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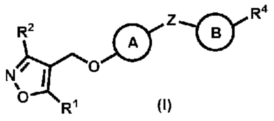
(54) Title: ISOXAZOLE ANALOGS AS FXR AGONISTS AND METHODS OF USE THEREOF



(I)

(57) **Abstract:** The present invention provides compounds of Formula I: pharmaceutical compositions comprising these compounds and methods of using these compounds to treat or prevent a disease or disorder mediated as FXR modulators. Specifically, the present invention relates to isoxazole derivatives useful as agonists for FXR, and methods for their preparation and use.

Isoxazole Analogs as FXR Agonists and Methods of Use Thereof

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/338,014, filed on May 18, 2016. 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 FXR modulators. Specifically, the present invention relates to isoxazole derivatives useful as agonists for FXR, and methods for their preparation and use.

BACKGROUND OF THE INVENTION

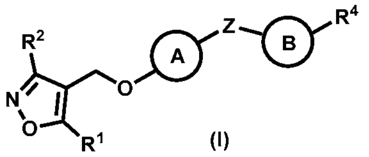
Farnesoid X Receptor (FXR) is an orphan nuclear receptor initially identified from a rat liver cDNA library (BM. Forman, et al., *Cell*, **1995,** *81(5)*, 687-693) that is most closely related to the insect ecdysone receptor. FXR is a member of the nuclear receptor family of ligand-activated transcription factors that includes receptors for the steroid, retinoid, and thyroid hormones (DJ. Mangelsdorf, et al., *Cell***, 1995,** *83(6)*, 841-850). The relevant physiological ligands of FXR are bile acids (D. Parks et al., Science, 1999, 284(5418), 1362-1365). The most potent one is chenodeoxycholic acid (CDCA), which regulates the expression of several genes that participate in bile acid homeostasis. Farnesol and derivatives, together called farnesoids, are originally described to activate the rat orthologue at high concentration but they do not activate the human or mouse receptor. FXR is expressed in the liver, throughout the entire gastrointestinal tract including the esophagus, stomach, duodenum, small intestine, colon, ovary, adrenal gland and kidney. Beyond controlling intracellular gene expression, FXR seems to be also involved in paracrine and endocrine signaling by upregulating the expression of the cytokine Fibroblast Growth Factor (J. Holt et al., *Genes Dev.*, **2003**, *17(13)*, 1581-1591; T. Inagaki et al., *Cell Metab.*, **2005**, *2(4)*, 217-225).

Small molecule compounds which act as FXR modulators have been disclosed in the following publications: WO 2000/037077, WO 2002/072598, WO 2003/015771, WO 2003/099821, WO 2004/00752, WO 2004/048349, WO 2005/009387, WO 2005/082925, US 2005/0054634, WO 2007/052843, WO 2007/070796, WO 2007/076260, WO 2007/092751, WO 2007/095174, WO 2007/140174, WO 2007/140183, US 2007/0142340, WO 2008/000643, WO 2008/002573, WO 2008/025539, WO 2008/025540, WO 2008/051942, WO 2008/073825, WO 2008/157270, US 2008/0299118, US 2008/0300235, WO 2009/005998, WO 2009/012125, WO 2009/027264, WO 2009/062874, WO 2009/127321, WO 2009/149795, US 2009/0131409, US 2009/0137554, US 2009/0163474, US 2009/0163552, US 2009/0215748, WO 2010/043513, WO 2011/020615, WO 2011/117163, WO 2012/087519, WO 2012/087520, WO 2012/087521, WO 2013/007387, WO 2013/037482, WO 2013/166176, WO 2013/192097, WO 2014/184271, US 2014/0186438, US 2014/0187633, and WO 2015/017813. Further small molecule FXR modulators have been recently reviewed (R. C. Buijsman, et al., *Curr. Med. Chem.* **2005**, *12(9)*, 1017-1075; Crawley, M. L. *Expert Opin. Ther. Patents* **2010**, *20(8)*, 1047-1057; V. Sepe, et al., *Expert Opin. Ther. Patents* **2015**, *25(8)*, 885-896.

There is a need for the development of FXR modulators for the treatment and prevention of disease.

SUMMARY OF THE INVENTION

In one aspect, the invention provides compounds represented by Formula I, or pharmaceutically acceptable salts thereof:



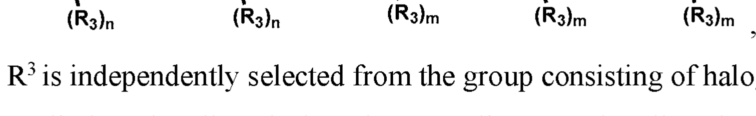
(I)

,

wherein R^1 is hydrogen, halogen, cyano, optionally substituted $-C_1-C_6$ alkyl, optionally substituted $-C_2-C_6$ alkenyl, optionally substituted $-C_2-C_6$ alkynyl, optionally substituted $-C_3-C_6$ cycloalkyl or optionally substituted 3- to 6- membered heterocycloalkyl. Preferably, R^1 is isopropyl, *tert*-butyl, or cyclopropyl.

R^2 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted $-C_3-C_{12}$ cycloalkyl or optionally substituted 3- to 12- membered heterocycloalkyl.

Ⓐ is selected from the group consisting of:



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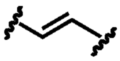
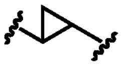
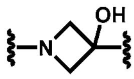
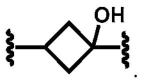
wherein R^3 is independently selected from the group consisting of halogen, optionally substituted $-C_1-C_6$ alkyl, optionally substituted $-C_1-C_6$ alkoxy, optionally substituted $-C_3-C_6$ cycloalkyl, optionally substituted $-C_3-C_6$ cycloalkenyl, optionally substituted 3- to 6-

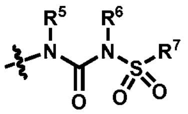
membered heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; n is 0, 1, 2, or 3; and m is 0, 1 or 2.

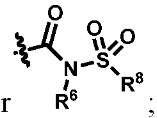
Z is selected from the group consisting of:



Ⓑ is phenyl, 3- to 8- membered heterocycloalkyl, or heteroaryl, wherein said phenyl, 3- to 8- membered heterocycloalkyl, or heteroaryl is optionally substituted with one or two groups independently selected from OH, halogen, optionally substituted -C_1-C_6 alkoxy, optionally substituted -C_1-C_6 alkyl, optionally substituted -C_2-C_6 alkenyl, optionally substituted -C_3-C_6 cycloalkyl, -$N(R^b)SO_2C_1$-C_6 alkyl, -$C(O)R^b$, and -$NHC(O)R^b$; R^b is optionally substituted -C_1-C_6 alkyl, optionally substituted -C_1-C_6 alkoxy, optionally substituted -C_3-C_6 cycloalkyl, or optionally substituted -C_3-C_6 cycloalkenyl;

R^4 is


or


; wherein:

$R^5$and R^6 are independently selected from the group consisting of:

1) Hydrogen;
2) Optionally substituted -C_1-C_8 alkyl;
3) Optionally substituted –C_2-C_8 alkenyl;
4) Optionally substituted –C_2-C_8 alkynyl; and
5) Optionally substituted –C_3-C_8 cycloalkyl;

R^7 is selected from the group consisting of:

1) Optionally substituted –C_1-C_8 alkyl;
2) Optionally substituted –C_2-C_8 alkenyl;
3) Optionally substituted –C_2-C_8 alkynyl;
4) Optionally substituted –C_3-C_{12} cycloalkyl;
5) Optionally substituted –C_3-C_{12} cycloalkenyl;
6) Optionally substituted aryl;
7) Optionally substituted arylalkyl;
8) Optionally substituted 3- to 12- membered heterocycloalkyl;
9) Optionally substituted heteroaryl;
10) Optionally substituted heteroarylalkyl; and

11) NR^9R^{10}; wherein R^9 and R^{10} are each independently selected from hydrogen, optionally substituted $–C_1$-C_8 alkyl, optionally substituted$–C_2$-C_8 alkenyl, optionally substituted$–C_2$-C_8 alkynyl, optionally substituted$–C_3$-C_8 cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted 3- to 8- membered heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl; alternatively, R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic ring.

R^8 is selected from the group consisting of:

1) Optionally substituted $-C_3$-C_{12} cycloalkyl;
2) Optionally substituted $-C_3$-C_{12} cycloalkenyl;
3) Optionally substituted 3- to 12- membered heterocycloalkyl ;
4) Optionally substituted aryl;
5) Optionally substituted arylalkyl;
6) Optionally substituted heteroaryl;
7) Optionally substituted heteroarylalkyl;
8) Optionally substituted cycloalkyl-C_1-C_6-alkyl;
9) Optionally substituted cycloalkenyl-C_1-C_6-alkyl;
10) Optionally substituted heterocycloalkyl-C_1-C_6-alkyl; and
11) $NR^{12}R^{13}$; wherein R^{12} and R^{13} are each independently selected from hydrogen, optionally substituted $–C_1$-C_8 alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, optionally substituted $–C_3$-C_8 cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted 3- to 8- membered heterocycloalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, alternatively R^{12} and R^{13} are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic ring; provided that at least one of R^{12} and R^{13} is not hydrogen.

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.

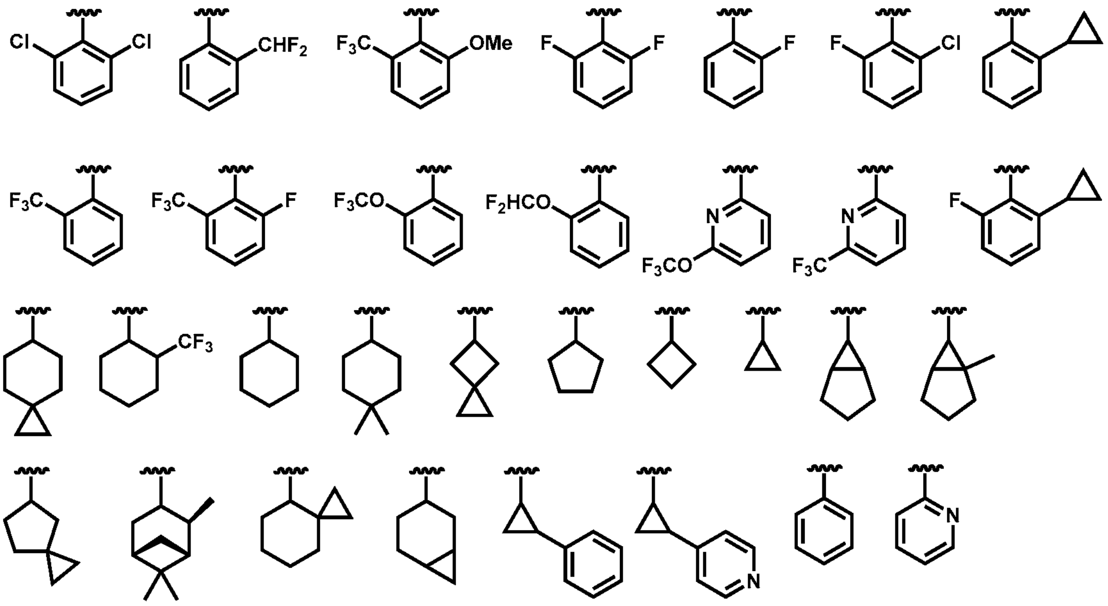
In another embodiment, the present invention provides a method for the prevention or treatment of an FXR mediated disease or condition. The method comprises administering a therapeutically effective amount of a compound of Formula (I). The present invention also provides the use of a compound of Formula (I) for the preparation of a medicament for the prevention or treatment of an FXR mediated disease or condition.

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 thereof.

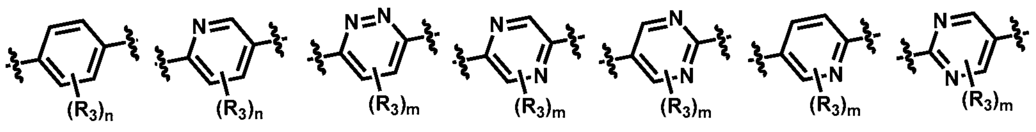
In certain embodiments of the invention is a compound represented by Formula I as described above, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted isopropyl, optionally substituted *tert*-butyl or optionally substituted cyclopropyl.

In certain embodiments of the invention is a compound represented by Formula I as described above, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the groups:



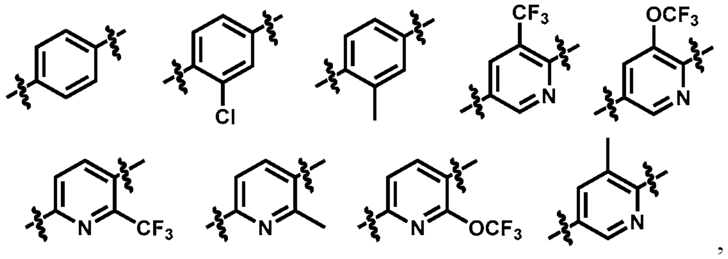
each of which can be optionally further substituted with halogen, optionally substituted -C_1-C_6 alkyl, optionally substituted -C_1-C_6 alkoxy, optionally substituted -C_3-C_6 cycloalkyl, , optionally substituted -C_3-C_6 cycloalkenyl, optionally substituted aryl, or optionally substituted heteroaryl.

In certain embodiments of the invention is a compound represented by Formula I as described above, or a pharmaceutically acceptable salt thereof, wherein Ⓐ is selected from:



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

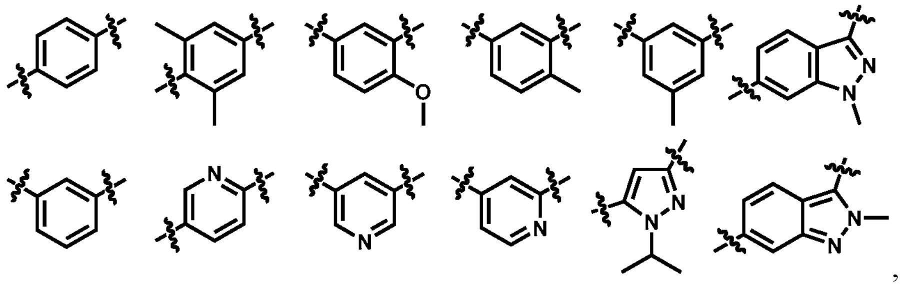
In certain embodiments of the invention is a compound represented by Formula I as described above, or a pharmaceutically acceptable salt thereof, wherein Ⓐ is selected from:



wherein each of these groups is optionally substituted.

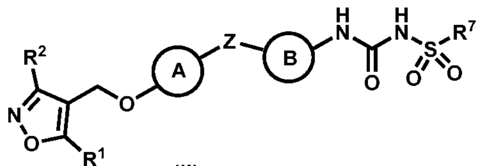
In certain embodiments of the invention is a compound represented by Formula I as described above, or a pharmaceutically acceptable salt thereof, wherein Ⓑ is phenyl, pyridyl, pyrimidinyl, pyrazolyl, thienyl, thiazolyl, triazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxazolyl, oxadiazolyl, imidazolyl, furanyl, indolyl, benzothienyl, indazolyl, benzisoxazolyl, benzofuranyl, benzotriazolyl, or benzothiazolyl, wherein each of these groups is optionally substituted.

In certain embodiments of the invention is a compound represented by Formula I as described above, or a pharmaceutically acceptable salt thereof, wherein Ⓑ is selected from:

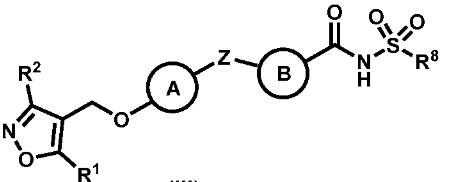


and wherein each of these groups is optionally substituted.

In certain embodiments, the compounds of the invention is represented by Formula **(II)**, or **(III)**, and pharmaceutically acceptable salts thereof:



(II)

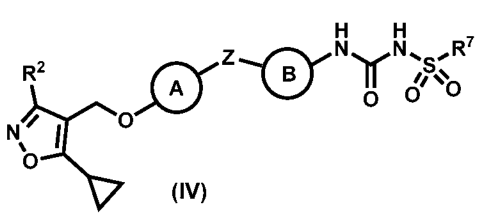


(III)

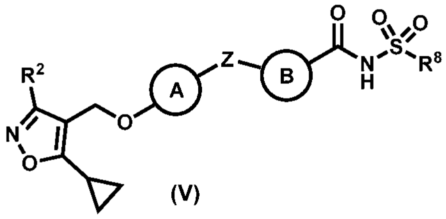
,

wherein R^1, R^2, Ⓐ, Z, Ⓑ, R^7 and R^8 are as previously defined.

In certain embodiments, the compounds of the invention are represented by Formula **(IV)** or **(V)**, and pharmaceutically acceptable salts thereof:



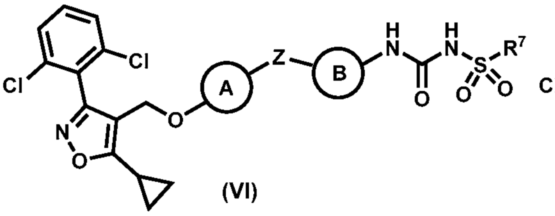
(IV)



(V)

wherein R^2, Ⓐ, Z, Ⓑ, R^7 and R^8 are as previously defined.

In certain embodiments, the compounds of the invention are represented by Formula **(VI)** or **(VII)**, and pharmaceutically acceptable salts thereof:



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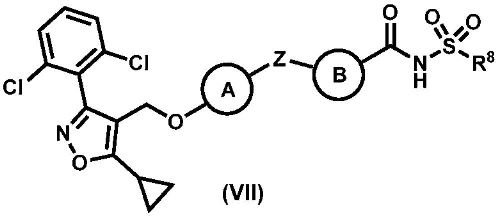
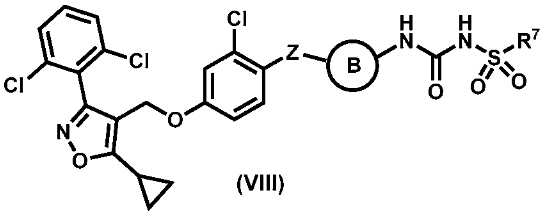


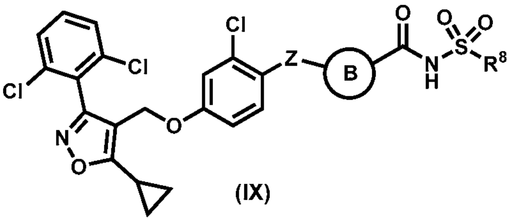
(VII)

wherein Ⓐ, Z, Ⓑ, R^7 and R^8 are as previously defined.

In certain embodiments, the compounds of the invention are represented by Formula **(VIII)** or **(IX)**, and pharmaceutically acceptable salts thereof:



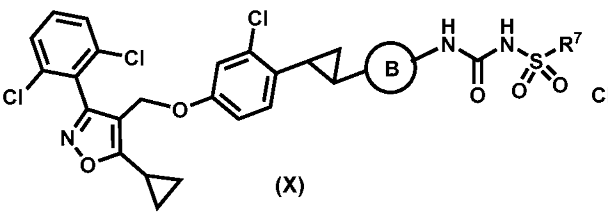
(VIII)



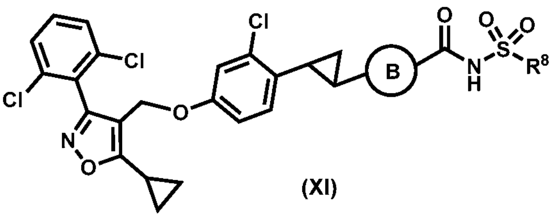
(IX)

wherein Z, Ⓑ, R^7 and R^8 are as previously defined.

In certain embodiments, the compounds of the invention is represented by Formula **(X)** or **(XI)**, and pharmaceutically acceptable salts thereof:



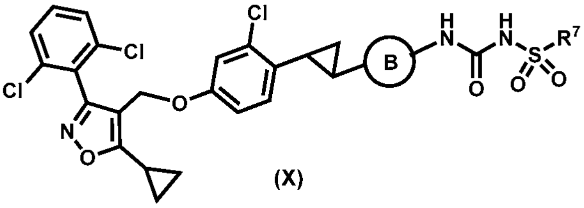
(X)



(XI)

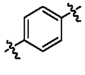
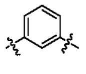
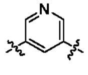
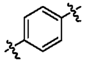
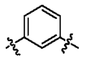
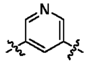
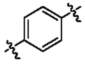
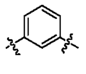
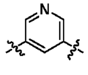
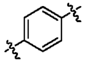
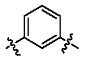
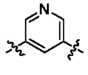
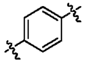
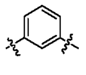
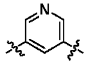
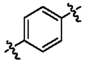
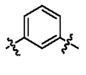
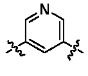
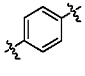
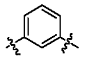
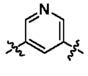
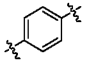
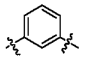
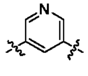
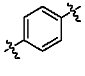
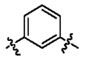
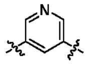
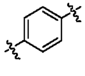
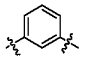
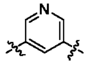
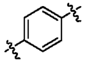
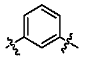
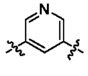
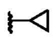
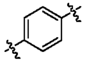
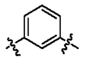
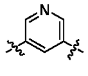
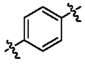
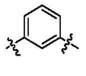
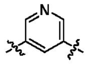
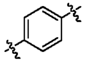
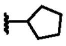
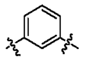
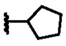
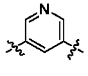
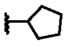
wherein Ⓑ, R^7 and R^8 are as previously defined.

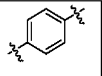
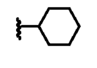
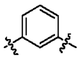
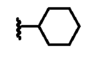
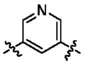
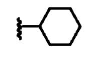
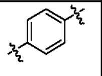
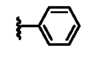
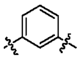
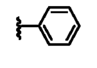
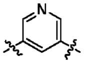
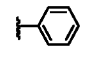
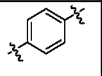
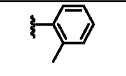
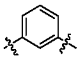
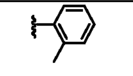
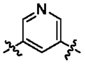
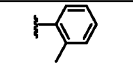
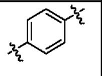
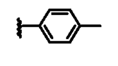
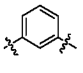
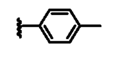
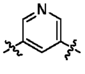
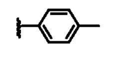
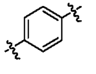
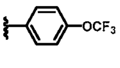
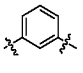
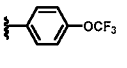
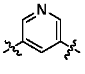
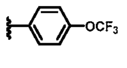
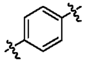
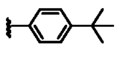
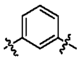
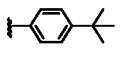
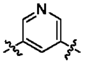
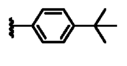
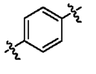
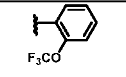
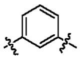
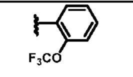
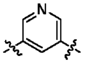
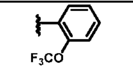
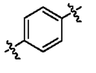
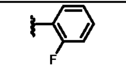
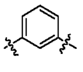
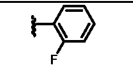
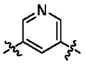
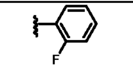
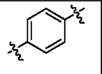
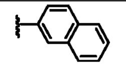
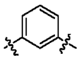
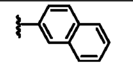
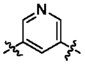
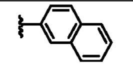
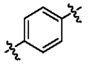
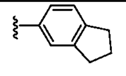
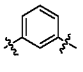
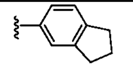
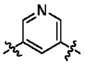
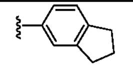
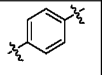
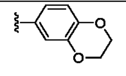
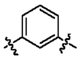
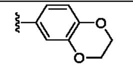
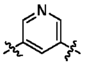
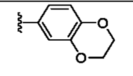
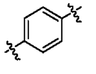
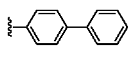
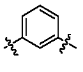
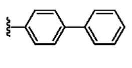
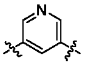
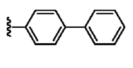
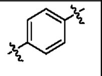
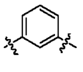
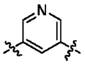
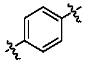
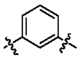
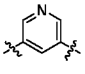
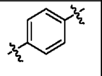
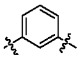
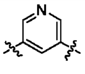
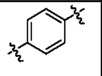
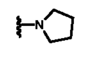
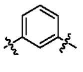
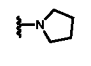
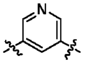
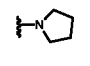
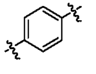
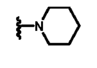
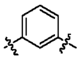
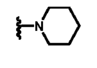
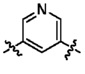
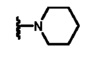
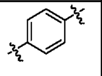
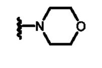
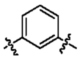
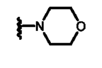
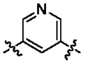
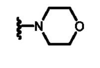
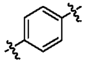
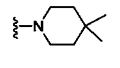
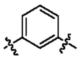
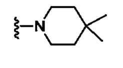
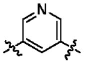
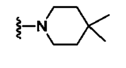
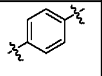
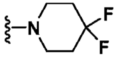
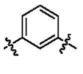
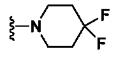
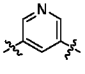
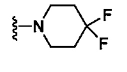
Representative compounds of the invention include, but are not limited to, the following compounds (compound 1 to compound 102 in Table 1) according to Formula X, and pharmaceutically acceptable salts thereof, wherein R^7 and Ⓑ are delineated for each compound in Table 1.



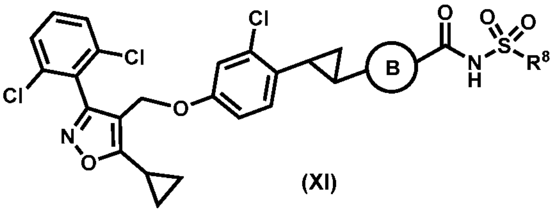
(X)

Table 1

Compound	Ⓑ	R^7	Compound	Ⓑ	R^7	Compound	Ⓑ	R^7
1		Methyl	35		Methyl	69		Methyl
2		Ethyl	36		Ethyl	70		Ethyl
3		Isopropyl	37		Isopropyl	71		Isopropyl
4		Butyl	38		Butyl	72		Butyl
5		t-Butyl	39		t-Butyl	73		t-Butyl
6		Propyl	40		Propyl	74		Propyl
7		Benzyl	41		Benzyl	75		Benzyl
8		Vinyl	42		Vinyl	76		Vinyl
9		Allyl	43		Allyl	77		Allyl
10		$-CF_3$	44		$-CF_3$	78		$-CF_3$
11			45			79		
12			46			80		
13			47			81		
14			48			82		

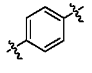
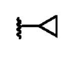
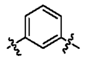
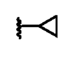
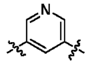
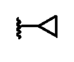
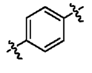
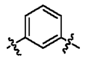
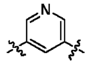
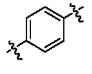
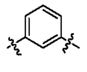
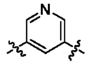
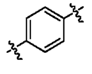
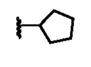
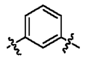
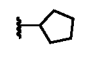
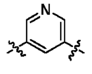
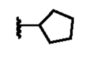
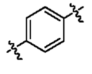
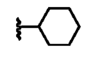
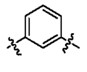
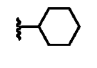
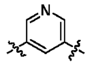
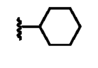
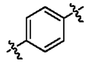
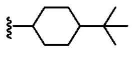
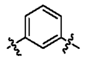
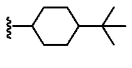
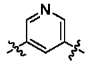
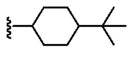
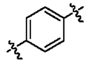
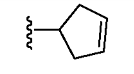
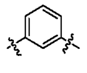
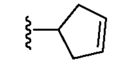
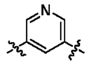
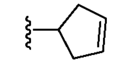
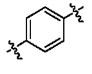
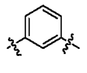
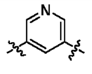
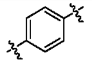
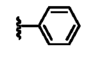
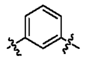
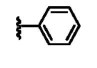
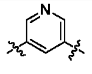
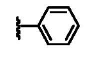
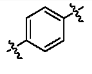
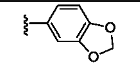
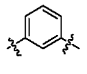
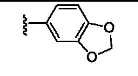
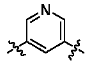
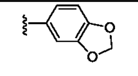
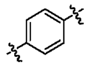
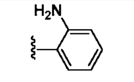
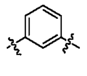
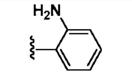
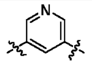
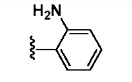
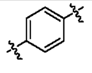
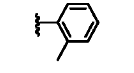
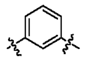
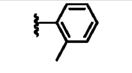
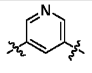
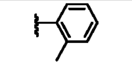
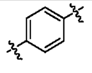
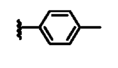
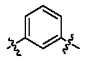
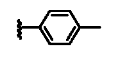
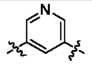
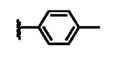
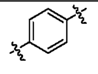
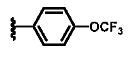
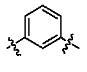
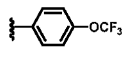
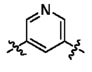
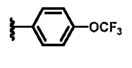
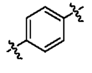
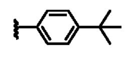
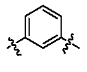
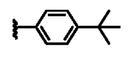
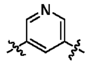
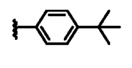
15			49			83		
16			50			84		
17			51			85		
18			52			86		
19			53			87		
20			54			88		
21			55			89		
22			56			90		
23			57			91		
24			58			92		
25			59			93		
26			60			94		
27		$-NH_2$	61		$-NH_2$	95		$-NH_2$
28		$-NHCH_3$	62		$-NHCH_3$	96		$-NHCH_3$
29		$-N(CH_3)_2$	63		$-N(CH_3)_2$	97		$-N(CH_3)_2$
30			64			98		
31			65			99		
32			66			100		
33			67			101		
34			68			102		

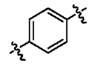
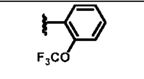
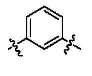
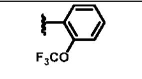
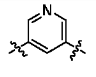
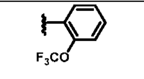
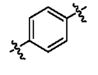
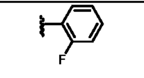
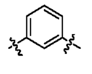
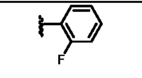
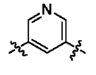
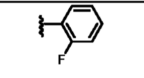
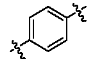
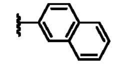
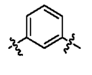
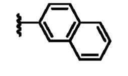
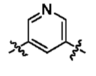
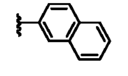
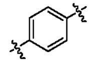
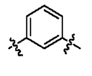
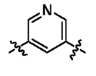
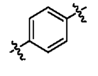
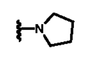
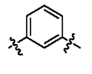
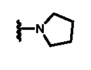
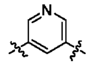
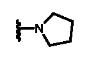
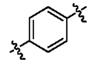
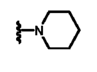
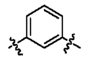
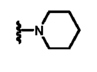
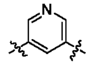
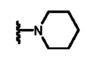
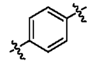
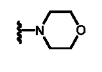
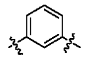
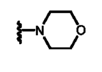
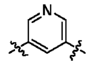
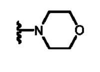
Representative compounds of the invention include, but are not limited to, the following compounds (compound 103 to compound 174 in Table 2) according to Formula XI, and pharmaceutically acceptable salts thereof, wherein R^8 and Ⓑ are delineated for each compound in Table 2.



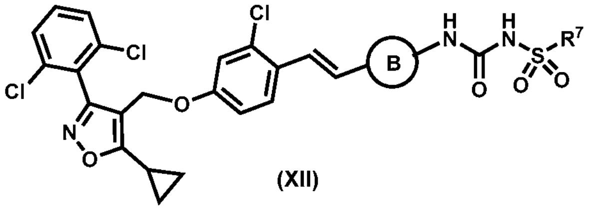
(XI)

Table 2

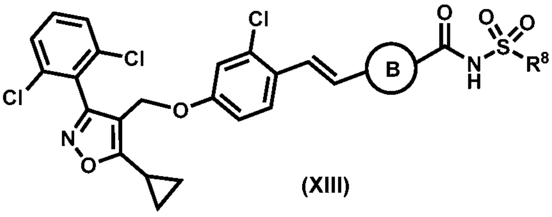
Compound	Ⓑ	R^8	Compound	Ⓑ	R^8	Compound	Ⓑ	R^8
103			127			151		
104			128			152		
105			129			153		
106			130			154		
107			131			155		
108			132			156		
109			133			157		
110		Benzyl	134		Benzyl	158		Benzyl
111			135			159		
112			136			160		
113			137			161		
114			138			162		
115			139			163		
116			140			164		
117			141			165		

118			142			166		
119			143			167		
120			144			168		
123		-N(CH3)2	147		-N(CH3)2	171		-N(CH3)2
124			148			172		
125			149			173		
126			150			174		

In certain embodiments, the compounds of the invention are represented by Formula (**XII**) or (**XIII**), and pharmaceutically acceptable salts thereof:



(XII)



(XIII)

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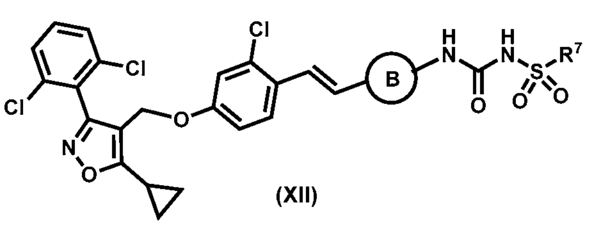
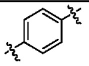
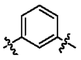
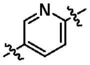
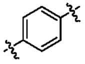
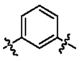
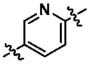
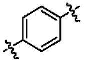
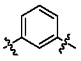
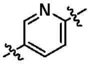
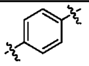
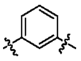
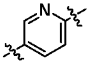
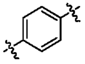
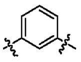
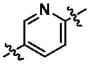
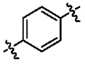
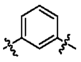
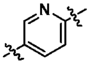
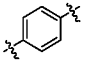
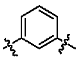
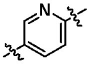
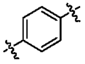
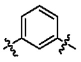
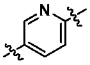
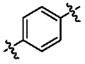
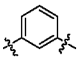
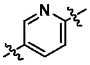
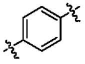
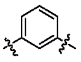
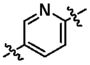
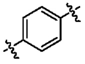
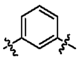
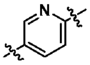
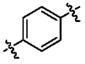
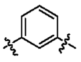
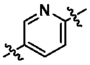
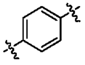
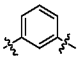
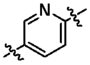
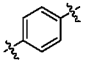
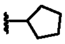
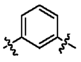
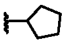
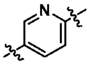
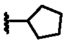
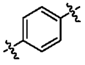
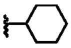
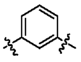
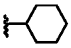
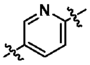
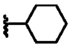
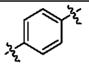
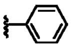
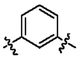
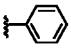
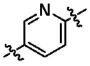
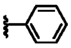
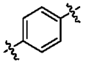
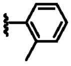
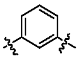
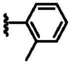
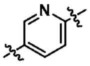
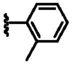
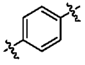
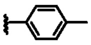
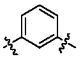
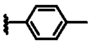
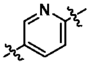
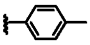
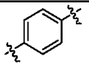
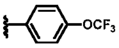
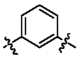
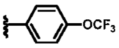
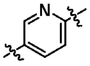
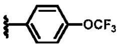
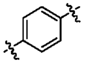
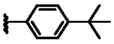
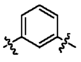
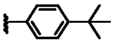
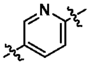
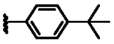
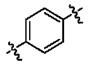
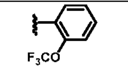
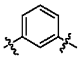
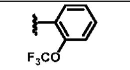
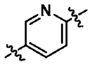
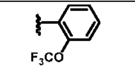
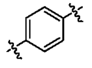
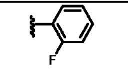
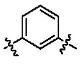
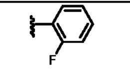
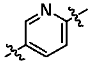
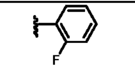
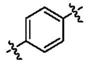
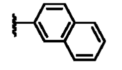
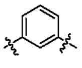
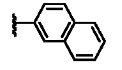
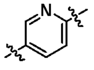
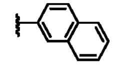
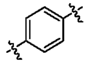
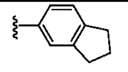
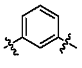
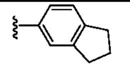
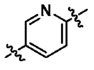
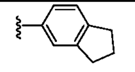
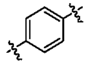
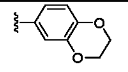
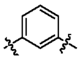
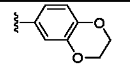
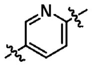
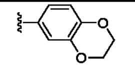
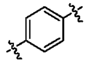
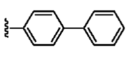
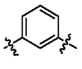
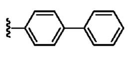
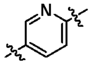
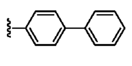
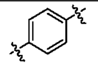
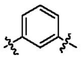
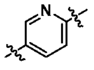
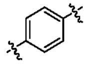
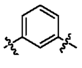
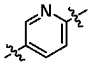
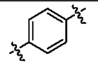
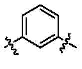
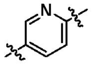
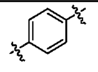
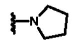
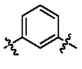
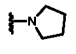
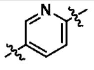
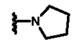
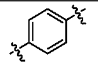
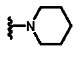
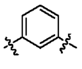
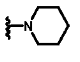
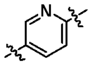
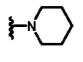
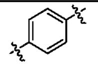
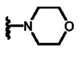
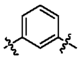
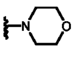
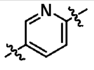
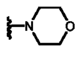
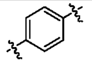
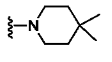
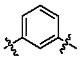
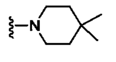
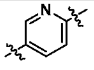
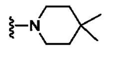
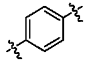
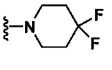
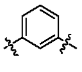
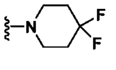
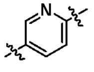
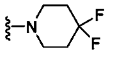
Representative compounds of the invention include, but are not limited to, the following compounds (compound 175 to compound 276 in Table 3) according to Formula XII, wherein R^7 and Ⓑ are delineated for each compound in Table 3.



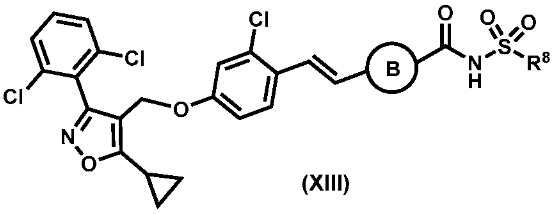
(XII)

Table 3

Compound	Ⓑ	R^7	Compound	Ⓑ	R^7	Compound	Ⓑ	R^7
175		Methyl	209		Methyl	243		Methyl
176		Ethyl	210		Ethyl	244		Ethyl
177		Isopropyl	211		Isopropyl	245		Isopropyl
178		Butyl	212		Butyl	246		Butyl
179		t-Butyl	213		t-Butyl	247		t-Butyl
180		Propyl	214		Propyl	248		Propyl
181		Benzyl	215		Benzyl	249		Benzyl
182		Vinyl	216		Vinyl	250		Vinyl
183		Allyl	217		Allyl	251		Allyl
184		-CF$_3$	218		-CF$_3$	252		-CF$_3$
185			219			253		
186			220			254		
187			221			255		
188			222			256		
189			223			257		
190			224			258		
191			225			259		
192			226			260		
193			227			261		
194			228			262		

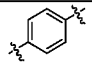
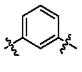
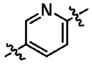
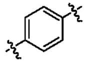
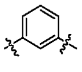
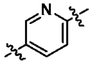
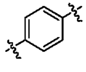
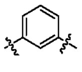
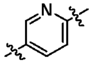
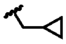
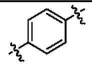
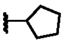
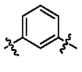
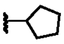
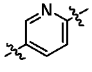
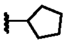
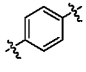
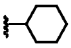
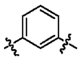
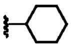
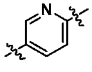
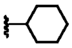
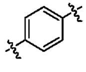
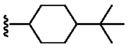
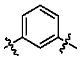
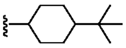
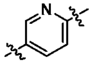
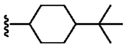
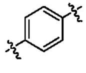
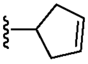
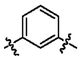
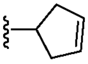
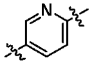
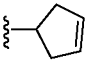
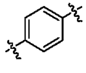
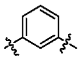
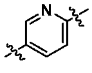
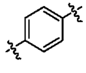
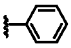
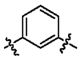
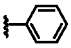
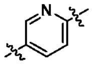
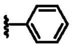
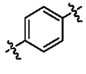
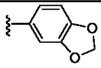
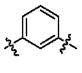
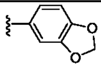
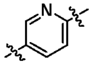
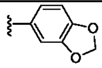
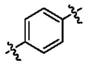
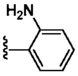
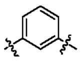
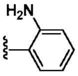
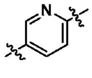
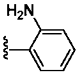
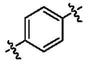
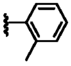
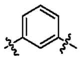
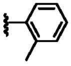
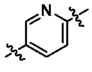
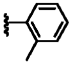
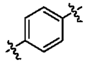
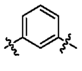
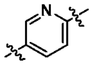
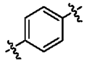
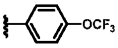
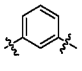
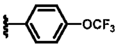
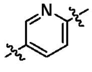
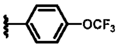
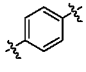
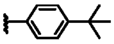
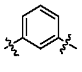
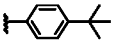
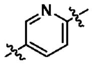
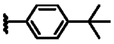
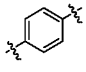
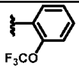
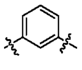
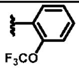
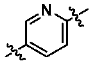
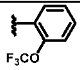
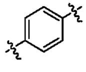
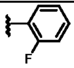
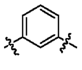
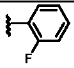
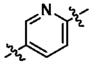
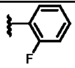
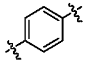
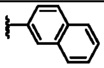
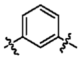
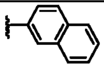
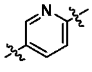
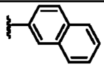
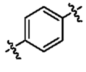
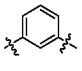
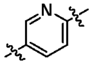
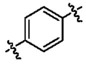
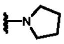
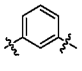
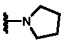
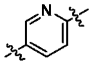
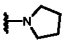
195			229			263		
196			230			264		
197			231			265		
198			232			266		
199			233			267		
200			234			268		
201		-NH$_2$	235		-NH$_2$	269		-NH$_2$
202		-NHCH$_3$	236		-NHCH$_3$	270		-NHCH$_3$
203		-N(CH$_3$)$_2$	237		-N(CH$_3$)$_2$	271		-N(CH$_3$)$_2$
204			238			272		
205			239			273		
206			240			274		
207			241			275		
208			242			276		

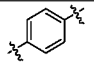
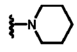
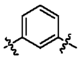
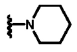
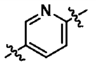
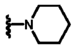
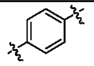
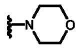
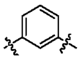
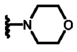
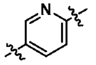
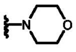
Representative compounds of the invention include, but are not limited to, the following compounds (compound 277 to compound 348 in Table 4) according to Formula XIII, wherein R^8 and Ⓑ are delineated for each compound in Table 4.



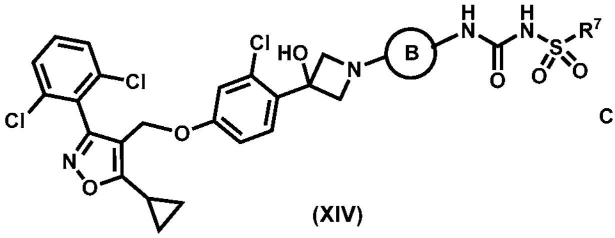
(XIII)

Table 4

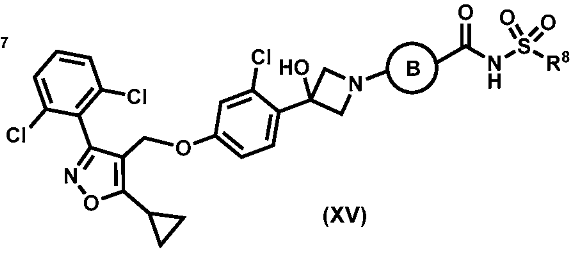
Compound	Ⓑ	R^8	Compound	Ⓑ	R^8	Compound	Ⓑ	R^8
277			301			325		
278			302			326		
279			303			327		
280			304			328		
281			305			329		
282			306			330		
283			307			331		
284		Benzyl	308		Benzyl	332		Benzyl
285			309			333		
286			310			334		
287			311			335		
288			312			336		
289			313			337		
290			314			338		
291			315			339		
292			316			340		
293			317			341		
294			318			342		
297		-N(CH$_3$)$_2$	321		-N(CH$_3$)$_2$	345		-N(CH$_3$)$_2$
298			322			346		

299			323			347		
300			324			348		

In certain embodiments, the compounds of the invention are represented by Formula **(XIV)** or **(XV)**, and pharmaceutically acceptable salts thereof:



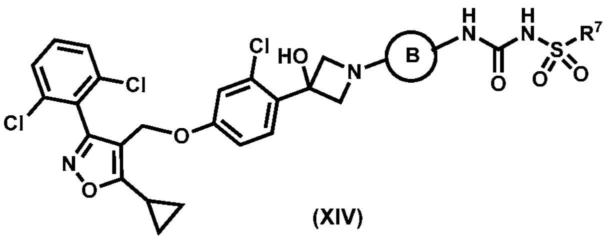
(XIV)



(XV)

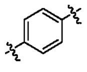
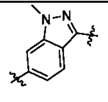
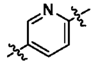
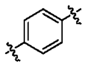
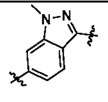
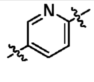
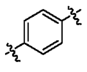
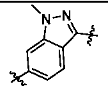
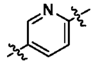
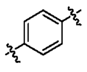
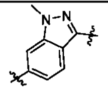
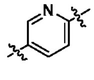
wherein Ⓑ, R^7 and R^8 are as previously defined.

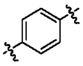
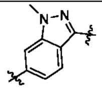
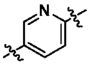
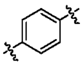
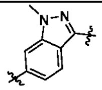
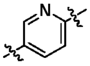
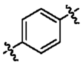
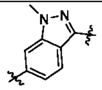
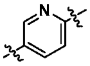
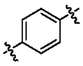
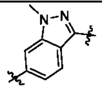
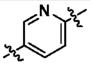
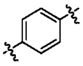
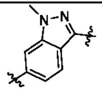
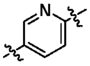
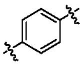
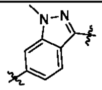
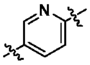
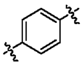
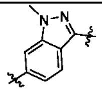
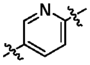
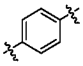
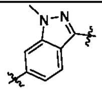
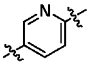
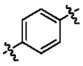
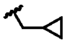
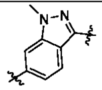
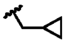
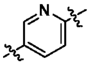
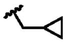
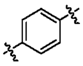
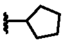
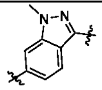
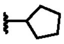
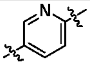
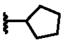
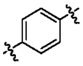
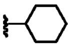
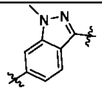
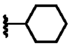
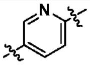
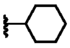
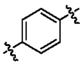
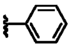
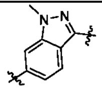
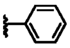
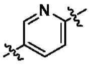
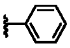
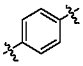
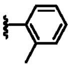
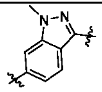
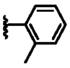
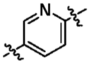
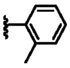
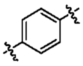
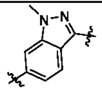
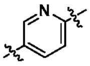
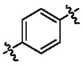
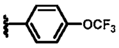
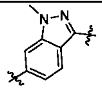
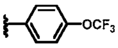
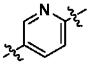
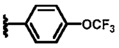
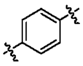
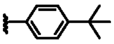
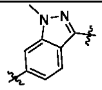
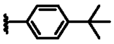
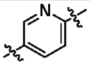
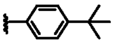
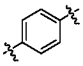
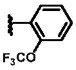
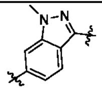
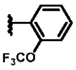
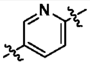
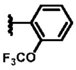
Representative compounds of the invention include, but are not limited to, the following compounds (compound 349 to compound 450 in Table 5) according to Formula XIV, wherein R^7 and Ⓑ are delineated for each compound in Table 5.

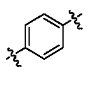
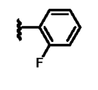
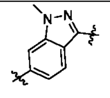
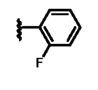
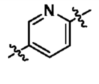
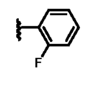
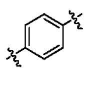
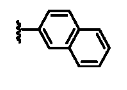
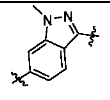
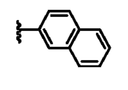
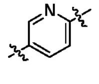
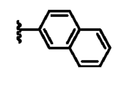
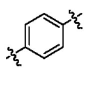
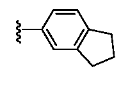
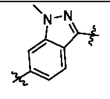
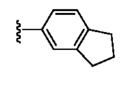
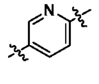
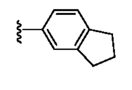
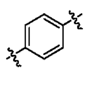
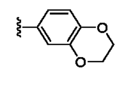
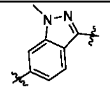
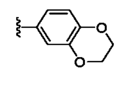
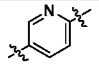
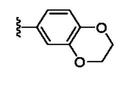
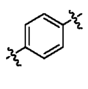
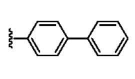
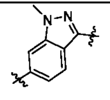
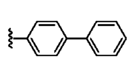
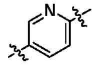
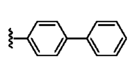
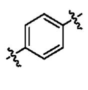
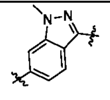
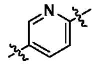
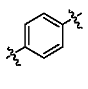
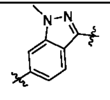
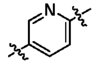
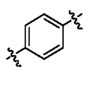
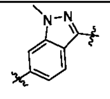
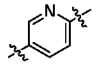
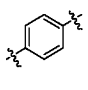
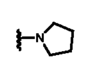
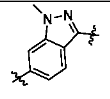
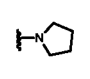
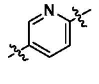
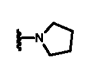
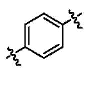
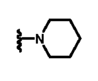
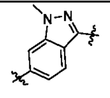
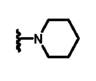
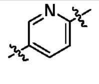
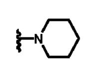
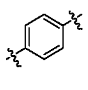
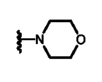
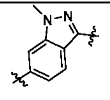
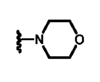
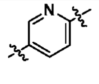
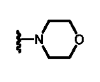
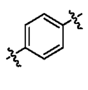
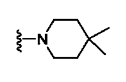
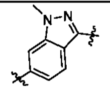
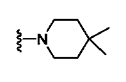
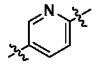
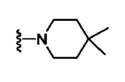
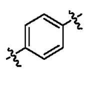
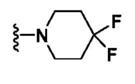
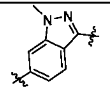
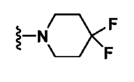
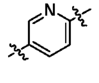
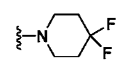


(XIV)

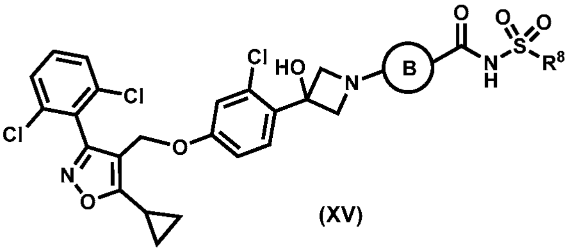
Table 5

Compound	Ⓑ	R^7	Compound	Ⓑ	R^7	Compound	Ⓑ	R^7
349		Methyl	383		Methyl	417		Methyl
350		Ethyl	384		Ethyl	418		Ethyl
351		Isopropyl	385		Isopropyl	419		Isopropyl
352		Butyl	386		Butyl	420		Butyl

353		t-Butyl	387		t-Butyl	421		t-Butyl
354		Propyl	388		Propyl	422		Propyl
355		Benzyl	389		Benzyl	423		Benzyl
356		Vinyl	390		Vinyl	424		Vinyl
357		Allyl	391		Allyl	425		Allyl
358		$-CF_3$	392		$-CF_3$	426		$-CF_3$
359			393			427		
360			394			428		
361			395			429		
362			396			430		
363			397			431		
364			398			432		
365			399			433		
366			400			434		
367			401			435		
368			402			436		
369			403			437		

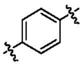
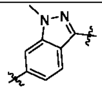
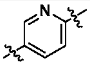
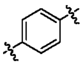
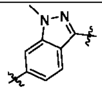
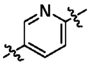
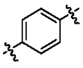
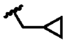
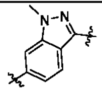
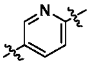
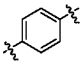
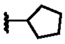
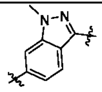
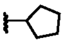
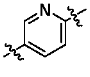
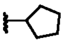
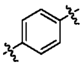
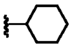
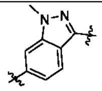
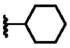
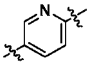
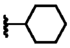
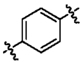
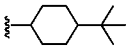
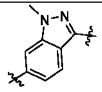
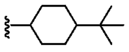
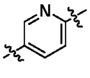
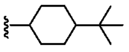
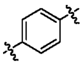
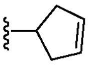
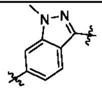
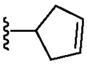
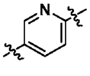
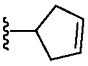
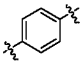
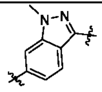
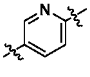
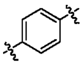
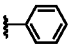
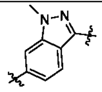
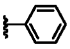
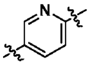
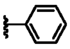
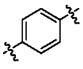
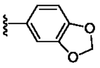
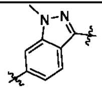
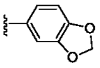
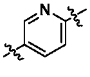
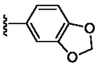
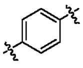
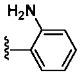
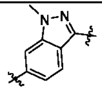
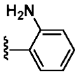
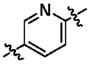
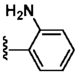
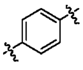
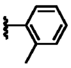
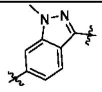
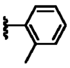
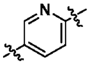
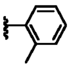
370			404			438		
371			405			439		
372			406			440		
373			407			441		
374			408			442		
375		$-NH_2$	409		$-NH_2$	443		$-NH_2$
376		$-NHCH_3$	410		$-NHCH_3$	444		$-NHCH_3$
377		$-N(CH_3)_2$	411		$-N(CH_3)_2$	445		$-N(CH_3)_2$
378			412			446		
379			413			447		
380			414			448		
381			415			449		
382			416			450		

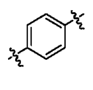
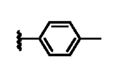
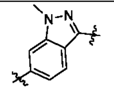
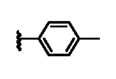
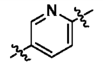
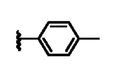
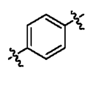
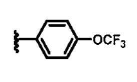
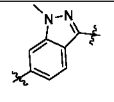
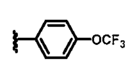
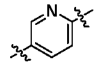
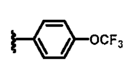
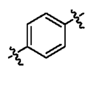
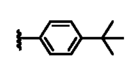
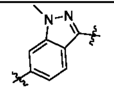
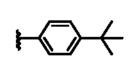
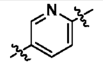
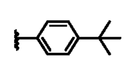
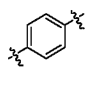
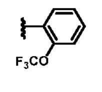
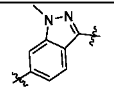
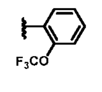
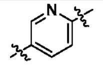
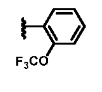
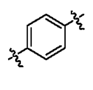
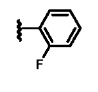
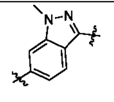
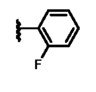
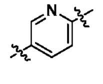
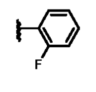
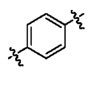
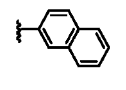
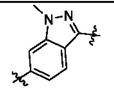
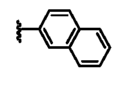
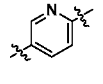
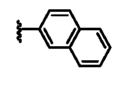
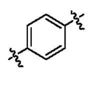
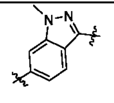
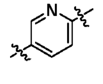
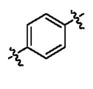
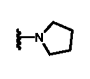
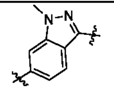
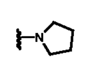
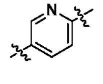
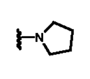
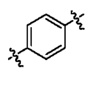
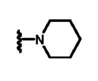
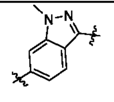
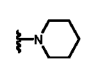
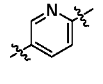
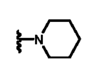
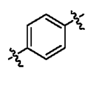
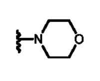
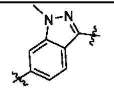
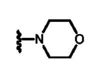
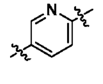
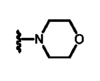
Representative compounds of the invention include, but are not limited to, the following compounds (compound 451 to compound 522 in Table 6) according to Formula XV, wherein R^8 and Ⓑ are delineated for each compound in Table 6.



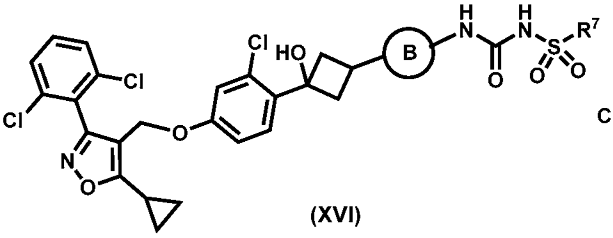
(XV)

Table 6

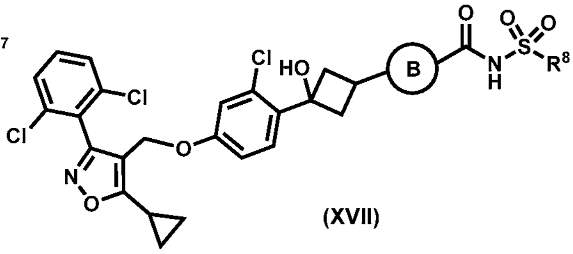
Compound	Ⓑ	R⁸	Compound	Ⓑ	R⁸	Compound	Ⓑ	R⁸
451			475			499		
452			476			500		
453			477			501		
454			478			502		
455			479			503		
456			480			504		
457			481			505		
458		Benzyl	482		Benzyl	506		Benzyl
459			483			507		
460			484			508		
461			485			509		
462			486			510		

463			487			511		
464			488			512		
465			489			513		
466			490			514		
467			491			515		
468			492			516		
471		$-N(CH_3)_2$	495		$-N(CH_3)_2$	519		$-N(CH_3)_2$
472			496			520		
473			497			521		
474			498			522		

In certain embodiments, the compounds of the invention are represented by Formula **(XVI)** or **(XVII)**, and pharmaceutically acceptable salts thereof:



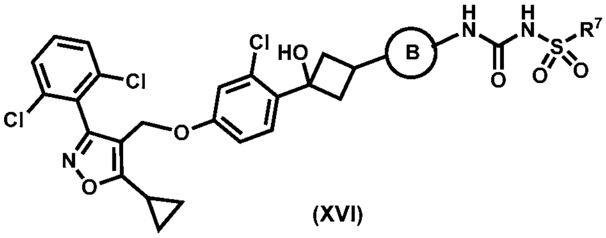
(XVI)



(XVII)

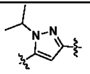
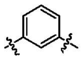
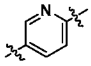
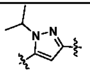
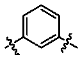
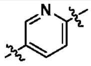
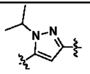
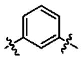
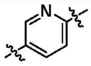
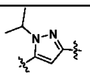
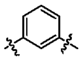
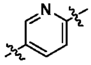
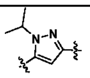
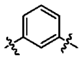
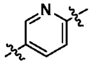
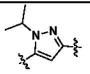
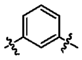
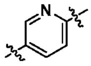
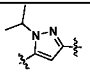
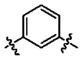
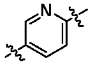
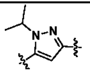
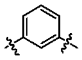
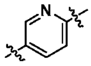
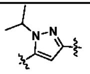
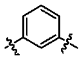
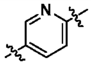
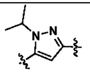
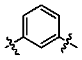
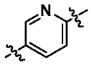
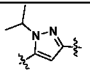
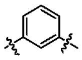
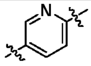
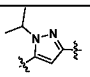
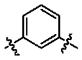
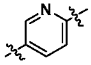
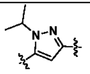
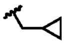
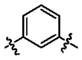
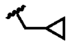
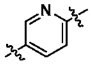
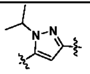
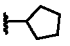
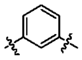
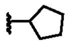
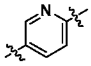
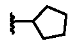
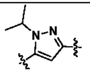
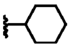
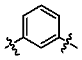
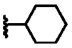
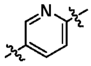
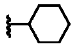
5 wherein Ⓑ, R^7 and R^8 are as previously defined.

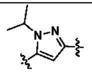
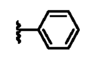
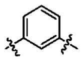
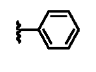
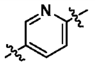
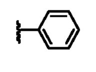
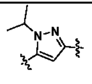
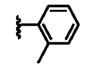
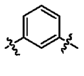
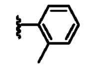
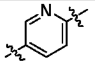
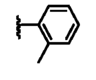
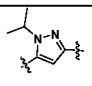
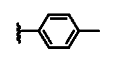
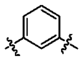
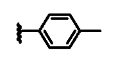
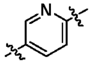
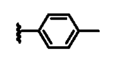
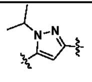
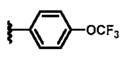
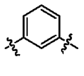
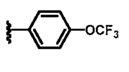
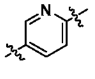
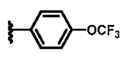
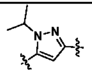
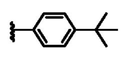
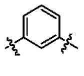
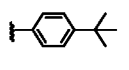
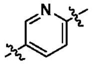
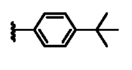
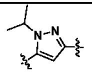
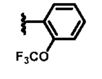
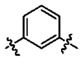
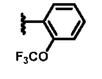
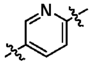
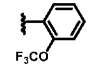
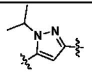
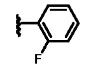
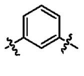
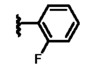
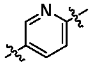
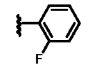
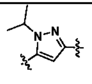
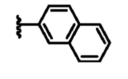
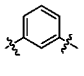
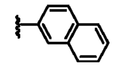
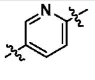
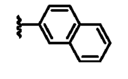
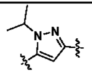
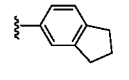
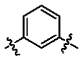
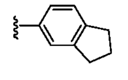
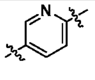
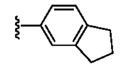
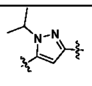
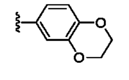
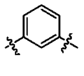
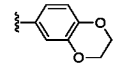
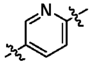
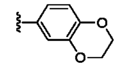
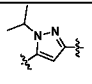
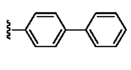
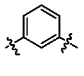
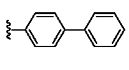
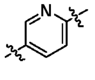
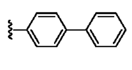
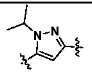
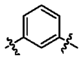
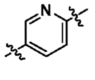
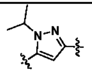
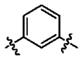
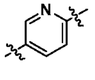
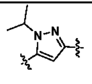
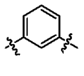
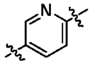
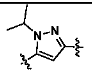
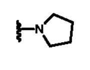
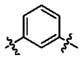
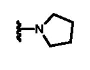
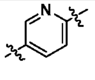
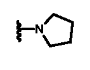
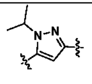
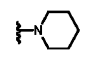
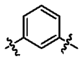
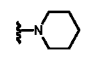
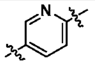
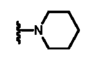
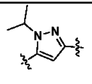
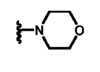
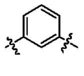
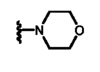
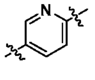
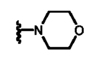
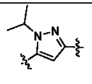
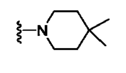
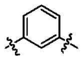
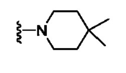
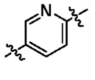
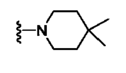
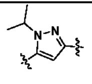
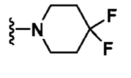
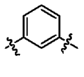
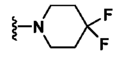
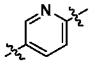
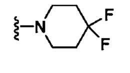
Representative compounds of the invention include, but are not limited to, the following compounds (compound 523 to compound 624 in Table 7) according to Formula XVI, wherein R^7 and Ⓑ are delineated for each compound in Table 7.



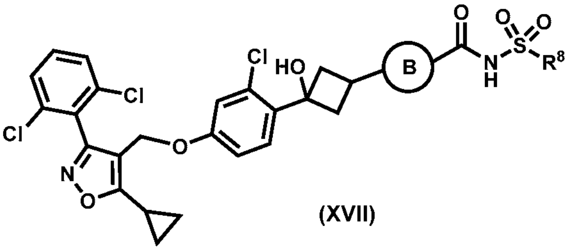
(XVI)

Table 7

Compound	Ⓑ	R^7	Compound	Ⓑ	R^7	Compound	Ⓑ	R^7
523		Methyl	557		Methyl	591		Methyl
524		Ethyl	558		Ethyl	592		Ethyl
525		Isopropyl	559		Isopropyl	593		Isopropyl
526		Butyl	560		Butyl	594		Butyl
527		t-Butyl	561		t-Butyl	595		t-Butyl
528		Propyl	562		Propyl	596		Propyl
529		Benzyl	563		Benzyl	597		Benzyl
530		Vinyl	564		Vinyl	598		Vinyl
531		Allyl	565		Allyl	599		Allyl
532		$-CF_3$	566		$-CF_3$	600		$-CF_3$
533			567			601		
534			568			602		
535			569			603		
536			570			604		
537			571			605		

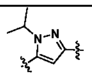
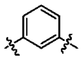
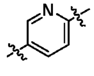
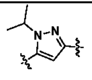
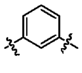
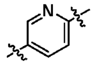
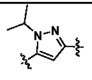
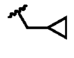
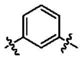
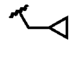
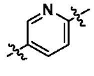
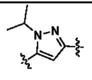
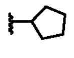
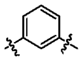
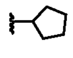
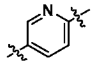
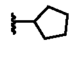
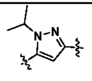
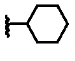
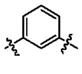
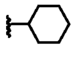
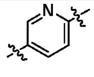
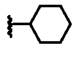
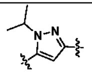
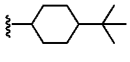
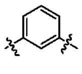
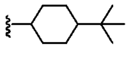
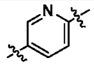
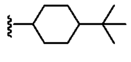
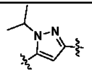
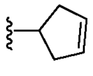
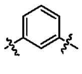
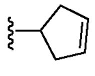
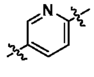
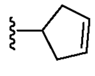
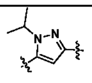
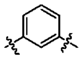
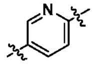
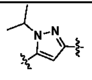
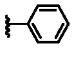
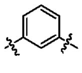
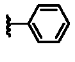
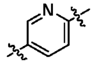
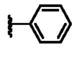
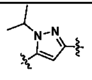
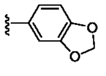
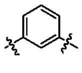
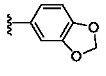
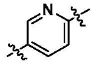
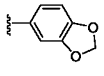
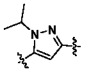
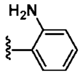
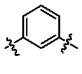
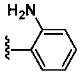
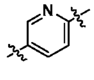
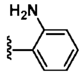
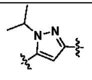
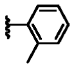
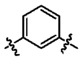
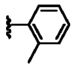
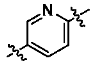
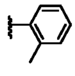
538			572			606		
539			573			607		
540			574			608		
541			575			609		
542			576			610		
543			577			611		
544			578			612		
545			579			613		
546			580			614		
547			581			615		
548			582			616		
549		$-NH_2$	583		$-NH_2$	617		$-NH_2$
550		$-NHCH_3$	584		$-NHCH_3$	618		$-NHCH_3$
551		$-N(CH_3)_2$	585		$-N(CH_3)_2$	619		$-N(CH_3)_2$
552			586			620		
553			587			621		
554			588			622		
555			589			623		
556			590			624		

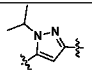
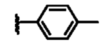
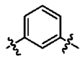
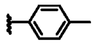
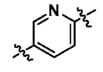
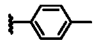
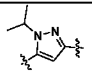
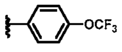
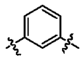
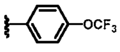
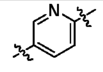
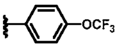
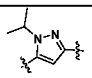
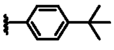
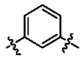
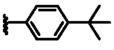
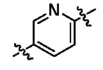
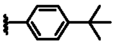
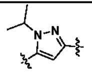
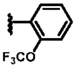
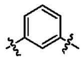
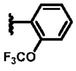
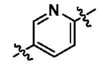
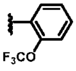
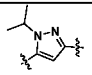
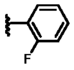
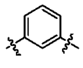
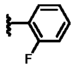
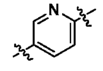
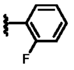
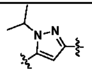
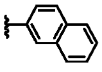
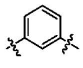
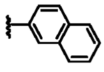
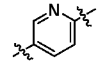
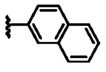
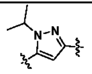
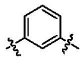
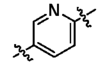
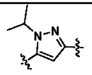
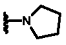
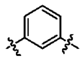
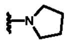
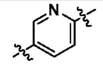
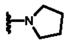
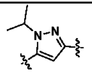
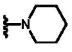
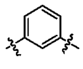
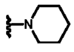
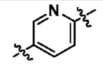
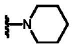
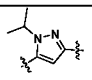
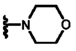
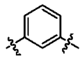
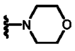
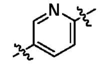
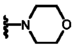
Representative compounds of the invention include, but are not limited to, the following compounds (compound 625 to compound 696 in Table 8) according to Formula XVII, wherein R^8 and Ⓑ are delineated for each compound in Table 8.



(XVII)

Table 8

Compound	Ⓑ	R^8	Compound	Ⓑ	R^8	Compound	Ⓑ	R^8
625			649			673		
626			650			674		
627			651			675		
628			652			676		
629			653			677		
630			654			678		
631			655			679		
632		Benzyl	656		Benzyl	680		Benzyl
633			657			681		
634			658			682		
635			659			683		
636			660			684		

637			661			685		
638			662			686		
639			663			687		
640			664			688		
641			665			689		
642			666			690		
645		-N(CH$_3$)$_2$	669		-N(CH$_3$)$_2$	693		-N(CH$_3$)$_2$
646			670			694		
647			671			695		
648			672			696		

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

In certain embodiments, the FXR-mediated disease or condition is cardiovascular disease, atherosclerosis, arteriosclerosis, hypercholesterolemia, or hyperlipidemia chronic liver disease, gastrointestinal disease, fibrotic diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, pulmonary fibrosis, renal fibrosis, liver fibrosis, renal disease, metabolic disease, cancer (i.e., colorectal cancer), or neurological indications such as stroke.

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

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

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

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

In one aspect, the compound is a selective FXR agonist over TGR5 activator.

In certain embodiments, the cancer is selected from colorectal cancer, liver cancer, heptacellular carcinoma, cholangio carcinoma, renal cancer, gastric cancer, pancreatic cancer, prostate cancer, and insulanoma.

In another aspect, the invention provides a method of treating a disease selected from an inflammatory disease, an autoimmune disease and a gastrointestinal disease in a subject in need thereof. The method comprises the step of administering to the subject a therapeutically effective amount of a compound of Formula I. In another aspect, the invention provides for the use of a compound of Formula I in the manufacture of a medicament for treating an inflammatory disease, an autoimmune disease or a gastrointestinal disease.

In certain embodiments, the inflammatory disease is selected from allergy, osteoarthritis, appendicitis, bronchial asthma, pancreatitis, allergic rash, and psoriasis.

In certain embodiments, the autoimmune disease is selected from rheumatoid arthritis, multiple sclerosis, and type I diabetes.

In certain embodiments, the gastrointestinal disease is selected from inflammatory bowel disease (Crohn's disease, ulcerative colitis), short bowel syndrome (post-radiation colitis), microscopic colitis, irritable bowel syndrome (malabsorption), and bacterial overgrowth.

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 a saturated, monovalent straight- or branched-chain hydrocarbon group. Preferred alkyl groups include C_1-C_6 alkyl and C_1-C_8 alkyl groups. Examples of C_1-C_6 alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, n-hexyl groups; and examples of C_1-C_8 alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, n-hexyl, heptyl, and octyl groups.

The term "alkenyl", as used herein, denote a monovalent group derived from a hydrocarbon moiety by the removal of a single hydrogen atom wherein the hydrocarbon moiety has at least one carbon-carbon double bond. Preferred alkenyl groups include C_2-C_6 alkenyl and C_2-C_8 alkenyl groups. 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, denotes a monovalent group derived from a hydrocarbon moiety by the removal of a single hydrogen atom wherein the hydrocarbon moiety has at least one carbon-carbon triple bond. Preferred alkynyl groups include C_2-C_6 alkynyl and C_2-C_8 alkynyl groups. 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, denotes a monovalent group derived from a monocyclic or polycyclic saturated carbocyclic ring, wherein the said polycyclic saturated carbocyclic ring is bi or tri cyclic group fused, bridged or spiro system, and one or more carbon atoms may be optionally oxo-substituted. Preferred cycloalkyl groups include C_3-C_8 cycloalkyl and C_3-C_{12} cycloalkyl groups. Examples of C_3-C_8-cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C_3-C_{12}-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.0]hexyl, spiro[2.5]octyl, spiro[4.4]nonanyl.

The term "cycloalkenyl" as used herein, denote a monovalent group derived from a monocyclic or polycyclic carbocyclic ring having at least one carbon-carbon double bond, wherein the said polycyclic cycloalkenyl ring is bi or tri cyclic group fused, bridged or spiro system, and one or more carbon atoms may be optionally oxo-substituted. Preferred cycloalkenyl groups include C_3-C_8 cycloalkenyl and C_3-C_{12} cycloalkenyl groups. Examples of C_3-C_8-cycloalkenyl include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C_3-C_{12}-cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cycloheptenyl, 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,and the like.

The term "aryl," as used herein, refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

The term “arylalkyl,” as used herein, refers to a C_1–C_3 alkyl or C_1–C_6 alkyl residue attached to an aryl ring. Examples include, but are not limited to, benzyl, phenethyl and the like.

The term "heteroaryl," as used herein, refers to a mono-, bi-, or tri-cyclic aromatic radical or ring having from five to ten ring atoms of which at least one ring atom is selected from S, O and N; wherein any N or S contained within the ring may be optionally oxidized. Preferred heteroaryl groups are monocyclic or bicyclic. Heteroaryl groups include, but are not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl, and the like.

The term “heteroarylalkyl,” as used herein, refers to a C_1–C_3 alkyl or C_1–C_6 alkyl residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

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 “substituted” as used herein, refers to independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited to, deuterium, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO_2, -CN, -NH_2, N_3, protected amino, alkoxy, thioalkoxy, oxo, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, C_2-C_{12}-alkynyl, C_3-C_{12}-cycloalkyl, -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, -OCON(C_1-C_{12}-alkyl$)_2$, -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 -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.

The term "heterocycloalkyl" and "heterocyclic" 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) each ring contains between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (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 a benzene ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted. 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, and tetrahydrofuryl. Such heterocyclic groups may be further substituted to give substituted heterocyclic. Heteroaryl or heterocyclic groups can be C-attached or N-attached (where possible).

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 “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 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 synthesized using methods known in the art, for example by employing deuterated starting materials. Unless stated to the contrary, isotopically labelled compounds are pharmaceutically acceptable.

When the compounds described herein contain one or more asymmetric centers they 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 or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. 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 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.

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

As used herein, the term "pharmaceutically acceptable ester" refers to esters of the compounds formed by the process of the present invention which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term “pharmaceutically acceptable prodrugs” as used herein refers to those prodrugs of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound, which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to afford any compound delineated by the Formulae of the instant invention. Various forms of prodrugs are known in the art, for example, as discussed in

Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed.), *Methods in Enzymology*, Vol. 4, Academic Press (1985); Krogsgaard-Larsen, *et al.*, (ed). "Design and Application of Prodrugs, *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991); Bundgaard, *et al.*, *Journal of Drug Deliver Reviews, 8*:1-38(1992); Bundgaard, J. of *Pharmaceutical Sciences, 77*:285 et seq. (1988); Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, *American Chemical Society* (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

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

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

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

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

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

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

The terms "protogenic organic solvent" or "protic solvent" as used herein, refer to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: *Organic Solvents Physical Properties and Methods of Purification*, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the *Techniques of Chemistry Series*, John Wiley & Sons, NY, 1986.

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

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, etc. delineated herein are for purposes of illustration only and variation of the reaction conditions can produce the desired isoxazole products of the present invention.

Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein include, for example, those described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995).

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

PHARMACEUTICAL COMPOSITIONS

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention Formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or Formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the Formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

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

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

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

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

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

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

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

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

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

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic Formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

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

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

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

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

ABBREVIATIONS

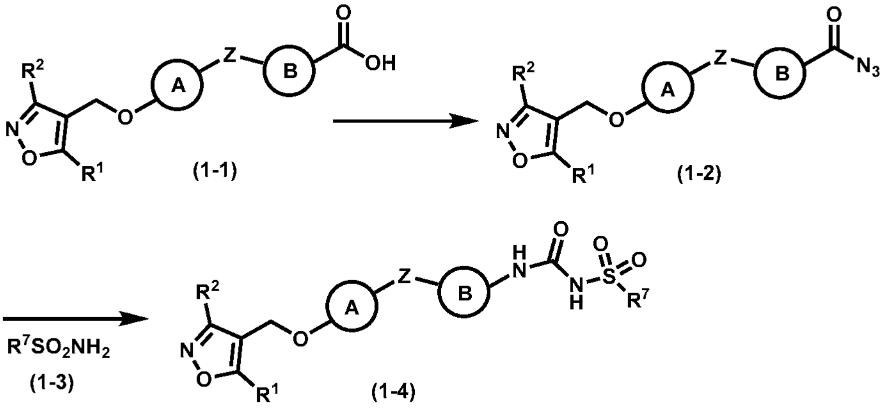
Abbreviations which have been used in the descriptions of the schemes and the examples that follow are:

BOP-Cl for bis(2-oxo-3-oxazolidinyl)phosphinic chloride;
CDI for carbonyldiimidazole;
DBU for 1,8-diazabicycloundec-7-ene;
DCC for *N,N'*-dicyclohexylcarbodiimide;
DCM for dichloromethane;
DMAP for *N,N*-dimethylaminopyridine;
DMF for *N,N*-dimethyl formamide;
DPPA for diphenylphosphoryl azide;
EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
Et_3N for triethylamine;
EtOAc for ethyl acetate;
HATU for 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate;
HCl for hydrochloric acid;
PyAOP for 7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate;
PyBOP for benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate;
TFFH for tetramethylfluoroformamidinium hexafluorophosphate;
THF for tetrahydrofuran.

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.

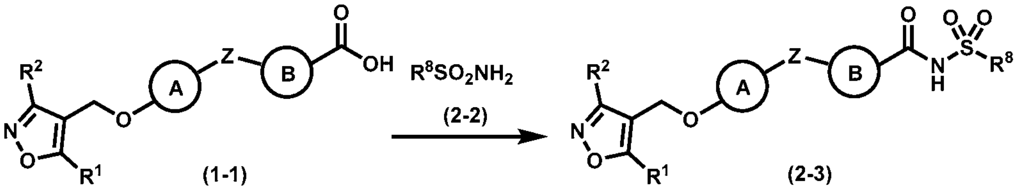
Scheme 1



As shown in Scheme 1, novel isoxazole sulfonyl urea analogs of the compound of formula (1-4) are prepared from the compound of formula (1-1), wherein R^1, R^2, Z, Ⓐ and Ⓑ are previously defined. Thus, the compound of formula (1-1) is converted to the acyl azide compound of formula (1-2) using a suitable reagent such as, but not limited to, DPPA. The reaction solvent can be, but not limited to, THF, DCM and toluene. The reaction temperature is from -20°C to 80°C. Alternatively, the acid (1-1) could be transformed to the acyl azide (1-2) via activated acid derivative such as acyl chlorides or anhydrides in presence of azide source. The reagents for activation of acid includes, but not limited to, tetramethylfluoroformadinium hexafluorophosphate, phenyl dichlorophosphate, $SOCl_2$-DMF, triphosgene, cyanuric chloride, NCS-Ph_3P and Cl_3CCN-Ph_3P. The azide source includes, but not limited to, sodium azide, tetrabutylammonium azide, trimethylsilyl azide and N,N,N',N'-tetramethylguanidinium azide. Curtius rearrangement of the compound of formula (1-2) at elevated temperature preferably from 50 °C to 120 °C lead to the isocyanate intermediate, which then can react with sulfonamide compound of formula (1-3) to afford the compound of formula (1-4). wherein R^1, R^2, Z, Ⓐ, Ⓑ and R^7 are previously defined.

As shown in Scheme 2, novel isoxazole acylsulfonamide analogs of the compound of Formula (2-1) are prepared from the compound of Formula (1-1), wherein R^1, R^2, Z, Ⓐ and Ⓑ, are as previously defined. The compound of Formula (1-1) is coupled with a sulfonamide using suitable coupling reagents in presence of suitable bases to give the compound of Formula (2-3), wherein R^1, R^2, Z, Ⓐ, Ⓑ, and R^8 are as previously defined. The coupling reagent can be selected from, but not limited to, DCC, EDC, CDI, diisopropyl carbodiimide, BOP-Cl, PyBOP, PyAOP, TFFH and HATU. Suitable bases include, but are not limited to, triethylamine, diisopropylethylamine, DBU, *N*-methylmorpholine and DMAP. The coupling reaction is carried out in an aprotic solvent such as, but not limited to, DCM, DMF or THF. The reaction temperature can vary from 0 °C to 80 °C.

Scheme 2

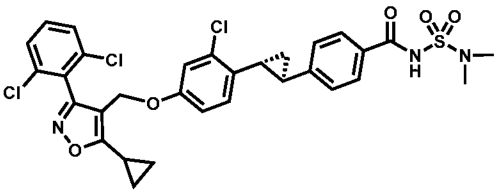


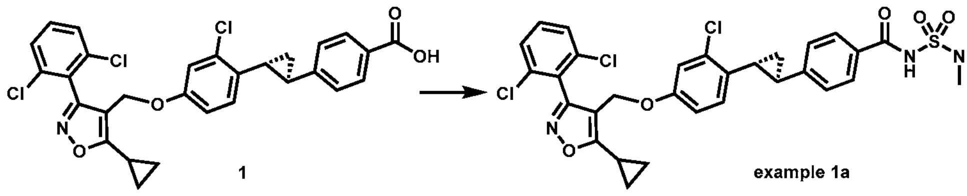
In the reactions described, reactive functional groups such as hydroxyl, amino, imino, thio or carboxy groups, may be protected to avoid unwanted participation in the reactions. These protecting groups may be removed at suitable steps via solovolysis, reduction, photolysis. The protection and deprotection are common practices in organic synthesis (see T.W. Greene and P.G.M Wuts, <u>Protective Groups in Organic Chemistry</u>, 4th Ed., Wiley-Interscience, 2006).

Examples

The following preparations and examples further illustrate the invention.

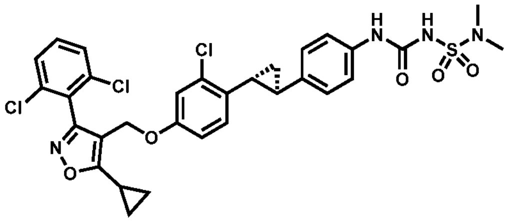
Example 1a

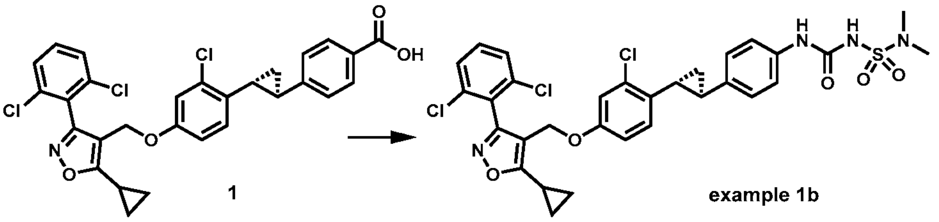




To the acid **1** (111 mg, 0.2 mmol) in DCM (2 mL) and DMF (1 mL) was added EDCI (77 mg, 0.4 mmol), DMAP (48.9 mg, 0.4 mmol) and N,N-dimethylsulfonamide (49.7 mg, 0.4 mmol) and the resulting mixture was stirred at room temperature for 16 hrs. The reaction was quenched with brine, extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and the filtrate was concentrated. The resulting residue was chromatographed with CombiFlash eluting with hexane to 50% acetone in hexane to give example **1a** (117 mg, 88%). LC/MS observed [M-H], 660.07.

Example 1b



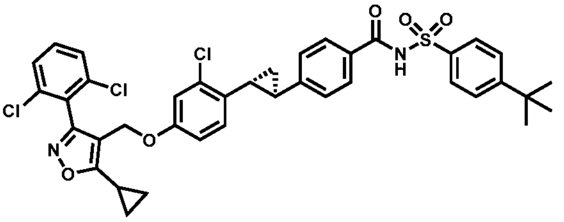


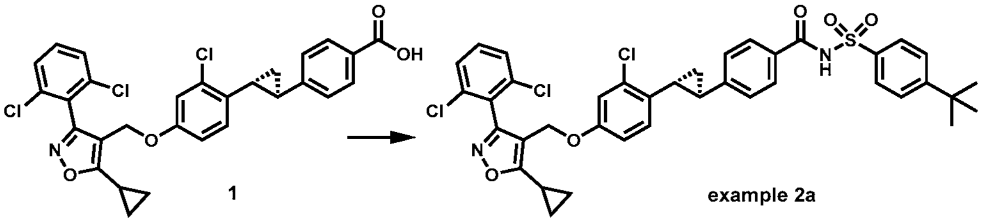
To the acid **1** (300 mg, 0.541 mmol) in toluene (3 mL) was added triethylamine (0.151 mL, 1.081 mmol), and diphenyl phosphorazidate (0.128 mL, 0.595 mmol) dropwise and the resulting mixture was stirred at room temperature for 1 hr, then at 85 °C for 3.5 hrs and 95 °C for 1 hr. The reaction was cooled down to room temperature and divided into two portions equally.

To one of the portion was added a solution of N,N-dimethylsulfamide (40.2 mg, 0.324 mmol) in THF (0.5 mL) and DBU (48.8 μL, 0.324 mmol) and the resulting mixture was stirred at room temperature for 14 hrs. The mixture was quenched with 1N HCl and extracted with ethyl acetate (2X). The combined organic layers was dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The resulting residue was chromatographed with silica gel eluting with hexane to 30% acetone in hexane which is further purified with C18 column eluted with

50% MeCN in water to 90% MeCN in water to give example **1b** (5 mg). LC/MS observed [M-H], 675.08; 673.08.

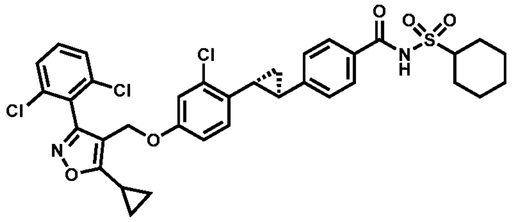
Example 2a

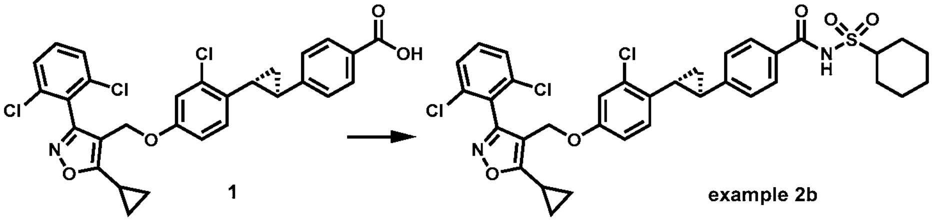




To the acid **1** (85 mg, 0.4 mmol) in DCM (2 mL) and DMF (1 mL) was added EDCI (77 mg, 0.4 mmol) DMAP (48.9 mg, 0.4 mmol) and 4-(tert-butyl)benzenesulfonamide (85 mg, 0.4 mmol) and the resulting mixture was stirred at room temperature for 16 hrs. The reaction was quenched with brine, extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and the filtrate was concentrated. The resulting residue was chromatographed with CombiFlash eluting with hexane to 55% acetone in hexane to give example 2a (102 mg, 68%). LC/MS observed [M-H], 751.13.

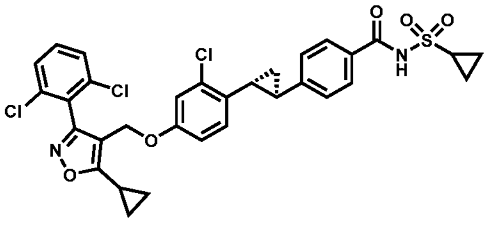
Example 2b

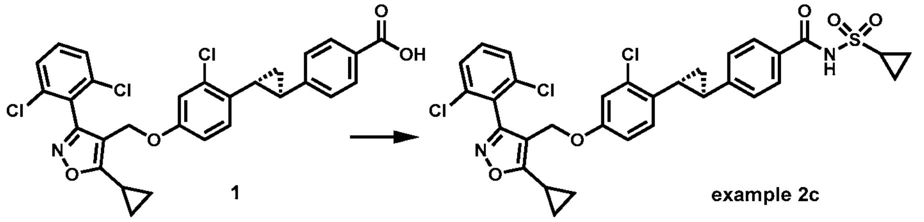




To the acid **1** (111 mg, 0.2 mmol) in DCM (2 mL) and DMF (1 mL) was added EDCI (77 mg, 0.4 mmol), DMAP (48.9 mg, 0.4 mmol) and piperidine-1-sulfonamide (65.7 mg, 0.4 mmol) and the resulting mixture was stirred at room temperature for 16 hrs. The reaction was quenched with brine, extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and the filtrate was concentrated. The resulting residue was chromatographed with CombiFlash eluting with hexane to 50% acetone in hexane to give example 2b (120 mg, 86%). LC/MS observed [M-H], 700.11.

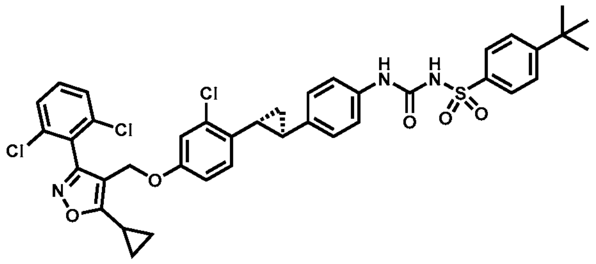
Example 2c

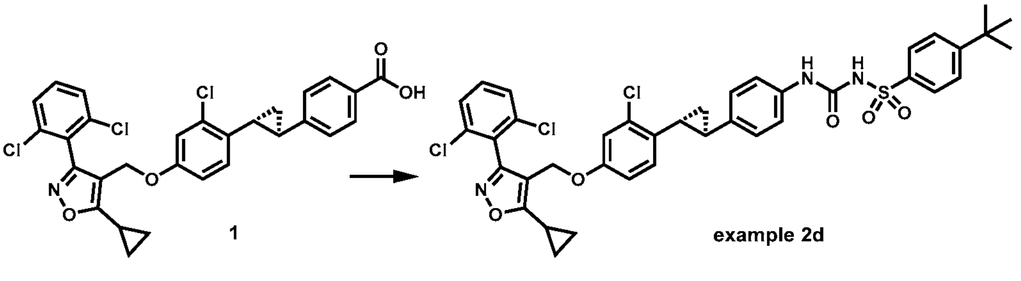




To the acid **1** (111 mg, 0.2 mmol) in DCM (2 mL) and DMF (1 mL) was added EDCI (77 mg, 0.4 mmol), DMAP (48.9 mg, 0.4 mmol) and cyclopropanesulfonamide (48.5 mg, 0.4 mmol) and the resulting mixture was stirred at room temperature for 16 hrs. The reaction was quenched with brine, extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and the filtrate was concentrated. The resulting residue was chromatographed with CombiFlash eluting with hexane to 60% acetone in hexane to give example 2c (79 mg, 60%). LC/MS observed [M-H], 657.06.

Example 2d





To the acid **1** (300 mg, 0.541 mmol) in toluene (3 mL) was added triethylamine (0.151 mL, 1.081 mmol), and diphenyl phosphorazidate (0.128 mL, 0.595 mmol) dropwise and the resulting mixture was stirred at room temperature for 1 hr, then at 85 °C for 3.5 hrs and 95 °C for 1 hr. The reaction was cooled down to room temperature and divided into two portions equally.

To one of the portion was added a solution of 4-(tert-butyl)benzenesulfonamide (69.1 mg, 0.324 mmol) in THF (0.5 mL) and DBU (48.8 uL, 0.324 mmol) and the resulting mixture was stirred at room temperature for 14 hrs. The mixture was quenched with 1N HCl and extracted with ethyl acetate (2X). The combined organic layers was dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The resulting residue was chromatographed with silica gel eluting with hexane to 30% acetone in hexane which is further purified with C18 column eluted with 50% MeCN in water to 90% MeCN in water to give example 2d (5.4 mg). LC/MS observed [M -H], 764.13; 762.14.

ASSAYS

Human FXR (NR1H4) Assay

Determination of a ligand mediated Gal4 promoter driven transactivation to quantify ligand binding mediated activation of FXR. FXR Reporter Assay kit purchased from Indigo Bioscience (Catalogue number: IB00601) to determine the potency and efficacy of compound developed by Enanta that can induce FXR activation. The principle application of this reporter assay system is to quantify functional activity of human FXR. The assay utilizes non-human mammalian cells, CHO (Chinese hamster ovary) cells engineered to express human NR1H4 protein (referred to as FXR). Reporter cells also incorporate the cDNA encoding beetle luciferase which catalyzes the substrates and yields photon emission. Luminescence intensity of the reaction is quantified using a plate-reading luminometer, Envision. Reporter Cells include the luciferase reporter gene functionally linked to an FXR responsive promoter. Thus, quantifying changes in luciferase expression in the treated reporter cells provides a sensitive surrogate measure of the changes in FXR activity. EC_{50} and efficacy (normalize to CDCA set as 100%) is determined by XLFit. The assay is according to the manufacturer's instructions. In brief, the assay was performed in white, 96 well plates using final volume of 100ul containing cells with different doses of compounds. Retrieve Reporter Cells from -80°C storage. Perform a rapid thaw of the frozen cells by transferring a 10 ml volume of 37°C cell recovery medium into the tube of frozen cells. Recap the tube of Reporter Cells and immediately place it in a 37°C water bath for 5 - 10 minutes. Retrieve the tube of Reporter Cell Suspension from the water bath. Sanitize the outside surface of the tube with a 70% alcohol swab, and then transfer it into the cell culture hood. Dispense 90 µl of cell suspension into each well of the 96-well Assay Plate. Transfer the plate into 37°C incubator, allowing the cells adherent to the bottom of the well. Dilute compounds in Dilution Plate (DP), and administrate to cells at Assay Plate (AP). DMSO content of the samples was kept at 0.2%. Cells were incubated for additional 22 hours before luciferase activities were measured. Thirty minutes before intending to quantify FXR activity, remove Detection Substrate and Detection Buffer from the refrigerator and place them in a low-light area so that they may equilibrate to room temperature. Remove the plate's lid and discard all media contents by ejecting it into an appropriate waste container. Gently tap the inverted plate onto a clean absorbent paper towel to remove residual droplets. Cells will remain tightly adhered to well bottoms. Add 100 µl of luciferase detection reagent to each well of the assay plate. Allow the assay plate to rest at room temperature for at least 5 minutes following the addition of LDR. Set the instrument (Envision) to perform a single 5 second "plate shake" prior to reading the first assay well. Read time may be 0.5 second (500mSec) per well. EC_{50} and Efficacy (normalize to CDCA set as 100%) is determined by XLFit.

To assess the FXR agonistic potency of the example compounds as well as for reference compound, potency ranges were determined in the Human FXR (NR1H4) Assay as listed below in Table 9. The efficacy was normalized to CDCA set as 100%. (A=EC50 < 0.1 µM; B= 0.1 µM < EC50 < 1.0 µM; C=1.0µM < EC50 < 10 µM; D= EC50 > 10 µM).

Table 9

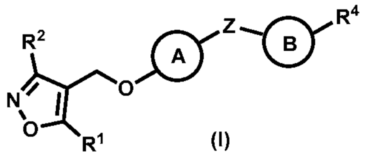
Example	EC50 (µM)	Efficacy (%)
CDCA	D	100
6-ECDCA	B	223
2a	C	115
2b	B	279
2c	B	209
2d	B	236
1a	B	271
1b	C	194

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

CLAIMS

WHAT IS CLAIMED IS:

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



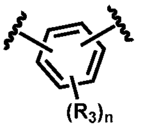
(I)

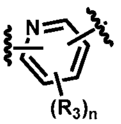
wherein:

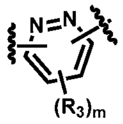
R^1 is hydrogen, halogen, cyano, optionally substituted -C_1-C_6 alkyl, optionally substituted -C_2-C_6 alkenyl, optionally substituted -C_2-C_6 alkynyl, optionally substituted -C_3-C_6 cycloalkyl or optionally substituted 3- to 6- membered heterocycloalkyl;

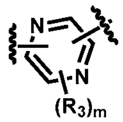
R^2 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted –C_3-C_{12} cycloalkyl or optionally substituted 3- to 12- membered heterocycloalkyl;

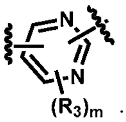
Ⓐ is selected from the group consisting of:







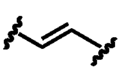


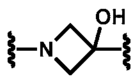


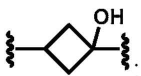
; wherein

R^3 is independently selected from group consisting of halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_3-C_6 cycloalkyl, optionally substituted C_3-C_6 cycloalkenyl, optionally substituted 3- to 6- membered heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl; m is 0, 1, or 2; n is 0, 1, 2, or 3;

Z is selected from the group consisting of:



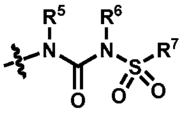
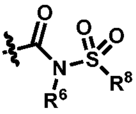




;

Ⓑ is phenyl, 3- to 8- membered heterocycloalkyl, or heteroaryl wherein said phenyl, 3- to 8- membered heterocycloalkyl, or heteroaryl is optionally substituted with one or two groups independently selected from OH, halogen, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_3-C_6 cycloalkyl, $N(R^b)SO_2C_1$-C_6 alkyl, -$C(O)R^b$, and $NHC(O)R^b$;

R^b is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_3-C_6 cycloalkyl, or optionally substituted C_3-C_6 cycloalkenyl;

R^4 is:  or ;

R^5 and R^6 are independently selected from the group consisting of:

1) hydrogen;
2) Optionally substituted $-C_1$-C_8 alkyl;
3) Optionally substituted $-C_2$-C_8 alkenyl;
4) Optionally substituted $-C_2$-C_8 alkynyl; and
5) Optionally substituted $-C_3$-C_8 cycloalkyl;

R^7 is selected from the group consisting of:

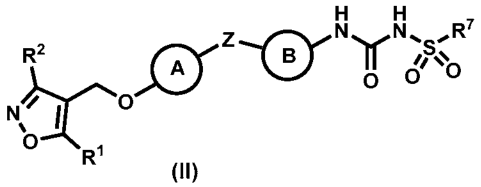
1) Optionally substituted $-C_1$-C_8 alkyl;
2) Optionally substituted $-C_2$-C_8 alkenyl;
3) Optionally substituted $-C_2$-C_8 alkynyl;
4) Optionally substituted $-C_3$-C_{12} cycloalkyl;
5) Optionally substituted $-C_3$-C_{12} cycloalkenyl;
6) Optionally substituted aryl;
7) Optionally substituted arylalkyl;
8) Optionally substituted 3- to 12- membered heterocycloalkyl;
9) Optionally substituted heteroaryl;
10) Optionally substituted heteroarylalkyl; and
11) NR^9R^{10}; wherein R^9 and R^{10} are each independently selected from hydrogen, optionally substituted $-C_1$-C_8 alkyl, optionally substituted$-C_2$-C_8 alkenyl, optionally substituted$-C_2$-C_8 alkynyl, optionally substituted$-C_3$-C_8 cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted 3- to 8- membered heterocycloalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl; alternatively, R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic ring;

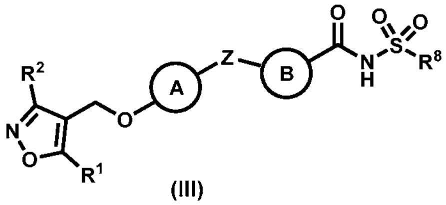
R^8 is selected from the group consisting of:

1) Optionally substituted $-C_3$-C_{12} cycloalkyl;
2) Optionally substituted $-C_3$-C_{12} cycloalkenyl;
3) Optionally substituted 3- to 12- membered heterocycloalkyl ;

4) Optionally substituted aryl;
5) Optionally substituted arylalkyl;
6) Optionally substituted heteroaryl;
7) Optionally substituted heteroarylalkyl; and
8) $NR^{12}R^{13}$; wherein R^{12} and R^{13} are each independently selected from hydrogen, optionally substituted $-C_1$-C_8 alkyl, optionally substituted$-C_2$-C_8 alkenyl, optionally substituted$-C_2$-C_8 alkynyl, optionally substituted$-C_3$-C_8 cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted 3- to 8-membered heterocycloalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, alternatively, R^{12} and R^{13} are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic ring; provided that at least one of R^{12} and R^{13} is not hydrogen.

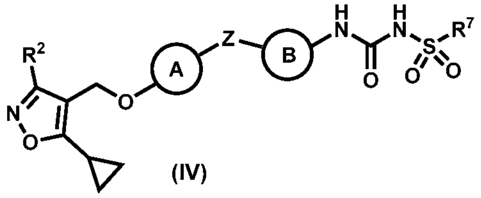
2. The compound of claim 1, represented by Formula II or III, or a pharmaceutically acceptable salt thereof:

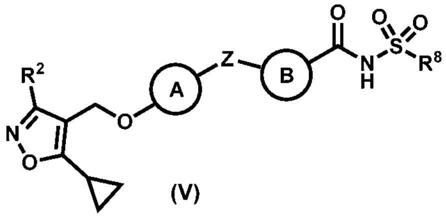

(II)


(III)

wherein R^1, R^2, Ⓐ, Z, Ⓑ, R^7 and R^8 are as defined in claim 1.

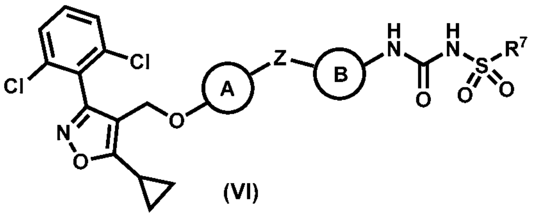
3. The compound of claim 1, represented by Formula IV or V, or a pharmaceutically acceptable salt thereof:

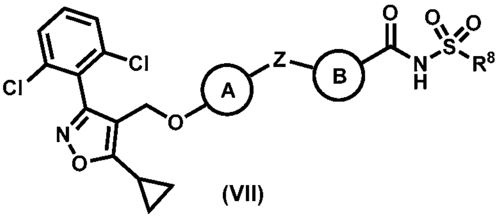

(IV)


(V)

wherein R^2, Ⓐ, Z, Ⓑ, R^7 and R^8 are as defined in claim 1.

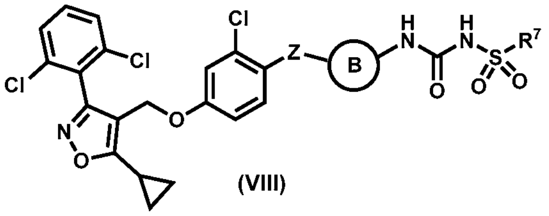
4. The compound of claim 1, represented by Formula VI or VII, or a pharmaceutically acceptable salt thereof:

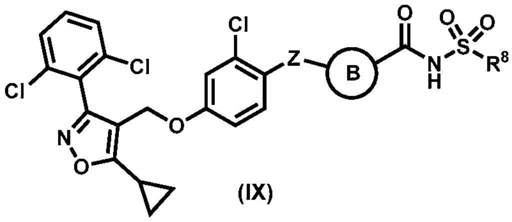

(VI)


(VII)

wherein Ⓐ, Z, Ⓑ, R^7 and R^8 are as defined in claim 1.

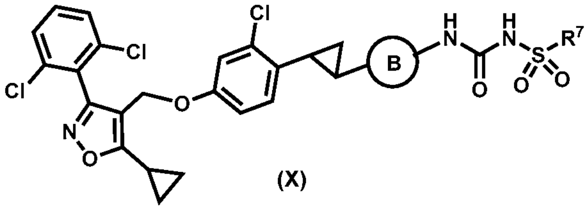
5. The compound of claim 1, represented by Formula VIII or IX, or a pharmaceutically acceptable salt thereof:

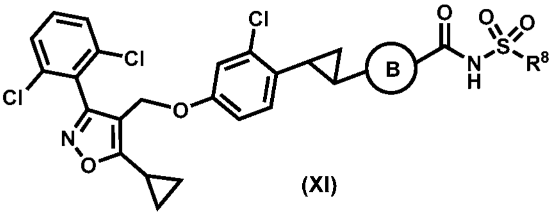

(VIII)

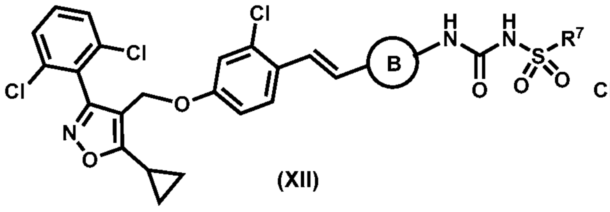

(IX)

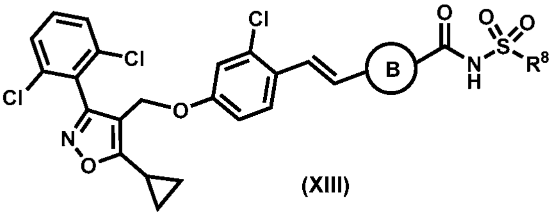
wherein Z, Ⓑ, R^7 and R^8 are as defined in claim 1.

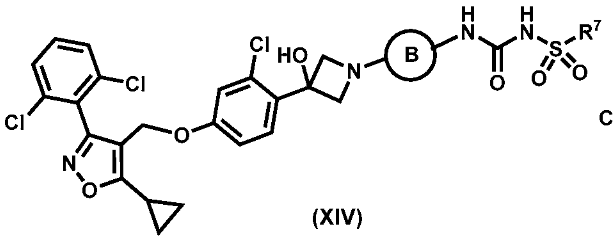
6. A compound of claim 1, represented by Formula X, XI, XII, XIII, XIV, XV, XVI or XVII, or a pharmaceutically acceptable salt thereof:

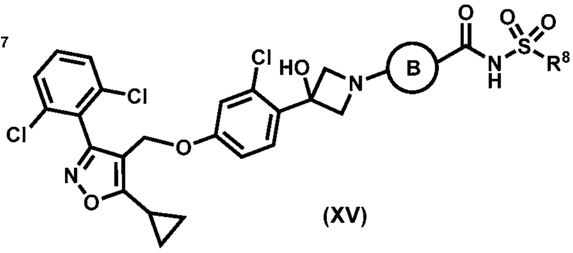

(X)

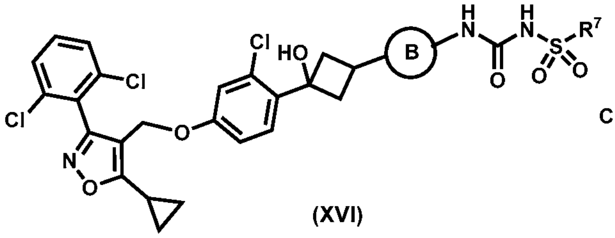

(XI)


(XII)

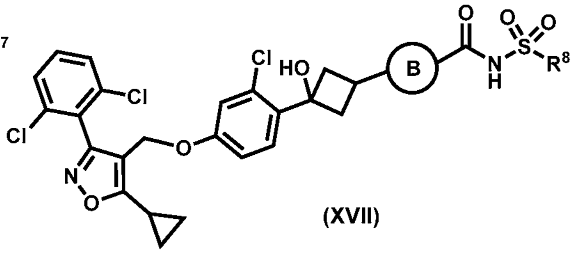

(XIII)


(XIV)


(XV)



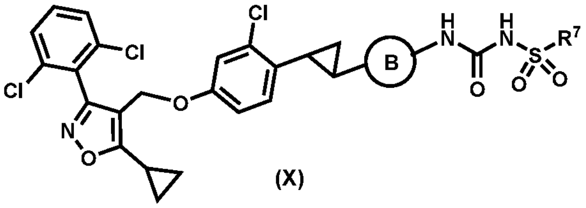
(XVI)



(XVII)

wherein B, R^7 and R^8 are as defined in claim 1.

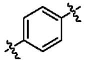
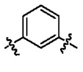
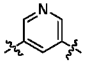
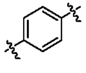
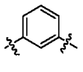
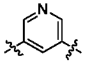
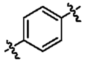
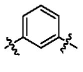
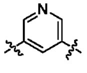
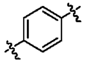
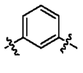
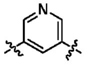
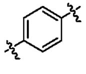
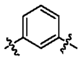
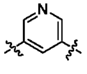
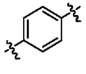
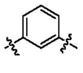
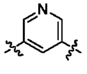
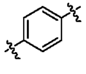
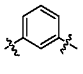
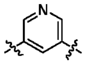
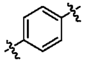
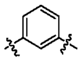
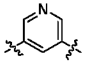
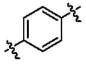
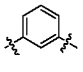
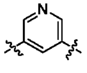
7. The compound of claim 1, which is selected from:
   (a) compounds of Formula (X) ,

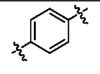
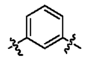
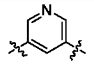
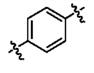
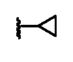
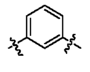
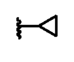
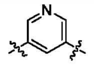
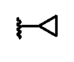
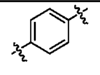
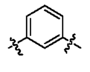
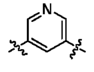
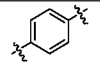
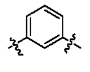
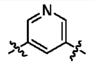
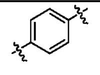
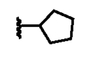
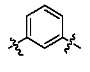
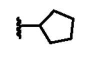
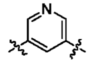
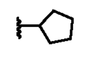
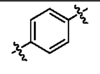
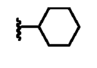
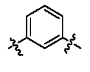
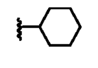
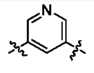
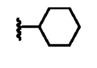
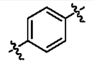
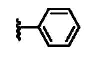
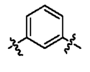
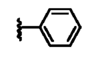
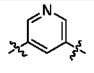
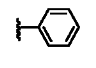
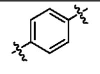
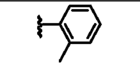
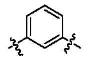
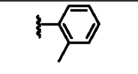
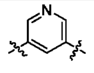
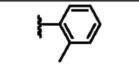
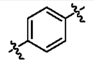
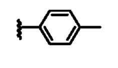
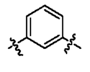
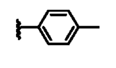
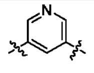
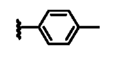
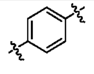
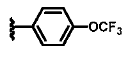
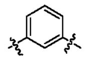
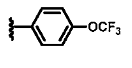
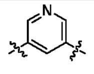
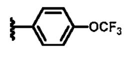
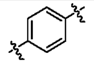
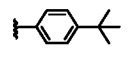
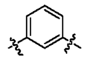
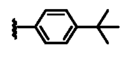
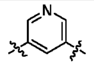
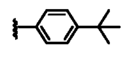
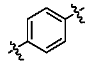
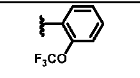
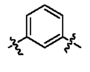
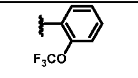
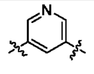
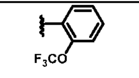
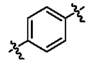
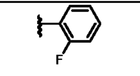
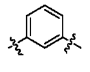
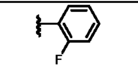
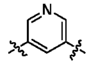
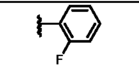
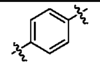
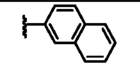
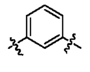
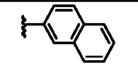
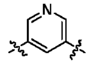
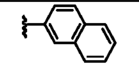
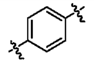
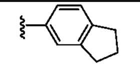
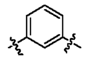
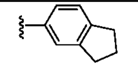
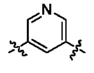
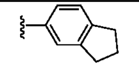
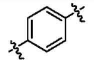
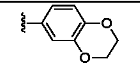
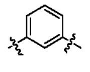
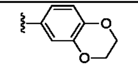
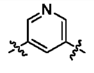
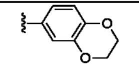
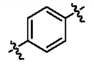
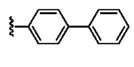
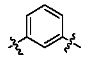
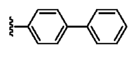
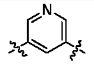
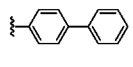
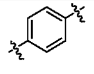
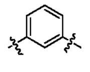
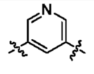
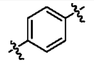
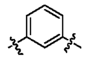
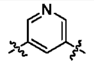
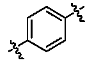
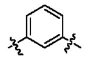
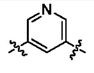
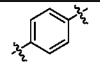
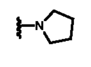
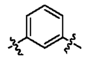
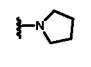
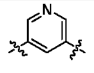
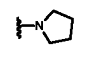
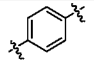
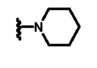
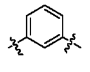
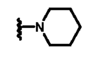
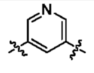
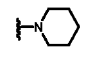


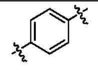
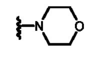
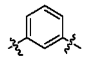
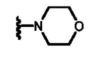
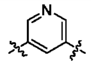
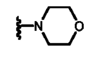
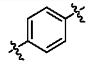
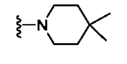
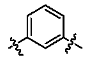
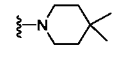
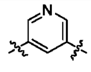
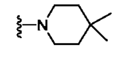
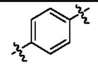
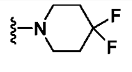
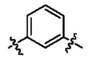
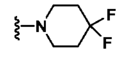
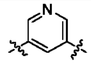
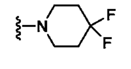
(X)

wherein R^7 and B are delineated for each compound in Table 1:

Table 1

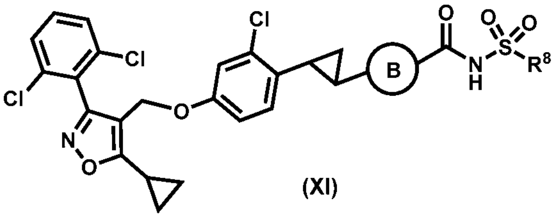
Compound	B	R^7	Compound	B	R^7	Compound	B	R^7
1		Methyl	35		Methyl	69		Methyl
2		Ethyl	36		Ethyl	70		Ethyl
3		Isopropyl	37		Isopropyl	71		Isopropyl
4		Butyl	38		Butyl	72		Butyl
5		t-Butyl	39		t-Butyl	73		t-Butyl
6		Propyl	40		Propyl	74		Propyl
7		Benzyl	41		Benzyl	75		Benzyl
8		Vinyl	42		Vinyl	76		Vinyl
9		Allyl	43		Allyl	77		Allyl

10		-CF_3	44		-CF_3	78		-CF_3
11			45			79		
12			46			80		
13			47			81		
14			48			82		
15			49			83		
16			50			84		
17			51			85		
18			52			86		
19			53			87		
20			54			88		
21			55			89		
22			56			90		
23			57			91		
24			58			92		
25			59			93		
26			60			94		
27		-NH_2	61		-NH_2	95		-NH_2
28		-$NHCH_3$	62		-$NHCH_3$	96		-$NHCH_3$
29		-$N(CH_3)_2$	63		-$N(CH_3)_2$	97		-$N(CH_3)_2$
30			64			98		
31			65			99		

32			66			100		
33			67			101		
34			68			102		

and

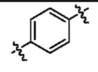
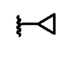
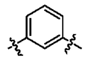
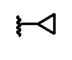
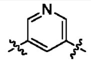
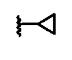
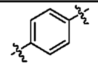
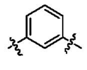
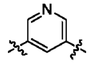
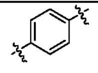
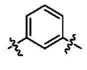
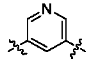
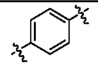
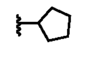
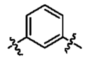
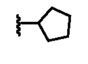
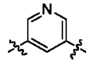
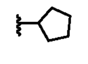
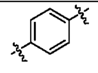
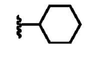
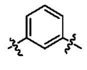
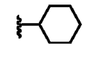
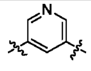
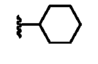
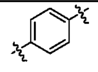
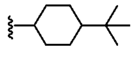
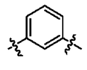
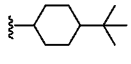
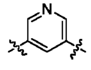
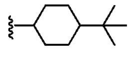
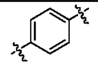
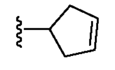
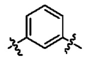
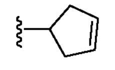
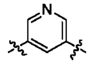
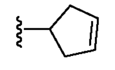
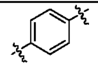
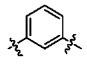
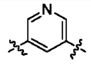
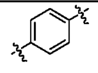
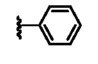
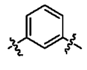
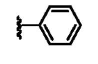
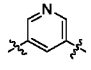
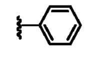
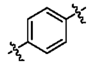
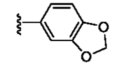
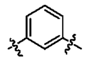
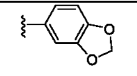
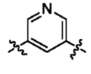
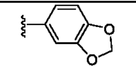
(b) compounds of Formula (XI),

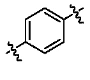
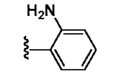
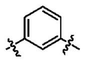
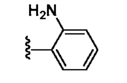
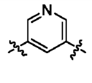
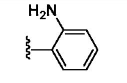
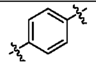
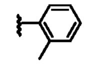
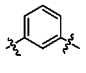
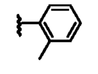
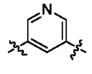
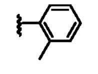
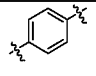
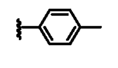
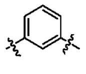
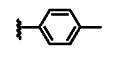
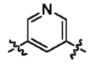
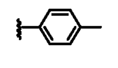
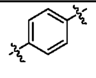
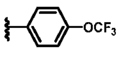
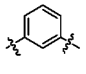
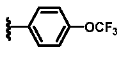
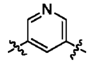
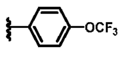
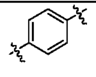
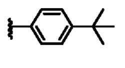
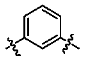
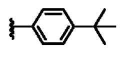
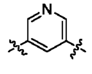
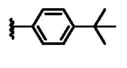
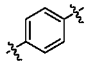
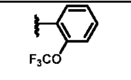
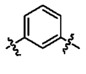
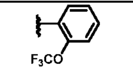
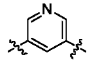
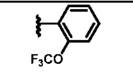
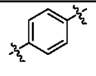
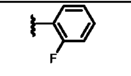
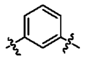
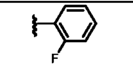
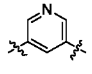
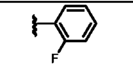
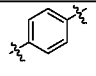
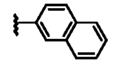
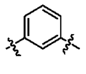
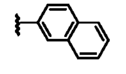
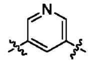
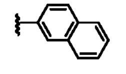
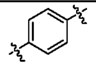
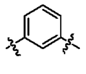
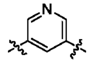
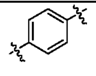
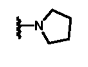
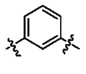
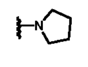
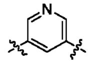
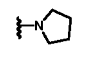
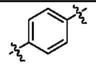
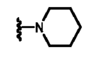
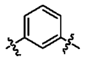
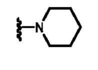
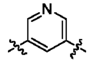
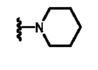
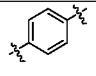
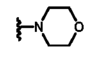
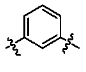
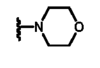
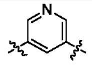
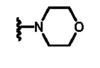


(XI)

wherein R^8 and Ⓑ are delineated for each compound in Table 2:

Table 2

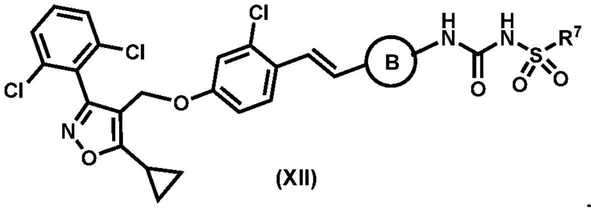
Compound	Ⓑ	R^8	Compound	Ⓑ	R^8	Compound	Ⓑ	R^8
103			127			151		
104			128			152		
105			129			153		
106			130			154		
107			131			155		
108			132			156		
109			133			157		
110		Benzyl	134		Benzyl	158		Benzyl
111			135			159		
112			136			160		

113			137			161		
114			138			162		
115			139			163		
116			140			164		
117			141			165		
118			142			166		
119			143			167		
120			144			168		
123		$-N(CH_3)_2$	147		$-N(CH_3)_2$	171		$-N(CH_3)_2$
124			148			172		
125			149			173		
126			150			174		

or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, which is selected from:

(a) compounds of Formula (XII),

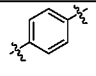
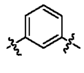
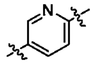


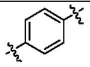
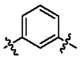
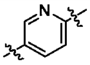
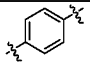
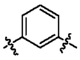
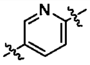
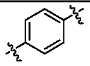
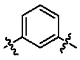
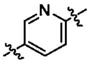
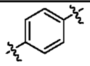
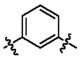
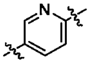
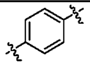
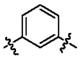
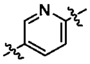
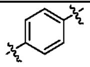
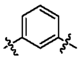
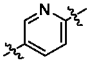
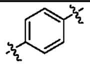
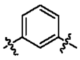
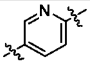
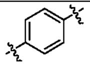
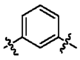
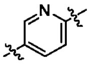
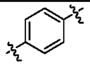
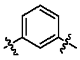
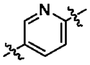
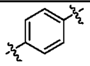
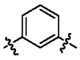
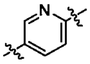
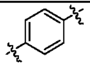
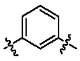
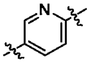
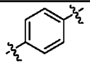
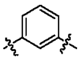
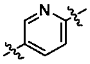
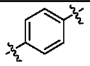
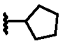
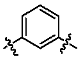
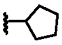
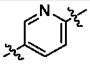
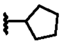
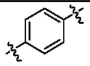
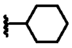
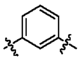
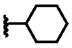
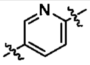
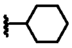
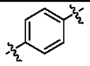
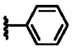
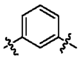
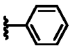
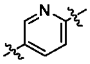
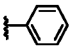
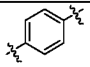
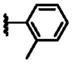
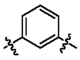
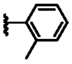
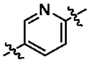
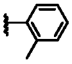
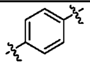
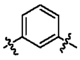
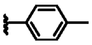
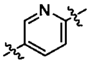
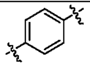
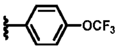
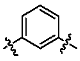
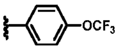
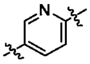
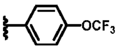
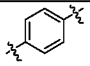
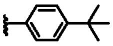
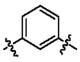
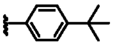
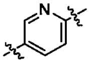
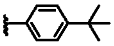
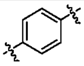
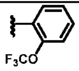
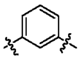
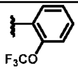
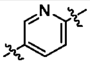
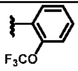
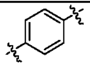
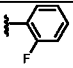
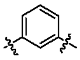
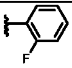
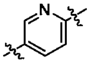
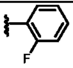
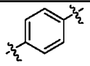
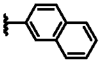
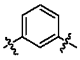
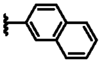
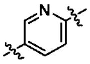
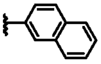
(XII)

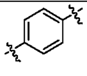
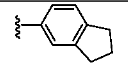
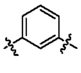
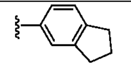
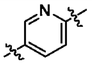
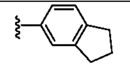
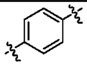
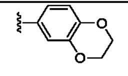
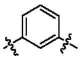
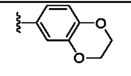
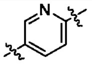
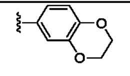
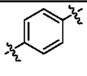
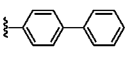
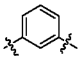
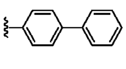
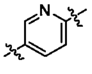
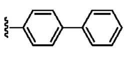
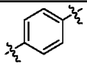
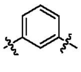
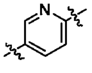
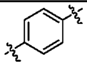
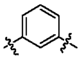
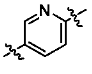
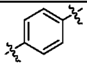
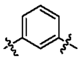
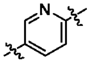
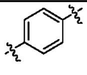
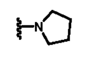
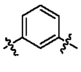
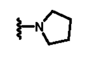
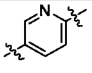
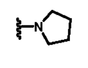
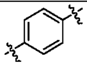
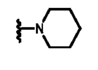
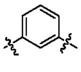
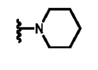
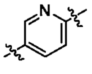
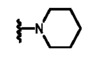
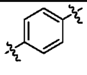
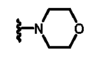
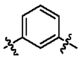
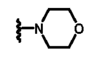
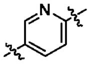
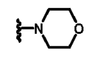
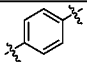
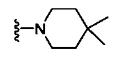
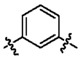
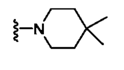
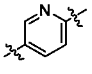
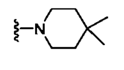
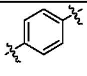
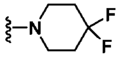
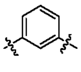
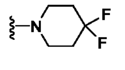
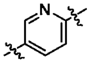
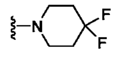
,

wherein R^7 and Ⓑ are delineated for each compound in Table 3:

Table 3

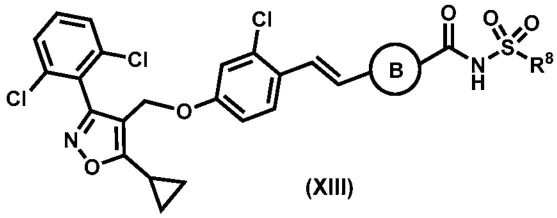
Compound	Ⓑ	R^7	Compound	Ⓑ	R^7	Compoud	Ⓑ	R^7
175		Methyl	209		Methyl	243		Methyl

176		Ethyl	210		Ethyl	244		Ethyl
177		Isopropyl	211		Isopropyl	245		Isopropyl
178		Butyl	212		Butyl	246		Butyl
179		t-Butyl	213		t-Butyl	247		t-Butyl
180		Propyl	214		Propyl	248		Propyl
181		Benzyl	215		Benzyl	249		Benzyl
182		Vinyl	216		Vinyl	250		Vinyl
183		Allyl	217		Allyl	251		Allyl
184		$-CF_3$	218		$-CF_3$	252		$-CF_3$
185			219			253		
186			220			254		
187			221			255		
188			222			256		
189			223			257		
190			224			258		
191			225			259		
192			226			260		
193			227			261		
194			228			262		
195			229			263		
196			230			264		
197			231			265		

198			232			266		
199			233			267		
200			234			268		
201		$-NH_2$	235		$-NH_2$	269		$-NH_2$
202		$-NHCH_3$	236		$-NHCH_3$	270		$-NHCH_3$
203		$-N(CH_3)_2$	237		$-N(CH_3)_2$	271		$-N(CH_3)_2$
204			238			272		
205			239			273		
206			240			274		
207			241			275		
208			242			276		

and

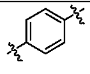
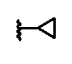
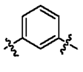
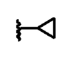
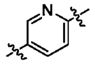
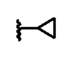
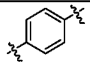
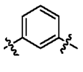
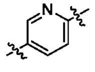
(b) compounds of Formula XIII,

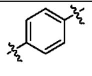
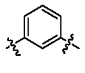
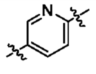
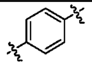
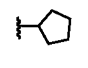
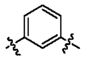
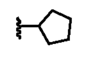
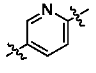
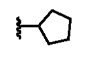
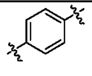
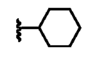
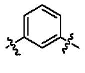
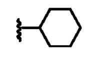
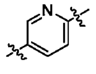
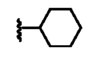
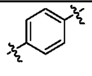
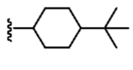
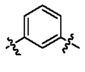
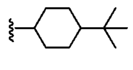
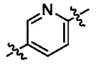
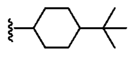
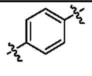
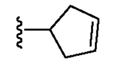
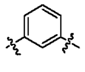
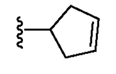
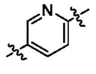
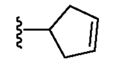
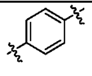
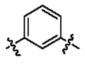
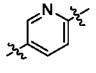
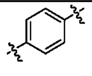
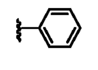
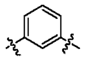
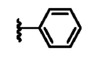
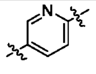
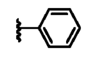
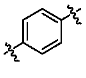
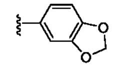
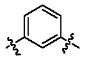
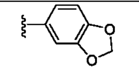
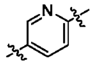
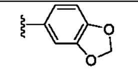
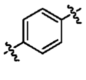
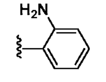
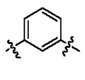
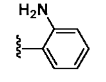
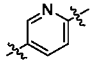
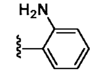
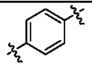
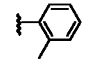
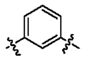
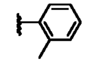
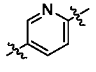
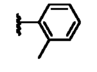
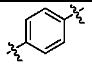
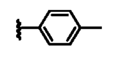
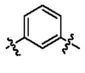
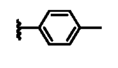
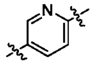
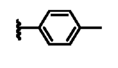
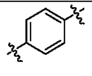
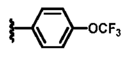
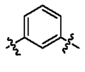
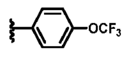
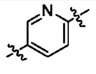
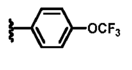
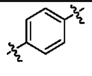
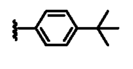
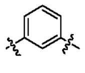
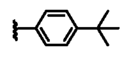
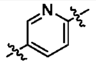
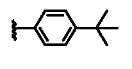
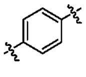
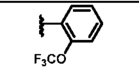
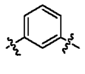
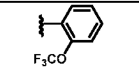
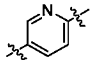
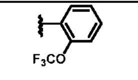
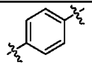
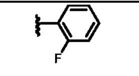
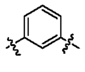
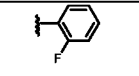
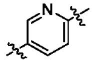
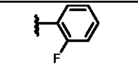
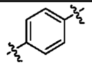
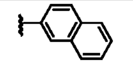
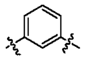
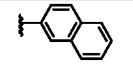
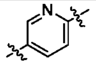
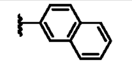
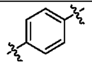
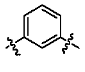
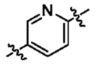
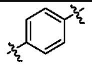
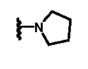
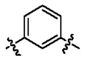
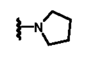
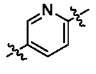
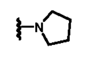
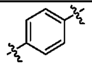
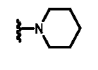
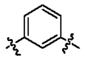
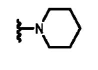
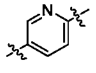
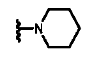
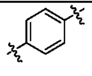
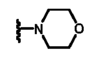
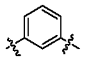
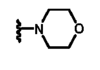
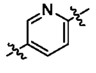
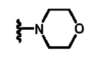


(XIII)

wherein R^8 and Ⓑ are delineated for each compound in Table 4:

Table 4

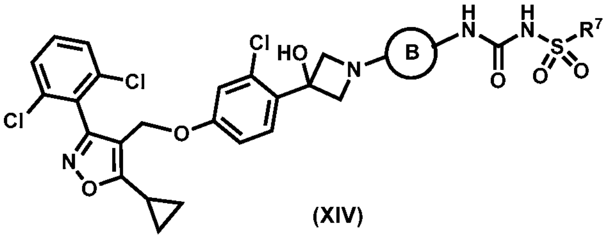
Compound	Ⓑ	R^7	Compound	Ⓑ	R^7	Compound	Ⓑ	R^7
277			301			325		
278			302			326		

279			303			327		
280			304			328		
281			305			329		
282			306			330		
283			307			331		
284		Benzyl	308		Benzyl	332		Benzyl
285			309			333		
286			310			334		
287			311			335		
288			312			336		
289			313			337		
290			314			338		
291			315			339		
292			316			340		
293			317			341		
294			318			342		
297		$-N(CH_3)_2$	321		$-N(CH_3)_2$	345		$-N(CH_3)_2$
298			322			346		
299			323			347		
300			324			348		

or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, which is selected from:

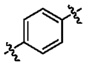
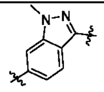
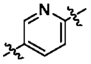
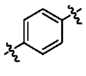
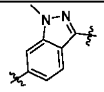
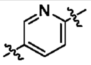
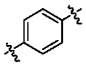
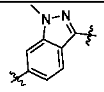
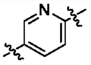
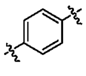
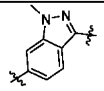
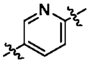
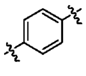
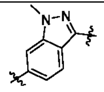
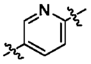
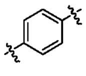
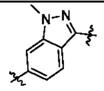
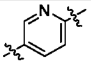
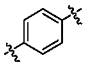
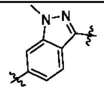
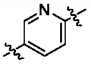
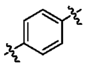
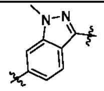
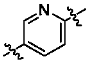
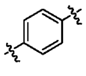
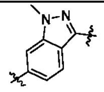
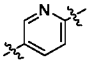
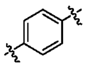
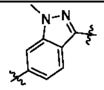
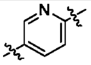
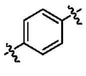
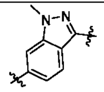
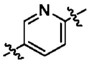
(a) compounds of Formula (XIV),

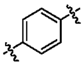
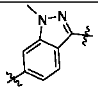
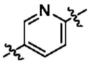
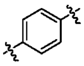
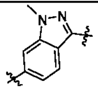
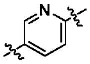
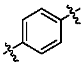
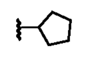
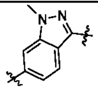
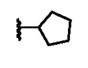
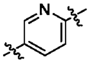
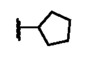
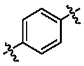
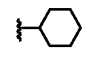
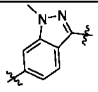
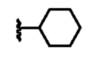
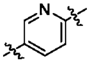
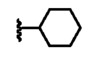
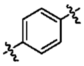
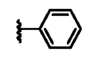
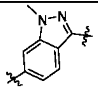
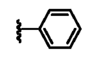
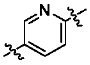
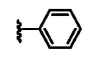
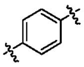
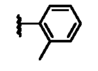
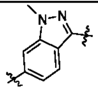
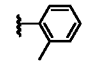
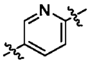
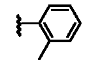
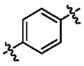
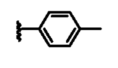
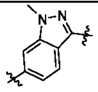
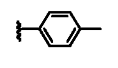
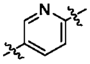
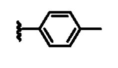
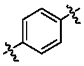
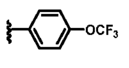
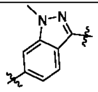
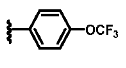
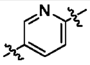
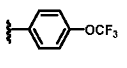
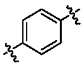
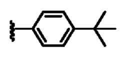
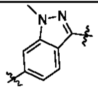
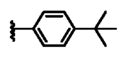
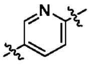
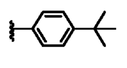
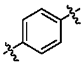
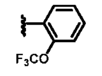
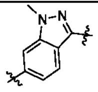
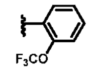
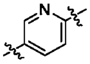
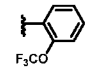
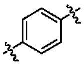
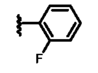
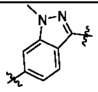
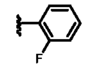
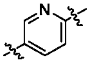
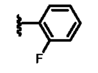
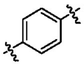
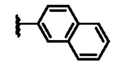
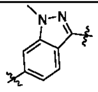
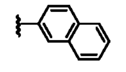
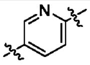
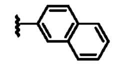
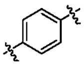
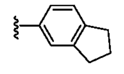
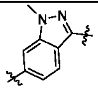
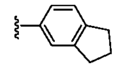
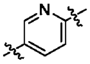
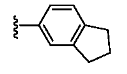
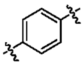
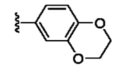
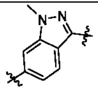
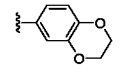
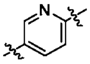
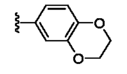
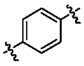
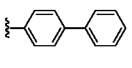
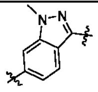
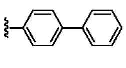
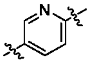
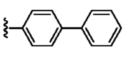
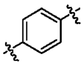
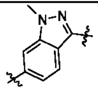
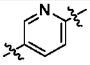
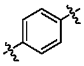
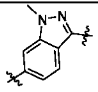
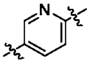


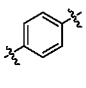
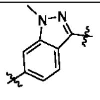
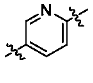
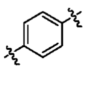
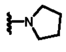
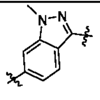
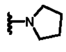
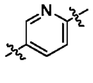
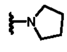
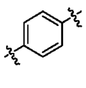
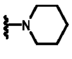
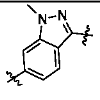
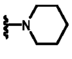
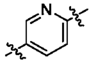
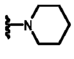
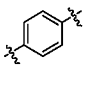
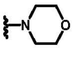
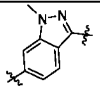
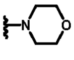
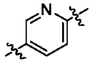
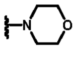
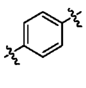
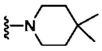
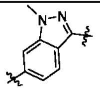
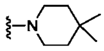
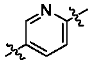
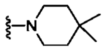
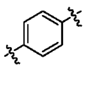
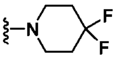
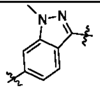
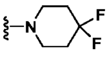
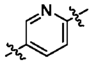
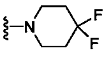
(XIV)

wherein R^7 and Ⓑ are delineated for each compound in Table 5:

Table 5

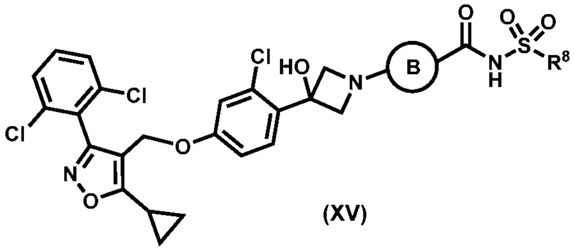
Compound	Ⓑ	R^7	Compound	Ⓑ	R^7	Compound	Ⓑ	R^7
349		Methyl	383		Methyl	417		Methyl
350		Ethyl	384		Ethyl	418		Ethyl
351		Isopropyl	385		Isopropyl	419		Isopropyl
352		Butyl	386		Butyl	420		Butyl
353		t-Butyl	387		t-Butyl	421		t-Butyl
354		Propyl	388		Propyl	422		Propyl
355		Benzyl	389		Benzyl	423		Benzyl
356		Vinyl	390		Vinyl	424		Vinyl
357		Allyl	391		Allyl	425		Allyl
358		$-CF_3$	392		$-CF_3$	426		$-CF_3$
359			393			427		

360			394			428		
361			395			429		
362			396			430		
363			397			431		
364			398			432		
365			399			433		
366			400			434		
367			401			435		
368			402			436		
369			403			437		
370			404			438		
371			405			439		
372			406			440		
373			407			441		
374			408			442		
375		-NH₂	409		-NH₂	443		-NH₂
376		-NHCH₃	410		-NHCH₃	444		-NHCH₃

377		-N(CH3)2	411		-N(CH3)2	445		-N(CH3)2
378			412			446		
379			413			447		
380			414			448		
381			415			449		
382			416			450		

and

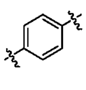
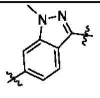
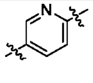
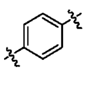
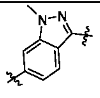
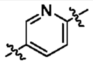
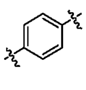
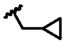
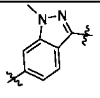
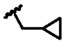
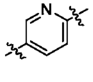
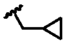
(b) compounds of Formula (XV),

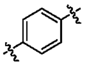
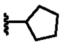
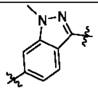
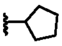
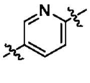
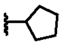
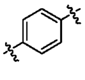
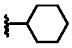
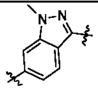
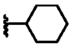
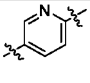
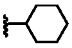
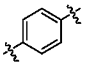
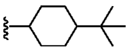
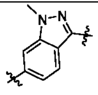
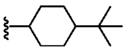
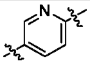
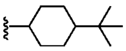
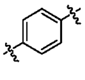
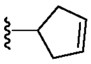
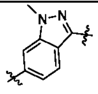
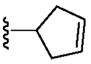
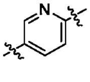
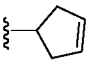
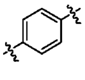
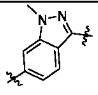
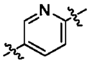
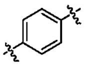
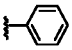
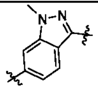
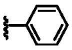
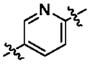
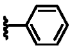
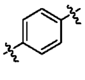
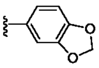
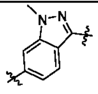
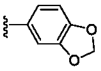
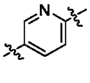
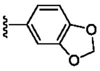
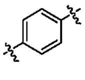
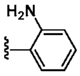
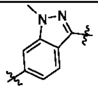
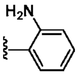
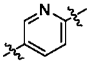
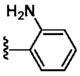
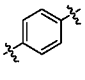
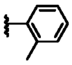
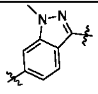
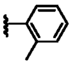
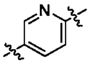
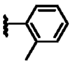
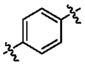
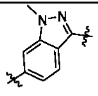
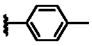
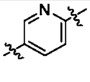
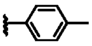
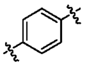
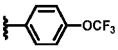
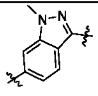
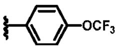
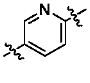
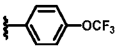
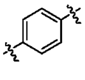
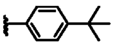
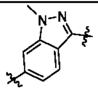
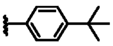
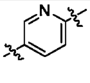
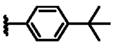
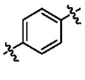
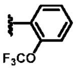
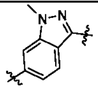
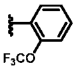
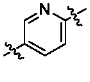
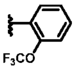
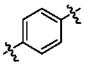
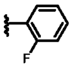
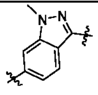
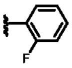
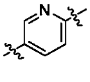
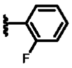
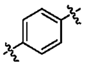
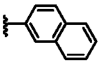
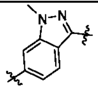
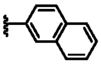
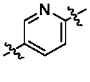
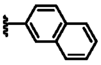
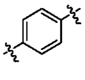
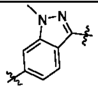
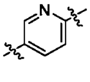
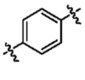
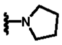
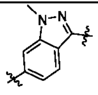
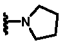
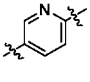
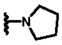


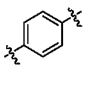
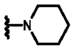
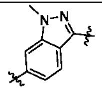
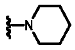
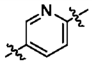
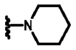
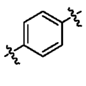
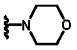
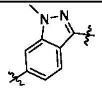
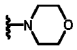
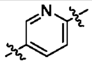
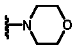
(XV)

wherein R^8 and Ⓑ are delineated for each compound in Table 6:

Table 6

Compound	Ⓑ	R^8	Compound	Ⓑ	R^8	Compound	Ⓑ	R^8
451			475			499		
452			476			500		
453			477			501		

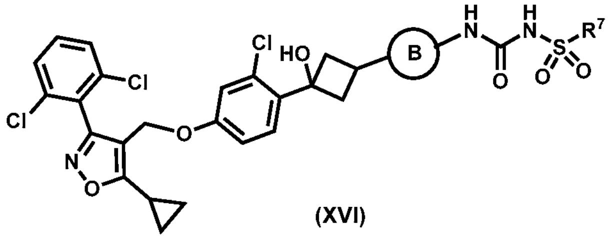
454			478			502		
455			479			503		
456			480			504		
457			481			505		
458		Benzyl	482		Benzyl	506		Benzyl
459			483			507		
460			484			508		
461			485			509		
462			486			510		
463			487			511		
464			488			512		
465			489			513		
466			490			514		
467			491			515		
468			492			516		
471		$-N(CH_3)_2$	495		$-N(CH_3)_2$	519		$-N(CH_3)_2$
472			496			520		

473			497			521		
474			498			522		

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1, which is selected from:

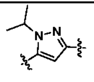
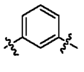
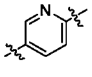
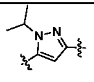
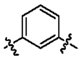
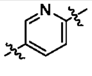
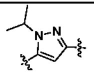
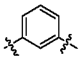
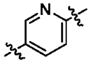
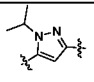
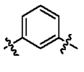
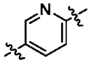
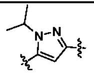
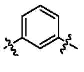
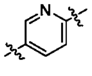
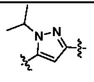
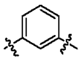
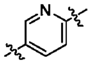
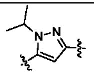
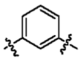
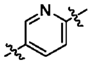
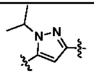
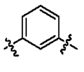
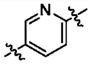
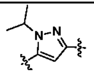
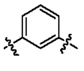
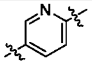
(a) compounds of Formula (XVI),

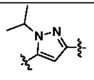
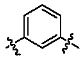
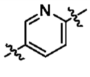
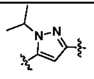
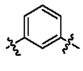
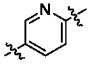
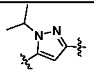
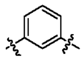
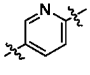
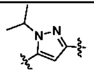
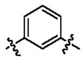
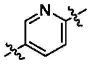
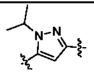
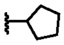
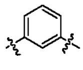
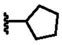
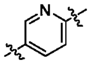
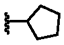
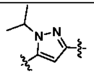
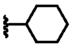
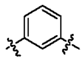
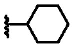
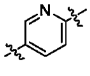
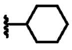
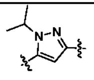
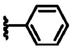
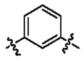
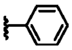
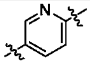
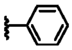
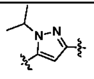
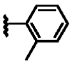
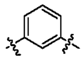
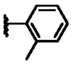
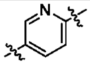
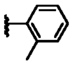
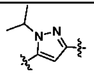
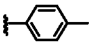
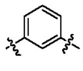
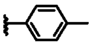
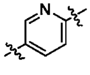
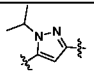
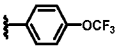
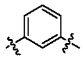
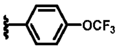
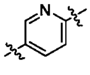
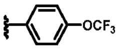
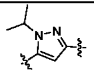
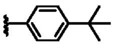
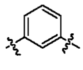
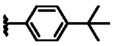
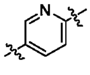
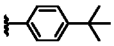
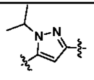
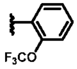
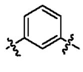
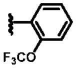
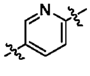
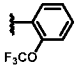
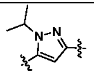
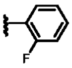
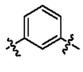
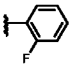
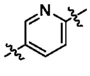
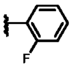
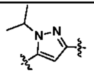
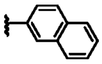
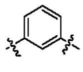
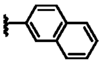
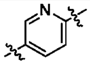
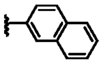
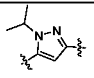
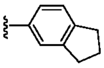
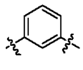
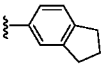
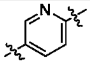
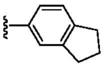
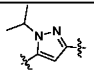
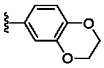
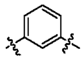
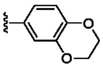
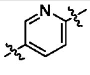
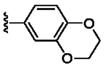
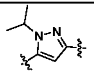
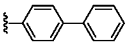
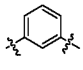
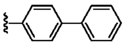
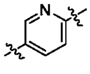
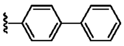
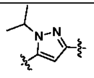
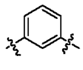
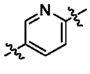
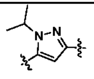
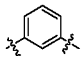
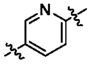
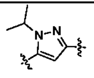
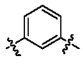
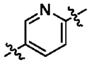


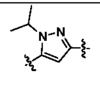
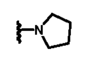
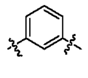
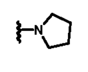
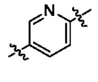
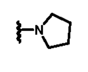
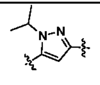
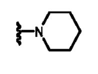
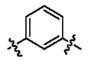
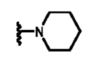
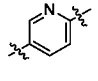
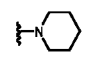
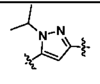
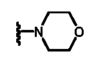
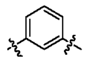
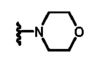
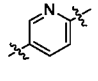
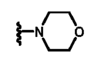
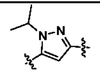
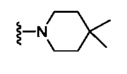
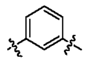
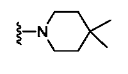
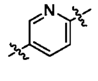
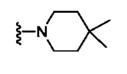
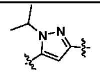
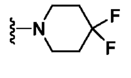
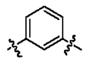
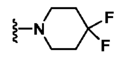
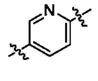
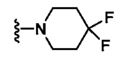
(XVI)

wherein R^7 and Ⓑ are delineated for each compound in Table 7:

Table 7

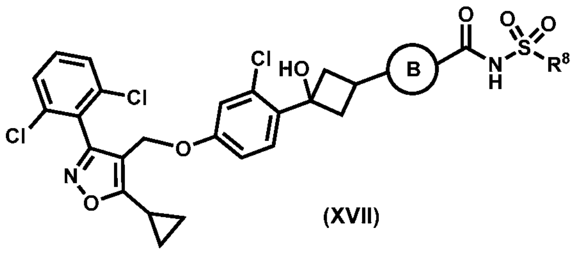
Compound	Ⓑ	R^7	Compound	Ⓑ	R^7	Compound	Ⓑ	R^7
523		Methyl	557		Methyl	591		Methyl
524		Ethyl	558		Ethyl	592		Ethyl
525		Isopropyl	559		Isopropyl	593		Isopropyl
526		Butyl	560		Butyl	594		Butyl
527		t-Butyl	561		t-Butyl	595		t-Butyl
528		Propyl	562		Propyl	596		Propyl
529		Benzyl	563		Benzyl	597		Benzyl
530		Vinyl	564		Vinyl	598		Vinyl
531		Allyl	565		Allyl	599		Allyl

532		$-CF_3$	566		$-CF_3$	600		$-CF_3$
533			567			601		
534			568			602		
535			569			603		
536			570			604		
537			571			605		
538			572			606		
539			573			607		
540			574			608		
541			575			609		
542			576			610		
543			577			611		
544			578			612		
545			579			613		
546			580			614		
547			581			615		
548			582			616		
549		$-NH_2$	583		$-NH_2$	617		$-NH_2$
550		$-NHCH_3$	584		$-NHCH_3$	618		$-NHCH_3$
551		$-N(CH_3)_2$	585		$-N(CH_3)_2$	619		$-N(CH_3)_2$

552			586			620		
553			587			621		
554			588			622		
555			589			623		
556			590			624		

and

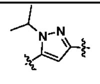
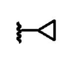
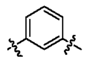
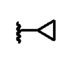
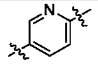
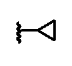
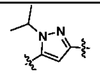
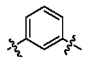
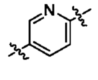
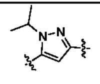
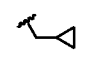
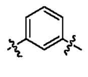
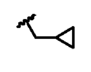
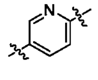
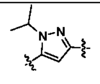
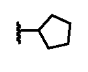
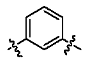
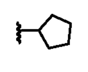
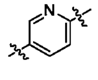
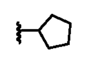
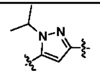
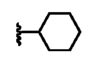
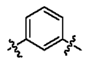
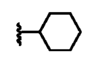
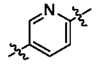
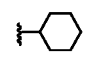
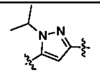
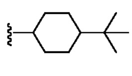
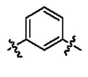
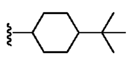
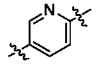
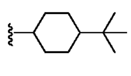
(b) compounds of Formula (XVII)

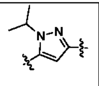
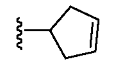
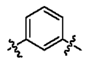
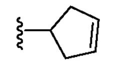
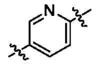
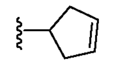
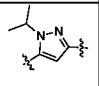
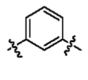
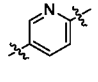
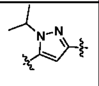
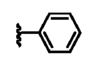
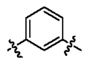
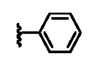
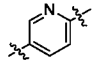
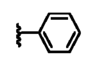
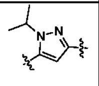
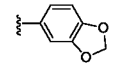
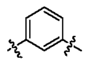
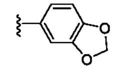
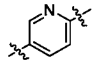
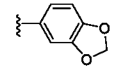
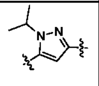
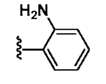
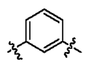
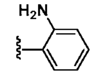
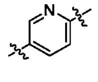
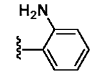
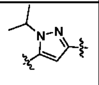
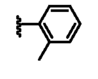
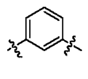
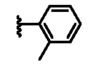
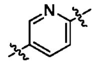
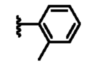
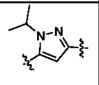
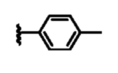
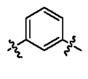
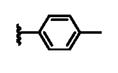
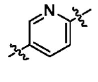
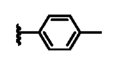
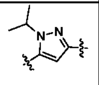
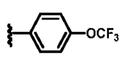
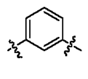
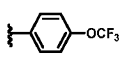
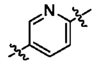
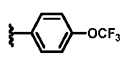
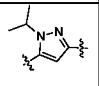
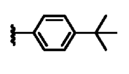
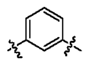
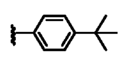
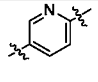
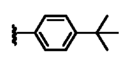
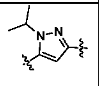
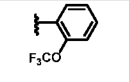
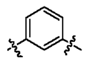
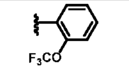
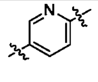
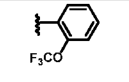
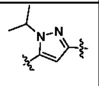
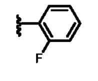
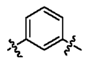
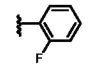
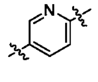
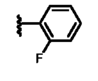
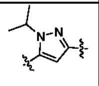
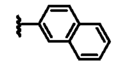
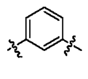
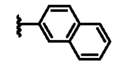
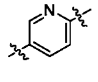
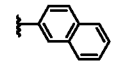
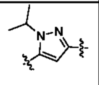
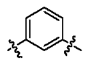
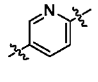
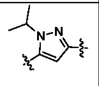
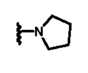
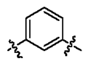
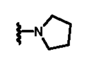
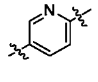
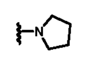
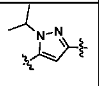
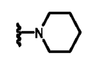
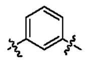
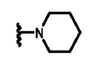
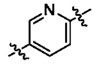
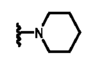
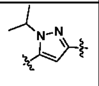
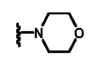
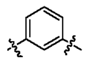
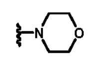
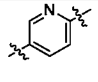
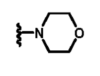


(XVII)

wherein R^8 and B are delineated for each compound in Table 8:

Table 8

Compound	B	R^8	Compound	B	R^8	Compound	B	R^8
625			649			673		
626			650			674		
627			651			675		
628			652			676		
629			653			677		
630			654			678		

631			655			679		
632		Benzyl	656		Benzyl	680		Benzyl
633			657			681		
634			658			682		
635			659			683		
636			660			684		
637			661			685		
638			662			686		
639			663			687		
640			664			688		
641			665			689		
642			666			690		
645		-N(CH3)2	669		-N(CH3)2	693		-N(CH3)2
646			670			694		
647			671			695		
648			672			696		

or a pharmaceutically acceptable salt thereof.

11. A method for preventing or treating an FXR-mediated disease or condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) according to any one of claims 1-10.

12. The method according to claim 11, wherein the FXR-mediated disease or condition is selected from the group consisting of chronic liver disease, gastrointestinal disease, renal disease, cardiovascular disease, fibrotic diseases, and metabolic disease.

13. The method according to claim 12, wherein the fibrotic disease is selected from primary biliary cirrhosis, primary sclerosing cholangitis, pulmonary fibrosis, renal fibrosis, and liver fibrosis.

14. The method according to claim 12, wherein the chronic liver disease is selected from the group consisting of primary biliary cirrhosis (PBC), cerebrotendinous xanthomatosis (CTX), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver transplant associated graft versus host disease, living donor transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, Sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, and alpha 1-antitrypsin deficiency.

15. The method according to claim 12, 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.

16. The method according to claim 12, wherein the cardiovascular disease is selected from the group consisting of atherosclerosis, arteriosclerosis, dyslipidemia, hypercholesterolemia, and hypertriglyceridemia.

17. The method according to claim 12, wherein the metabolic disease is selected from the group consisting of insulin resistance, Type I and Type II diabetes, and obesity.

18. A pharmaceutical composition comprising a compound of Formula (I) according to any one of claims 1-10 and a pharmaceutically acceptable carrier.

19. Use of a compound of any one of claims 1-10 for the preparation of pharmaceutical compositions for the prevention or treatment of FXR-mediated diseases or conditions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/33074

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/551, A61K 31/42, A61K 31/496 (2017.01)
CPC - A61K 38/212, A61K 31/42, A61K 31/513, A61K 31/7072, A61K 31/55

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 8,952,042 B2 (Kremoser et al.) 10 February 2015 (10.02.2015); col 4, ln 21-29, col 15, ln 28-34, col 20, ln 19-25, 30-31, 46, col 22, ln 27, 32-35, col 23, ln 45-50, col 98, Scheme 7, col 118, ln 30-65	1-8, (11-19)/(1-8)
Y	US 2016/130297 A1 (Enanta Pharmaceuticals, Inc.) 12 May 2016 (12.05.2016); para [0002], [0057], [0064]	1-19
Y	WO 2013/007387 A1 (PHENEX PHARMACEUTICALS AG) 17 January 2013 (17.01.2013); pg. 1, ln 1-5, pg. 7, ln 3-4, pg. 17, ln 22-23, 32, pg. 19, ln 12-14, 25-35, pg. 21, ln 4-8, pg. 27, ln 1, pg. 37	1, 9-10, (11-19)/(9-10)
A	US 7,863,302 B2 (Bell et al.) 04 January 2011 (04.01.2011); entire document	1-19
A	WO 2015/036442 A1 (INSERM (INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE)) 19 March 2015 (19.03.2015); entire document	1-19
A	US 2015/366856 A1 (Tully et al.) 24 December 2015 (24.12.2015); entire document	1-19

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

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

Date of the actual completion of the international search 24 July 2017	Date of mailing of the international search report 22 AUG 2017
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: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774