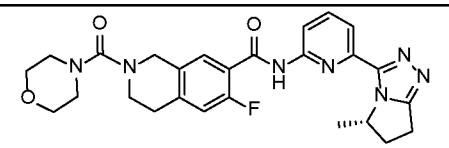
Table 3

compound	Structure	compound	Structure
193		241	

194		242	
195		243	
196		244	
197		245	
198		246	
199		247	
200		248	
201		249	
202		250	
203		251	
204		252	
205		253	

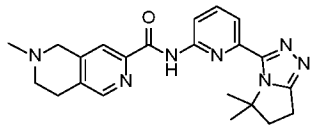
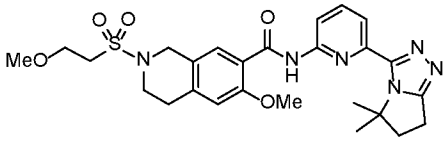
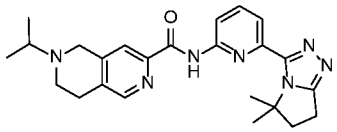
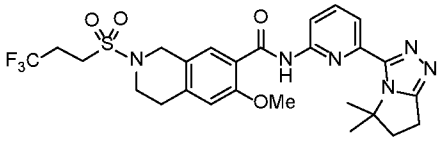
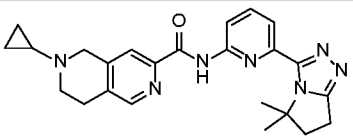
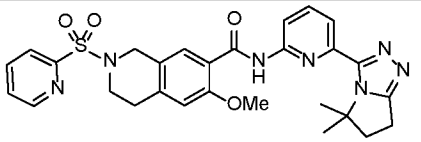
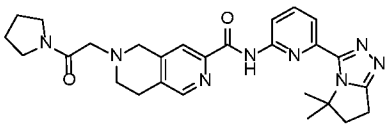
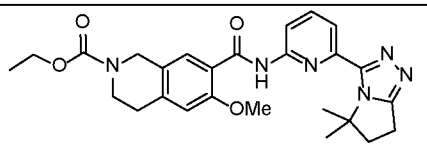
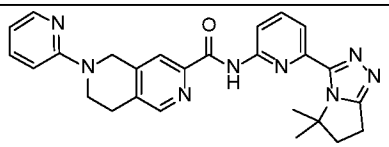
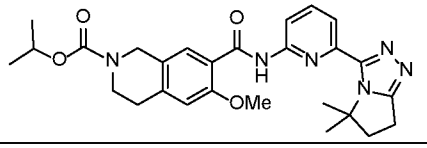
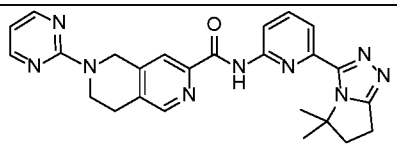
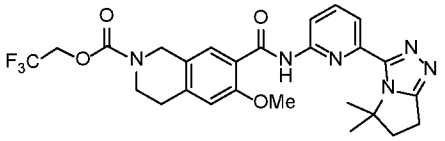
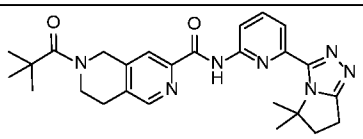
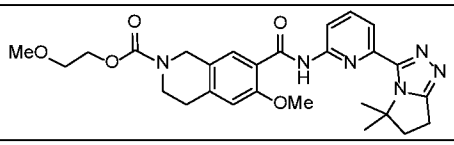
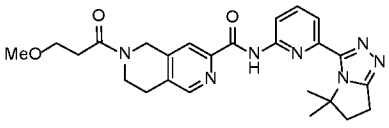
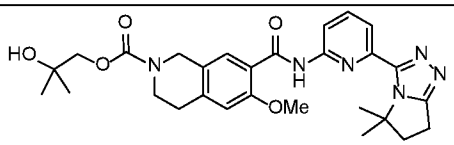
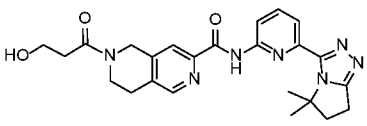
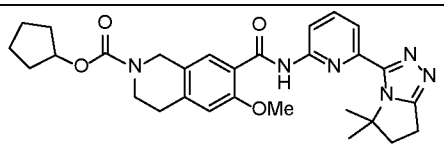
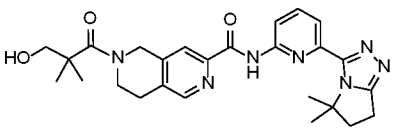
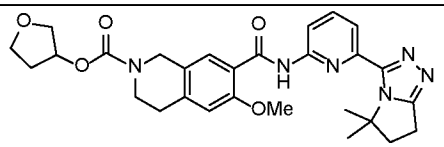
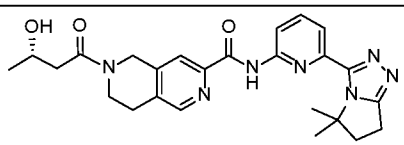
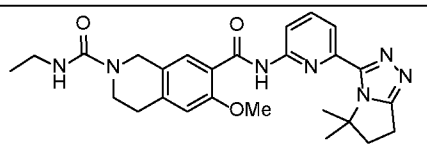
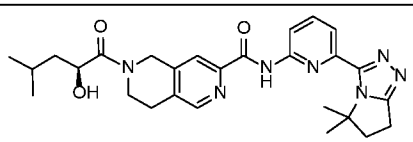
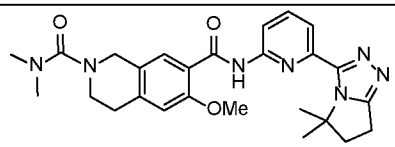
206		254	
207		255	
208		256	
209		257	
210		258	
211		259	
212		260	
213		261	
214		262	
215		263	
216		264	
217		265	

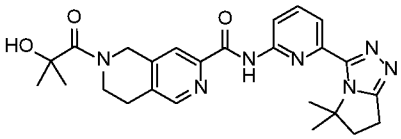
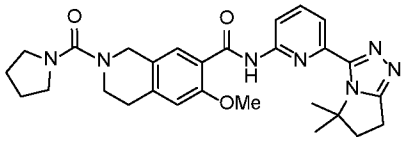
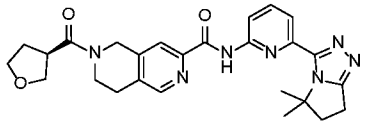
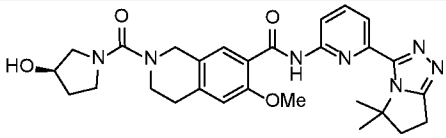
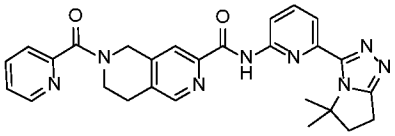
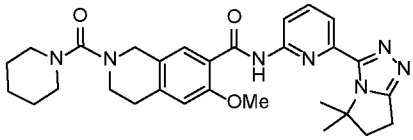
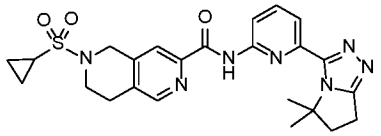
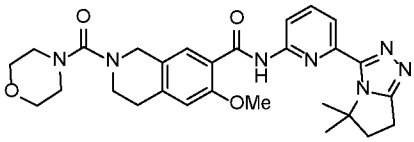
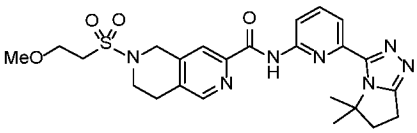
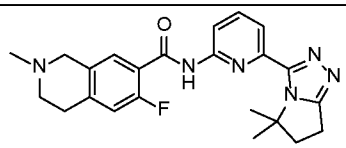
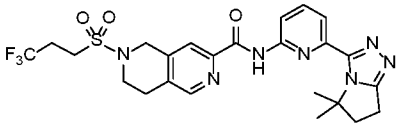
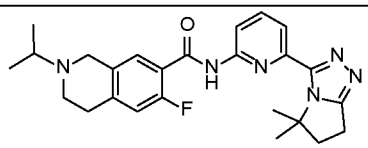
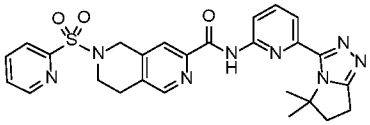
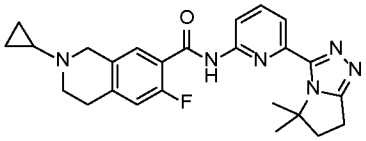
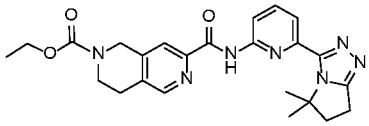
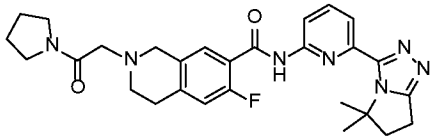
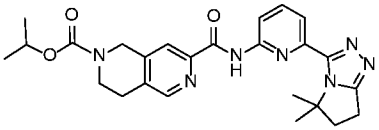
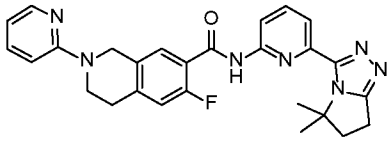
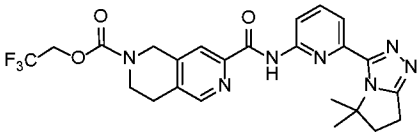
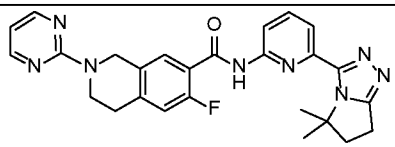
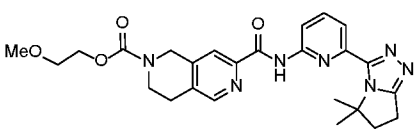
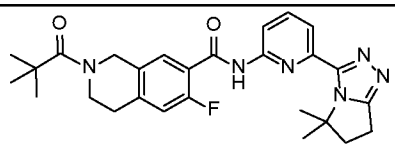
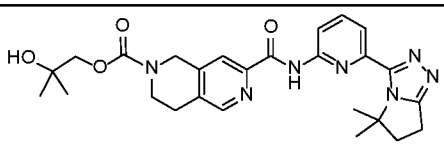
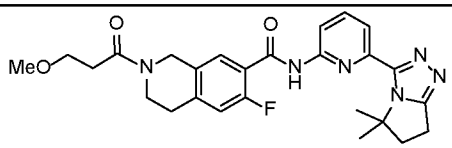
218		266	
219		267	
220		268	
221		269	
222		270	
223		271	
224		272	
225		273	
226		274	
227		275	
228		276	
229		277	

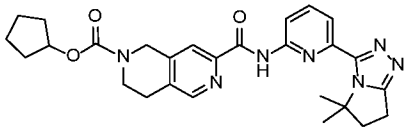
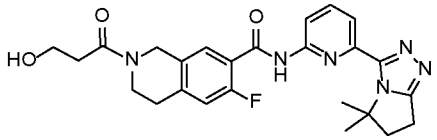
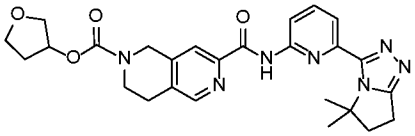
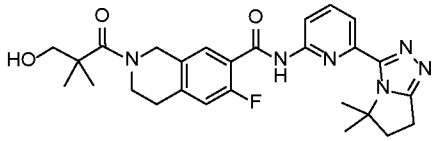
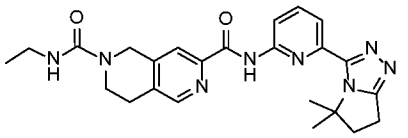
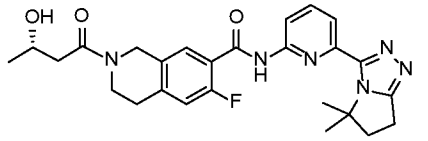
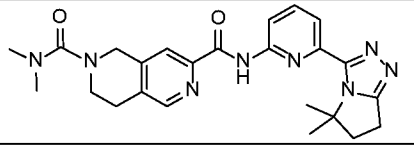
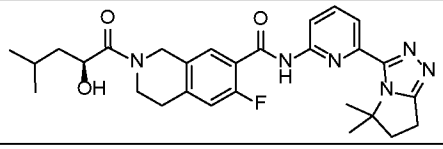
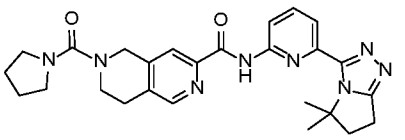
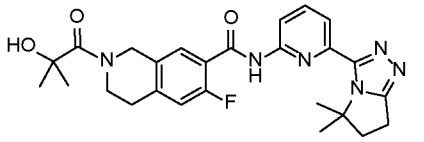
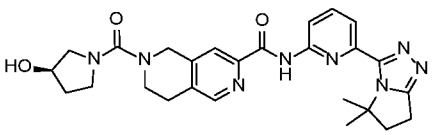
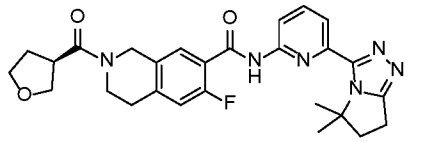
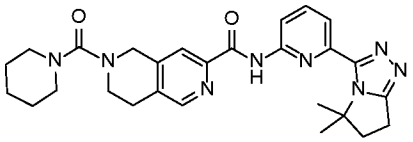
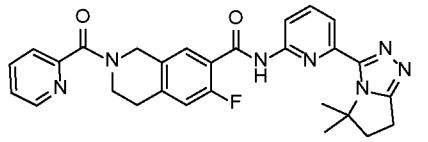
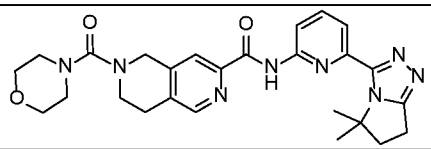
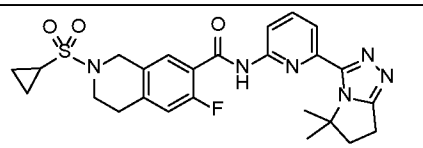
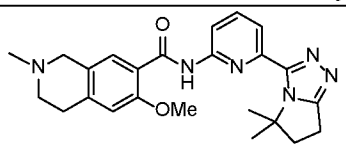
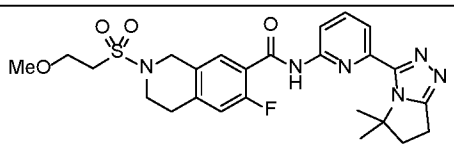
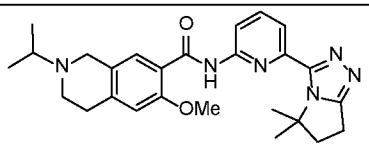
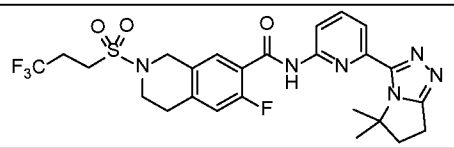
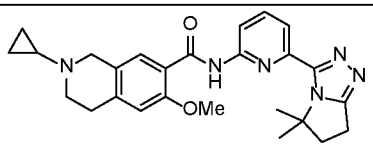
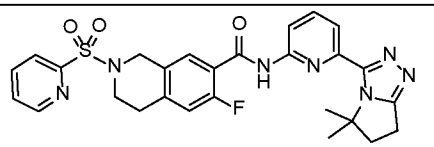
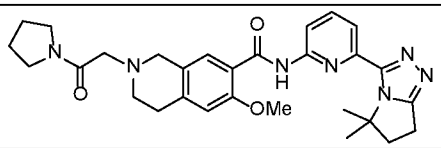
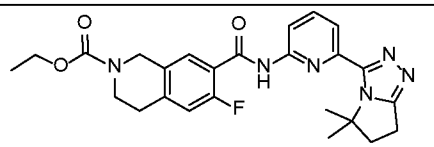
230		278	
231		279	
232		280	
233		281	
234		282	
235		283	
236		284	
237		285	
238		286	
239		287	
240		288	

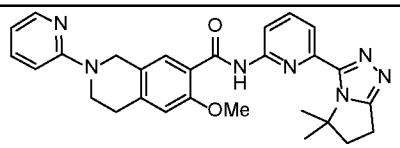
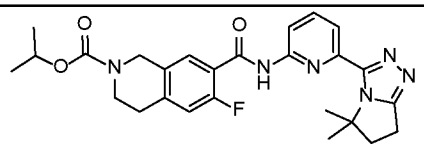
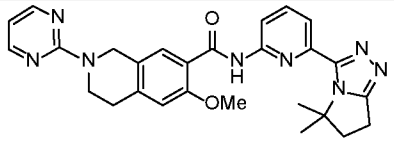
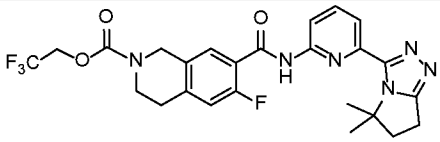
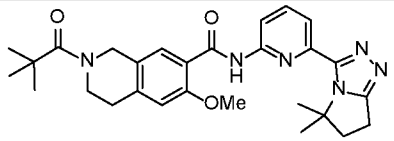
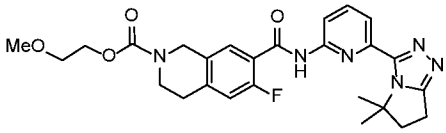
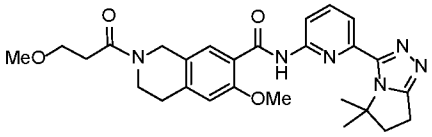
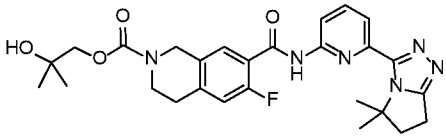
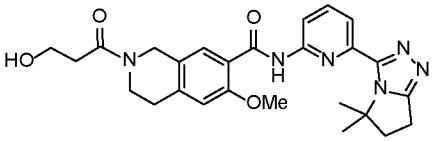
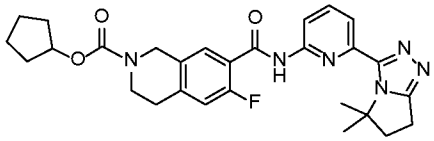
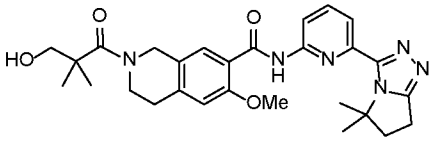
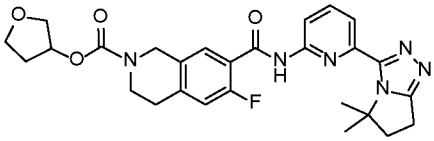
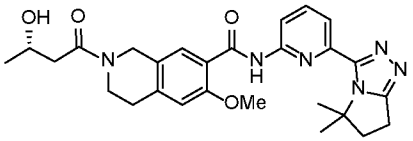
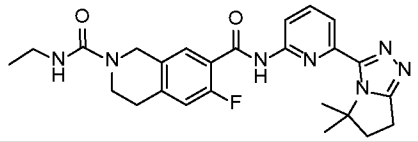
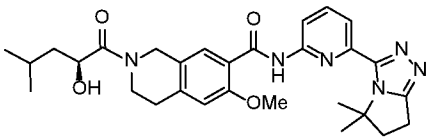
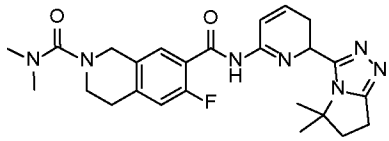
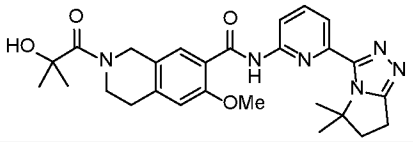
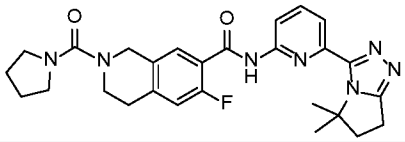
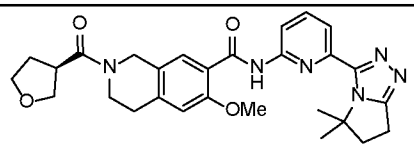
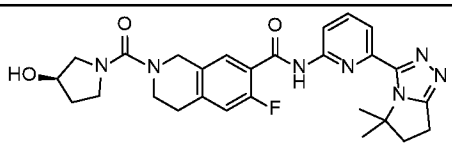
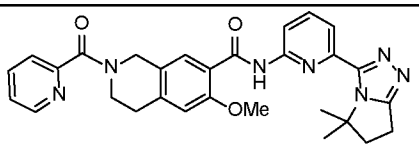
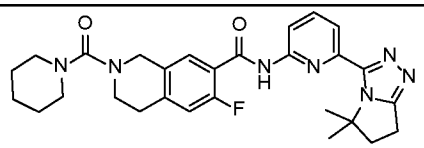
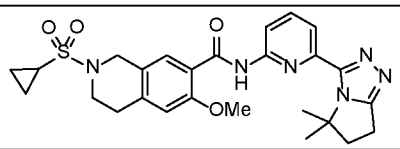
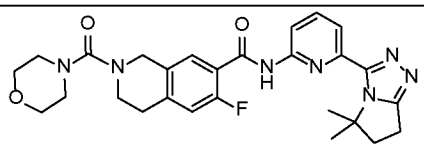
10. The compound of claim 1, selected from the compounds set forth in Table 4, or a pharmaceutically acceptable salt thereof:

Table 4

compound	Structure	compound	Structure
289		337	
290		338	
291		339	
292		340	
293		341	
294		342	
295		343	
296		344	
297		345	
298		346	
299		347	
300		348	

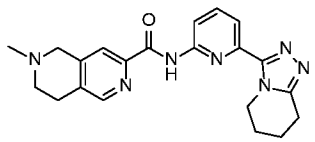
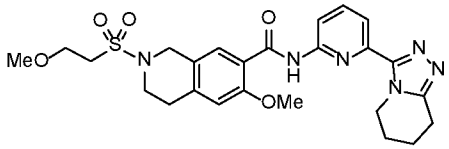
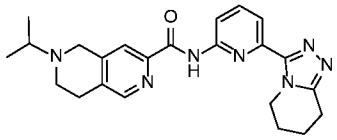
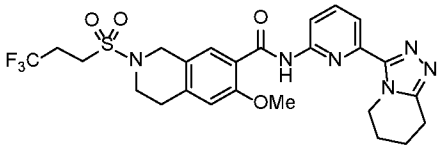
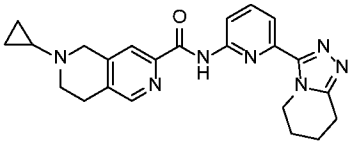
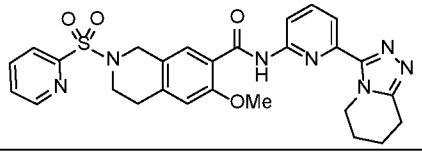
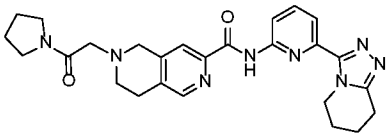
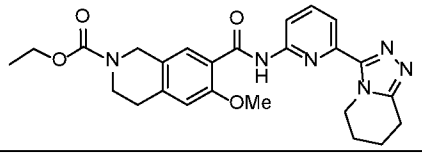
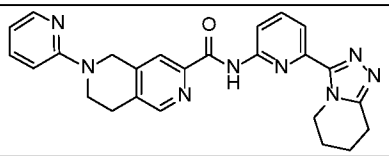
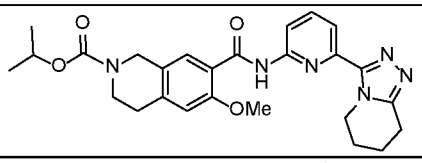
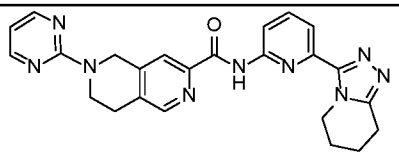
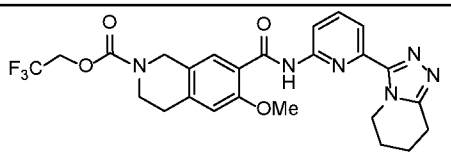
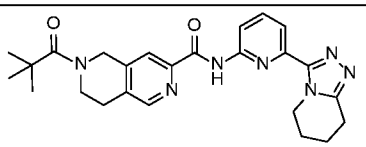
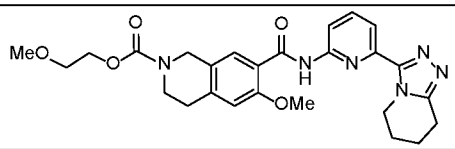
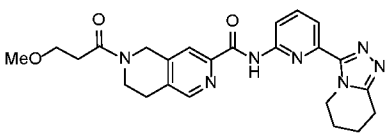
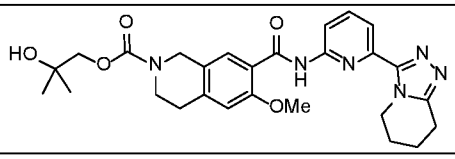
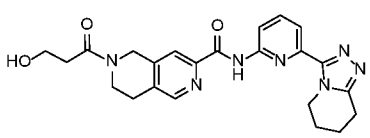
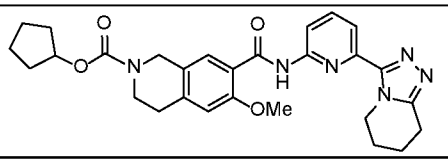
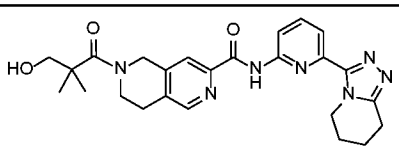
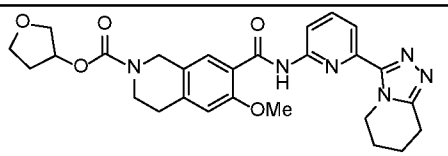
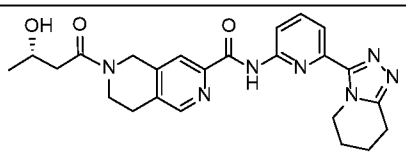
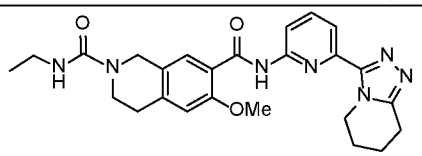
301		349	
302		350	
303		351	
304		352	
305		353	
306		354	
307		355	
308		356	
309		357	
310		358	
311		359	
312		360	

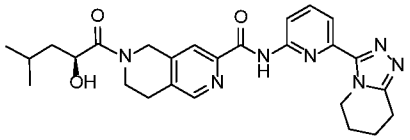
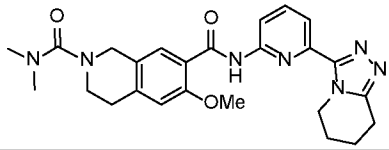
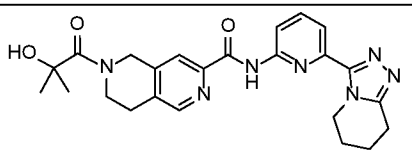
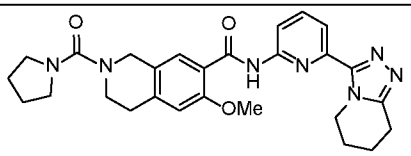
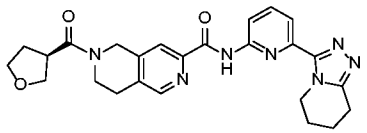
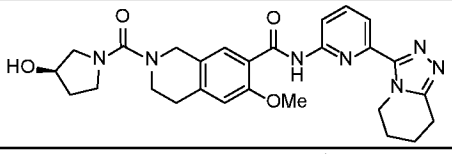
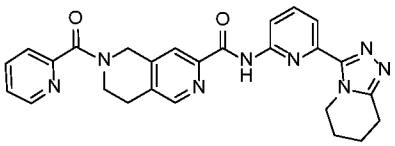
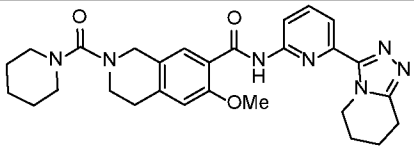
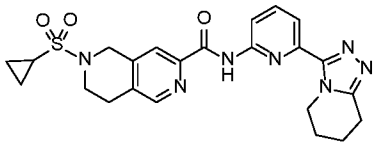
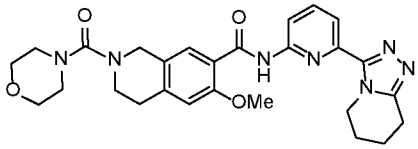
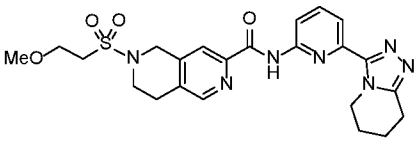
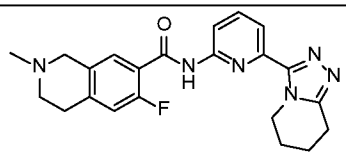
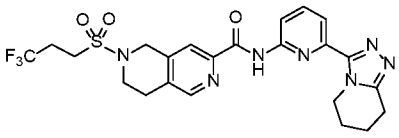
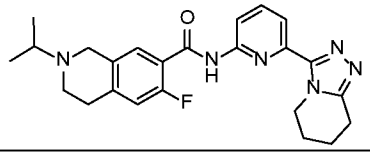
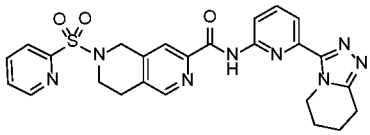
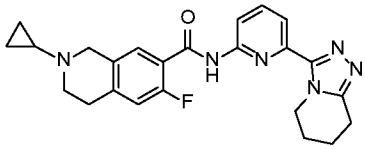
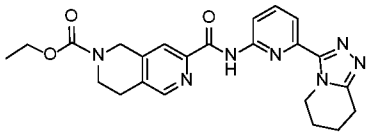
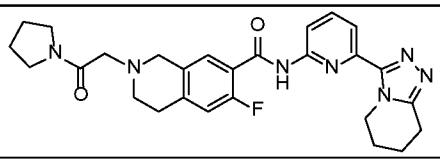
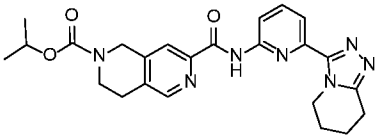
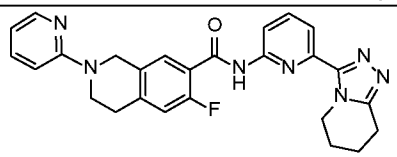
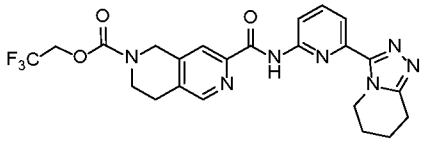
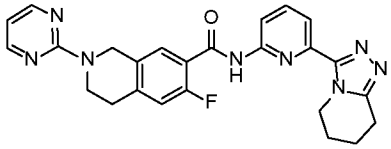
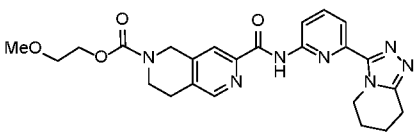
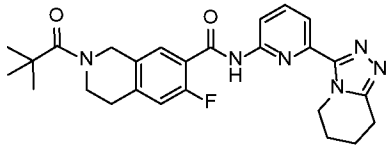
313		361	
314		362	
315		363	
316		364	
317		365	
318		366	
319		367	
320		368	
321		369	
322		370	
323		371	
324		372	

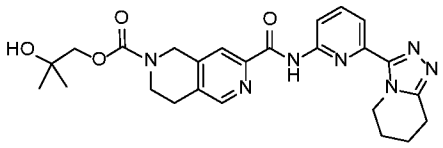
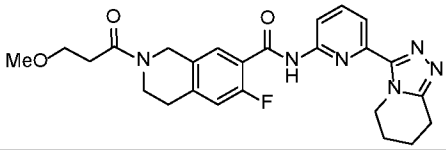
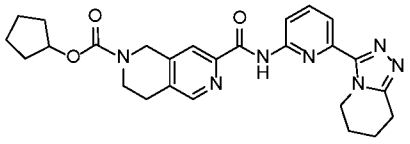
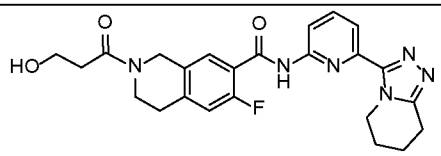
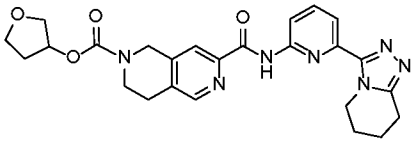
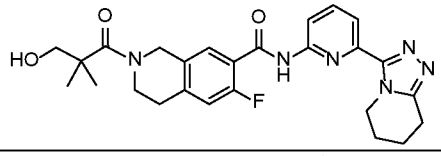
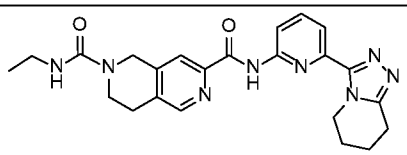
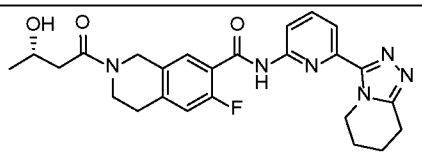
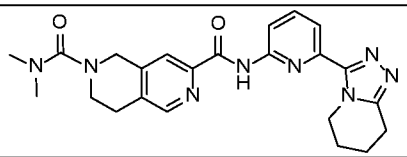
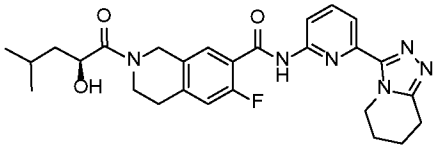
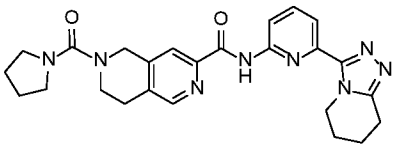
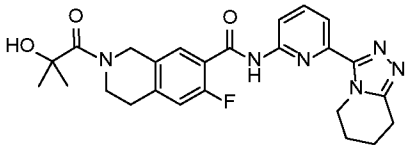
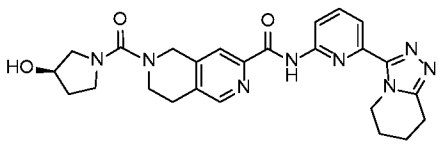
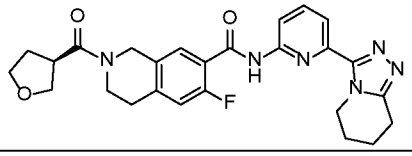
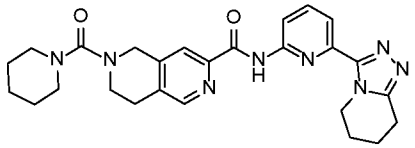
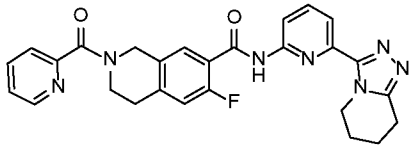
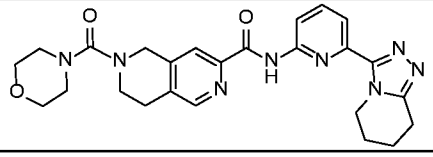
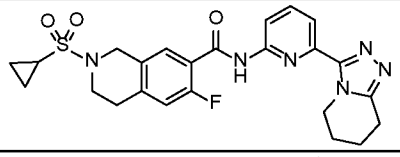
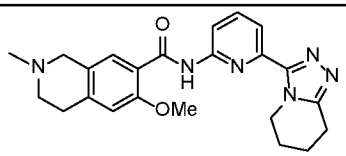
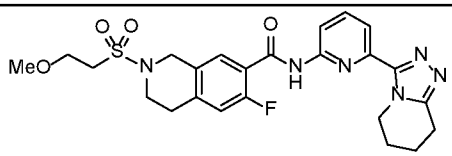
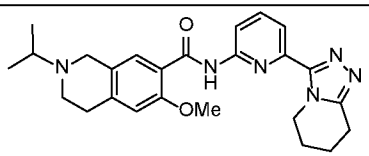
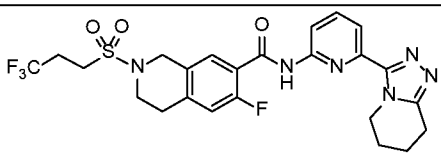
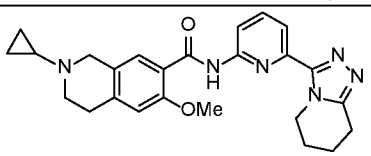
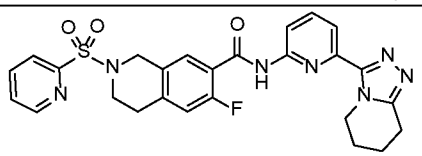
325		373	
326		374	
327		375	
328		376	
329		377	
330		378	
331		379	
332		380	
333		381	
334		382	
335		383	
336		384	

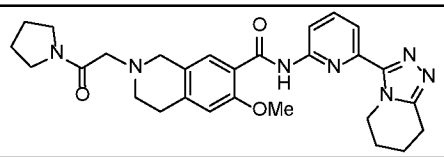
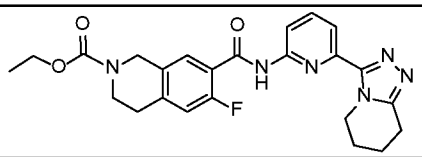
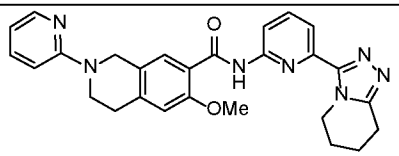
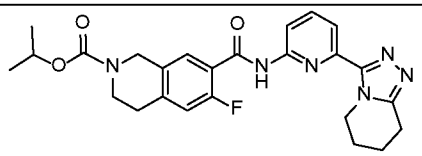
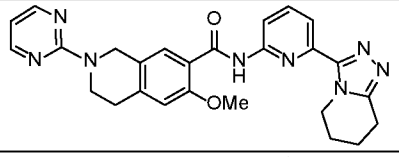
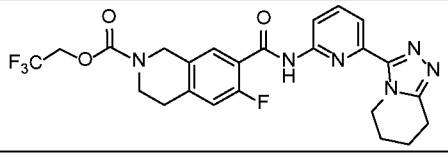
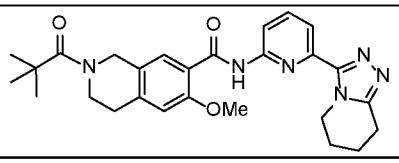
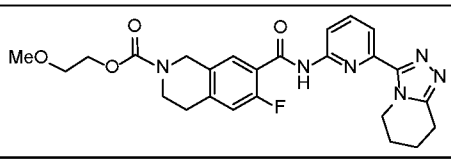
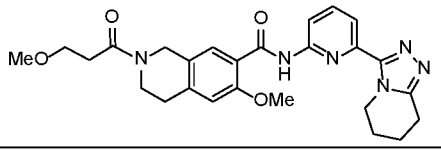
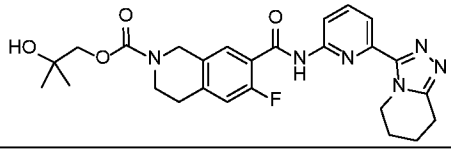
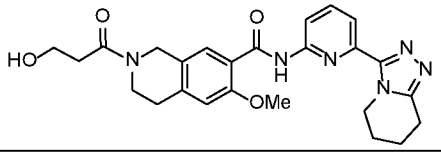
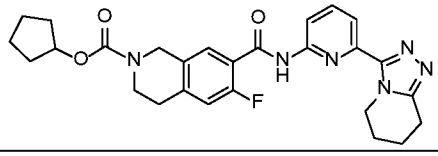
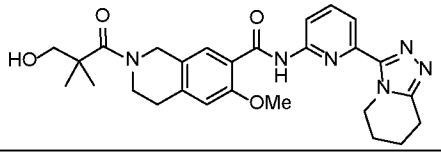
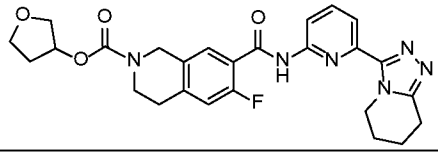
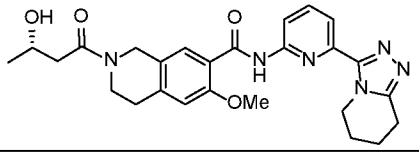
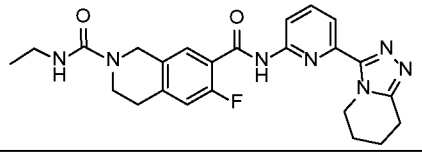
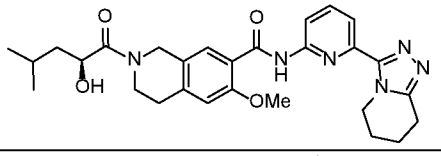
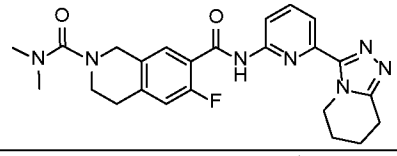
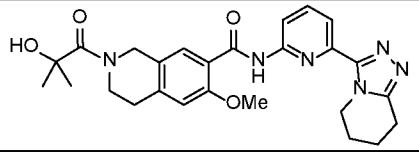
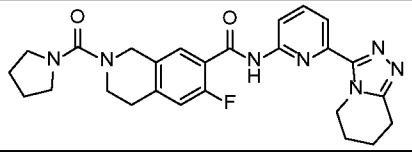
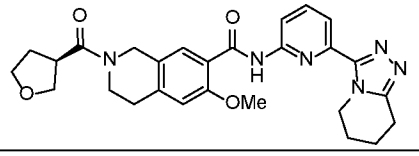
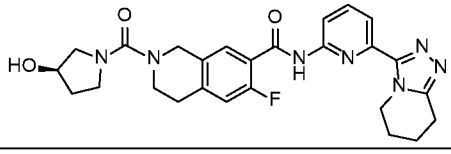
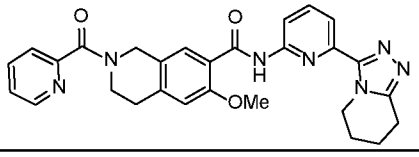
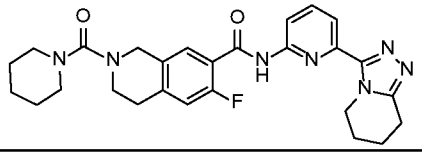
11. The compound of claim 1, selected from the compounds set forth in Table 5, or a pharmaceutically acceptable salt thereof:

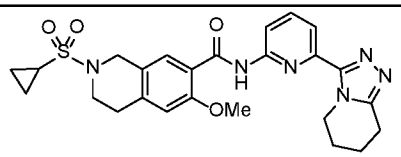
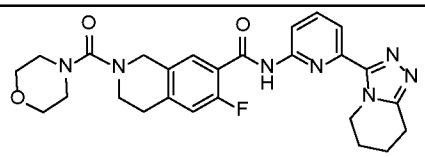
Table 5

compound	Structure	compound	Structure
385		433	
386		434	
387		435	
388		436	
389		437	
390		438	
391		439	
392		440	
393		441	
394		442	
395		443	

396		444	
397		445	
398		446	
399		447	
400		448	
401		449	
402		450	
403		451	
404		452	
405		453	
406		454	
407		455	

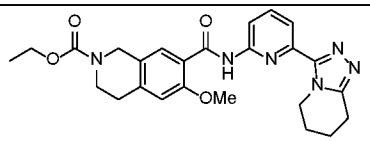
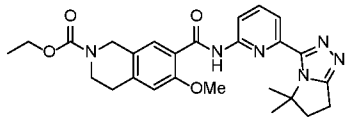
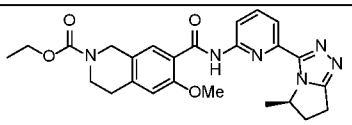
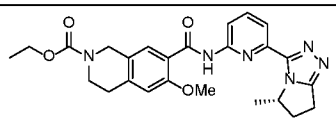
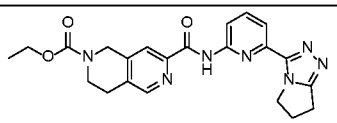
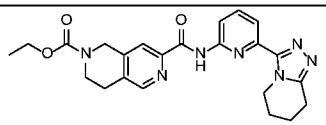
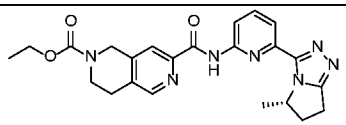
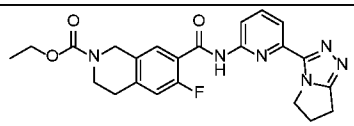
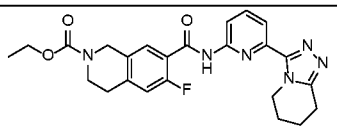
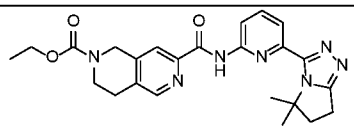
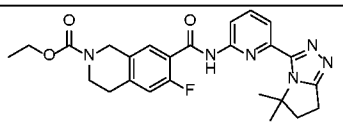
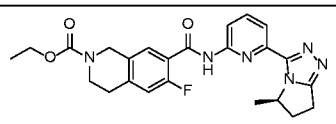
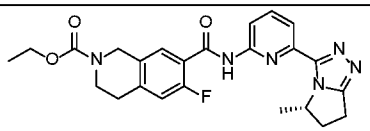
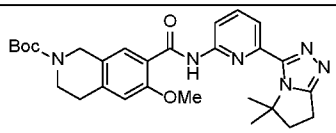
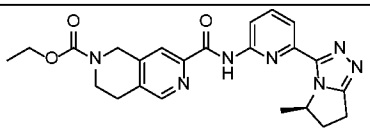
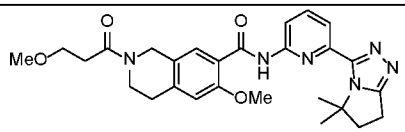
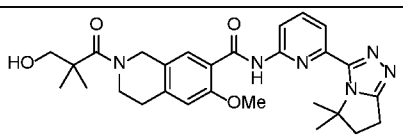
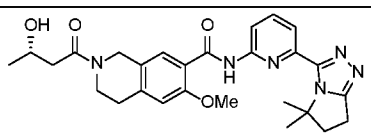
408		456	
409		457	
410		458	
411		459	
412		460	
413		461	
414		462	
415		463	
416		464	
417		465	
418		466	
419		467	

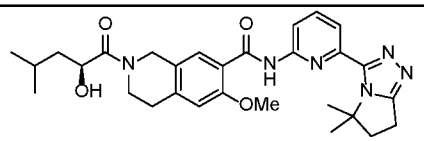
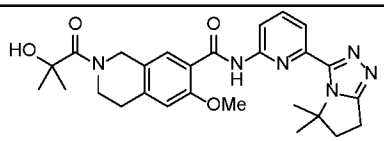
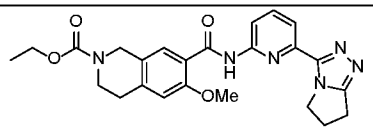
420		468	
421		469	
422		470	
423		471	
424		472	
425		473	
426		474	
427		475	
428		476	
429		477	
430		478	
431		479	

432		480	

12. The compound of claim 1, selected from the compounds set forth below in Table 6, or a pharmaceutically acceptable salt thereof:

Table 6

Compound	Structure	Compound	Structure
1		2	
3		4	
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	
17		18	

19		20	
21			

13. A pharmaceutical composition comprising a compound according to any one of claims 1-12 and a pharmaceutically acceptable excipient or carrier.

14. 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 a compound according to any one of claims 1-12.

15. The method according to claim 14, 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, or an acute or chronic liver disease.

16. The method according to claim 15, 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, or alpha 1-antitrypsin deficiency.

17. The method according to claim 15, 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, and polycystic kidney disease.

18. The method according to claim 15, wherein the cardiovascular disease is selected from the group consisting of atherosclerosis, arteriosclerosis, reperfusion/ischemia in stroke, cardiac hypertrophy, respiratory diseases, heart attacks, myocardial ischemia.

19. The method according to claim 15, wherein the metabolic disease is selected from the group consisting of insulin resistance, Type I and Type II diabetes, and obesity.

20. The method according to claim 15, wherein chronic kidney disease is selected from the group consisting of polycystic kidney disease, pyelonephritis, kidney fibrosis and glomerulonephritis.

21. A method for treating a disease selected from the group consisting of glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, multiple sclerosis, or Sjoegren's syndrome in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-12.

22. A method for treating a disease selected from the group consisting of ischemia/reperfusion in stroke, heart attacks, myocardial ischemia, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, hepatic ischemia, congestive heart failure, pathologic immune responses such as that caused by T cell activation, and thrombin-induced platelet aggregation in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-12.

23. A method for treating a disease selected from the group consisting of osteoporosis, osteoarthritis and multiple myeloma-related bone disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-12.

24. A method for treating a disease selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), epilepsy, seizures, Huntington's disease, polyglutamine diseases, traumatic brain injury, ischemic and hemorrhaging stroke, cerebral ischemias or neurodegenerative disease, including apoptosis-driven neurodegenerative disease, caused by traumatic injury, acute hypoxia, ischemia or glutamate neurotoxicity in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-12.

25. A pharmaceutical composition comprising a compound according to claims 1-12 and a pharmaceutically acceptable excipient or carrier.

26. Use of a compound of any one of claims 1-12 in the preparation of a medicament for the treatment of an ASK-1 mediated disease or condition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/24436

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:

-***-Continued 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.:

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.:

1-6, 13/1-6, 14/1-6, 15/14/1-6, 16/15/14/1-6, 17/15/14/1-6, 18/15/14/1-6, 19/15/14/1-6, 20/15/14/1-6, 21/1-6, 22/1-6, 24/1-6, 25/1-6, 26/1-6

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/US20/24436

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07D 401/14; A61K 31/4196 (2020.01)

CPC - C07D 401/14; A61K 31/4196

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	US 2018/0362503 A1 (ENANTA PHARMACEUTICALS, INC.) 20 December 2018; paragraphs [0009], [0020]-[0021], [0039], [0054]-[0058], [0088]-[0092]	1-6, 13/1-6, 14/1-6, 15/14/1-6, 16/15/14/1-6, 17/15/14/1-6, 18/15/14/1-6, 19/15/14/1-6, 20/15/14/1-6, 21/1-6, 22/1-6, 24/1-6, 25/1-6, 26/1-6
Y	WO 2018/187506 A1 (SEAL ROCK THERAPEUTICS, INC.) 11 October 2018; paragraphs [0092], [0131]	1-6, 13/1-6, 14/1-6, 15/14/1-6, 16/15/14/1-6, 17/15/14/1-6, 18/15/14/1-6, 19/15/14/1-6, 20/15/14/1-6, 21/1-6, 22/1-6, 24/1-6, 25/1-6, 26/1-6
Y	US 2014/0329850 A1 (TAKEDA PHARMACEUTICAL COMPANY LIMITED) 06 November 2014; abstract; paragraphs [0027], [0308]	23/1-6

☐ 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
"D" document cited by the applicant in the international application
"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
04 May 2020 (04.05.2020)	25 JUN 2020
Name and mailing address of the ISA/US 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 Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/24436

-***-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 1-26; and a compound of Formula I, wherein X1 and X2 are each C(R6) wherein R6 is hydrogen; X3 is C(R7) wherein R7 is hydrogen; R2 is hydrogen; R3 is hydrogen; R8 and R9 are each hydrogen; R10 and R11 are each hydrogen; and n is 0 (compound structure); are directed toward compounds, pharmaceutical compositions comprising the compounds, and methods and uses associated therewith.
The compounds, compositions, methods and uses will be searched to the extent the compound encompasses a compound of Formula I, wherein X1 and X2 are each C(R6) wherein R6 is hydrogen; X3 is C(R7) wherein R7 is hydrogen; R2 is hydrogen; R3 is hydrogen; R8 and R9 are each hydrogen; R10 and R11 are each hydrogen; and n is 0 (first exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure(s) thereof (e.g. no optional or variable atoms, bonds, or substituents) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1-6 (in-part) and 13-26 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula I, wherein X1 and X2 are each C(R6) wherein R6 is hydrogen; X3 is C(R7) wherein R7 is hydrogen; R2 is hydrogen; R3 is hydrogen; R8 and R9 are each hydrogen; R10 and R11 are each hydrogen; and n is 0 (first exemplary compound structure). Applicants must specify the claims that encompass any additionally elected compound structure(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 of Formula I, wherein X1 is C(R6) wherein R6 is hydrogen; X2 is N; X3 is C(R7) wherein R7 is hydrogen; R2 is hydrogen; R3 is hydrogen; R8 and R9 are each hydrogen; R10 and R11 are each hydrogen; and n is 0 (compound structure).
Groups I+ share the technical features including: a compound represented by Formula I, as shown, wherein one of X1 and X2 is C(R6), and the other is C(R6) or N; X3 is C(R7) or N, wherein R7 is selected from the group consisting of hydrogen, optionally substituted -C1-C8 alkyl, optionally substituted -C1-C8 alkoxy and halo; A is optionally substituted heterocycloalkyl or optionally substituted heteroaryl which is fused with 1,2,4-triazolyl; R2 and R6 are each independently selected from the group consisting of: 1) Hydrogen; 2) Halogen; 3) -NO2; 4) Cyano; 5) Substituted or unsubstituted -C1-C8 alkyl; 6) Substituted or unsubstituted -C2-C8 alkenyl; 7) Substituted or unsubstituted -C2-C8 alkynyl; 8) Substituted or unsubstituted -C3-C8 cycloalkyl; 9) Substituted or unsubstituted aryl; 10) Substituted or unsubstituted arylalkyl; 11) Substituted or unsubstituted 3- to 8- membered heterocycloalkyl; 12) Substituted or unsubstituted heteroaryl; 13) Substituted or unsubstituted heteroarylalkyl; 14) -N(R4)(R5); 15) -S(O)2N(R4)(R5); 16) -N(R4)C(O)R5; and 17) -N(R4)S(O)2R5; R3 is selected from the group consisting of: 1) Hydrogen; 2) Substituted or unsubstituted-C1-C8 alkyl; 3) Substituted or unsubstituted -C2-C8 alkenyl; 4) Substituted or unsubstituted -C2-C8 alkynyl; 5) Substituted or unsubstituted -C3-C8 cycloalkyl; 6) Substituted or unsubstituted aryl; 7) Substituted or unsubstituted arylalkyl; 8) Substituted or unsubstituted 3- to 8- membered heterocycloalkyl; 9) Substituted or unsubstituted heteroaryl; 10) Substituted or unsubstituted heteroarylalkyl; 11) -C(O)R4;12) -C(O)OR4; 13) -C(O)N(R4)(R5); and 14) -SO2R4; R4 and R5 are independently hydrogen, -C1-C8 alkyl, -C1-C8 alkenyl, -C1-C8 alkynyl, -C3-C8 cycloalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroarylalkyl, wherein the -C1-C8 alkyl, -C1-C8 alkenyl, -C1-C8 alkynyl, -C3-C8 cycloalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, and heteroarylalkyl is optionally substituted with 1-3 substituents independently selected from halo, alkyl, oxo, -C3-C8 cycloalkyl, alkylamino, dialkylamino, alkyl-C(O)-NH-, aryl-C(O)NH-, heteroaryl-C(O)NH-, heterocycloalkyl, heteroceycloalkyl-C(O)-, -OH, -CN, alkoxy, -CF3, aryl, and heteroaryl; alternatively R4 and R5 are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocycloalkyl; R8 and R9 are each independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted -C1-C8 alkyl; alternatively, R8 and R9 are taken together with the carbon atom to which they are attached to form C(O), spiro-C3-C8 cycloalkyl, or spiro-3- to 8- membered heterocycloalkyl; R10 and R11 are each independently selected from the group consisting of hydrogen, halo, and optionally substituted -C1-C8 alkyl; and n is 0, 1 or 2; a pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient or carrier; 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 a compound; and use of a compound in the preparation of a medicament for the treatment of an ASK-1 mediated disease or condition.
However, these shared technical features are previously disclosed by US 2018/0362503 A1 (ENANTA PHARMACEUTICALS, INC.) (hereinafter 'Enanta') in view of WO 2018/187506 A1 (SEAL ROCK THERAPEUTICS, INC.) (hereinafter 'Seal').
Enanta discloses a compound similar to a compound represented by Formula I, as shown, wherein X1 and X2 are each C(R6) wherein R6 is hydrogen; X3 is C(R7) wherein R7 is hydrogen; R2 is hydrogen; R3 is hydrogen; R8 and R9 are each hydrogen; R10 and R11 are each hydrogen; and n is 0 (compound of formula I wherein X1 and X2 are each CR8 (CR6) wherein each R8 (R6) is hydrogen, X3 is CR9 (CR7) wherein R9 (R7) is hydrogen, R2 is hydrogen, R3 is hydrogen, R10 and R11 (R8 and R9) are hydrogen, R12 and R13 (R10 and R11) are hydrogen, and n is 0; paragraphs [0009], [0020]-[0021], [0039], [0054]-[0056]); a pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient or carrier (pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient or carrier; paragraph [0057]); 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 a compound (method of treating an ASK-1 mediated disease or condition, wherein the method comprises administering a therapeutically effective amount of a compound; paragraph [0058]); and use of a compound in the preparation of a medicament for the treatment of an ASK-1 mediated disease or condition (use of a compound for preparation of a medicament for prevention or treatment of an ASK-1 mediated disease or condition; paragraph [0058]), but Enanta does not disclose wherein A is optionally substituted heterocycloalkyl which is fused with 1,2,4-triazolyl. However, Seal discloses wherein A is optionally substituted heterocycloalkyl which is fused with 1,2,4-triazolyl (compound of formula I wherein A is the first recited moiety wherein R1 is C5-9heteroaryl-cycloalkyl, specifically the first recited moiety in paragraph [0131] (A is heterocycloalkyl which is fused with 1,2,4-triazolyl); paragraphs [0092], [0131]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Enanta, in order to have provided wherein A is optionally substituted heterocycloalkyl which is fused with 1,2,4-triazolyl, as previously disclosed by Seal, for providing pharmaceutical compositions and heterocycle compounds useful as ASK1 inhibitors in the treatment of ASK1 mediated diseases and conditions (Seal; paragraphs [0004]-[0005]; Enanta; paragraphs [0009], [0058]).
Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Enanta and Seal references, unity of invention is lacking.