



(51) International Patent Classification:

A61K 31/454 (2006.01) C07D 417/14 (2006.01)

A61K 31/55 (2006.01)

(21) International Application Number:

PCT/US2017/029518

(22) International Filing Date:

26 April 2017 (26.04.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/327,866 26 April 2016 (26.04.2016) US

(71) Applicant: ENANTA PHARMACEUTICALS, INC.

[US/US]; 500 Arsenal Street, Watertown, MA 02472 (US).

(72) Inventors: **OR, Yat, Sun**; 169 Fayette Street, Watertown, MA 02472 (US). **SHEN, Ruichao**; 563 Lagrange Street, West Roxbury, MA 02132 (US). **XING, Xuechao**; 20 Cedar Street, Wilmington, MA 01887 (US). **GRANGER, Brett**; 1 Lillian Avenue, Sudbury, MA 01776 (US). **WANG, Bin**; 1925 Commonwealth Ave., Apt. 1416, Brighton, MA 02135 (US). **MA, Jun**; 53 Hill Road, Apt. 304, Belmont, MA 02478 (US). **HE, Jing**; 289 Highland Ave, Apt. 205, Somerville, MA 02144 (US). **HE, Yong**; 34 Calvin Street, Lexington, MA 02420 (US). **LONG, Jiang**; 15 Wallace Road, Wayland, MA 01778 (US). **WANG, Guoqiang**; 65 Becket Road, Belmont, MA 02478 (US).

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

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

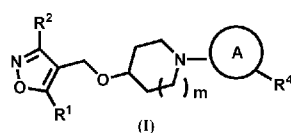
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

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



(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 DERIVATIVES AS FXR AGONISTS AND METHODS OF USE THEREOF

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No.
5 62/327,866, filed on April 26, 2016. The entire teachings of the above applications
are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates generally to compounds and pharmaceutical
compositions useful as FXR agonists. Specifically, the present invention relates to
10 isoxazole compounds containing an acylsulfonamide or sulfonylurea moiety and
methods for their preparation and use.

BACKGROUND OF THE INVENTION

Farnesoid X Receptor (FXR, NR1H4) is a member of the nuclear receptor
15 family of ligand-activated transcription factors that includes receptors for the steroid,
retinoid, and thyroid hormones (D. J. Mangelsdorf, et al., *Cell*, **1995**, 83(6), 841-850).
FXR was originally identified from a rat liver cDNA library. Farnesol and derivatives,
collectively termed farnesoids, activate the rat ortholog at high concentration, but they
do not modulate the human or mouse receptors. FXR is primarily expressed in the
20 liver, kidney, and intestine (W. Seol, et al., *Mol. Endocrinol.*, **1995**, 9(1), 72-85; B. M.
Forman, et al., *Cell*, **1995**, 81(5), 687-693). The relevant physiological ligands of
FXR include the primary bile acids cholic acid (CA) and chenodeoxycholic acid
(CDCA) and the secondary bile acids deoxycholic acid (DCA) and lithocholic acid
(LCA) (D. Parks, et al., *Science*, **1999**, 284(5418), 1362-1365). The most potent
25 physiological ligand for FXR is CDCA, which plays a key role in regulating the
expression of several genes that participate in bile acid homeostasis. FXR functions as
a heterodimer with the retinoid X receptor (RXR) and binds to response elements in
the promoter region of target genes to regulate gene transcription. FXR seems to be
also involved in paracrine and endocrine signaling by upregulating the expression of
30 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).

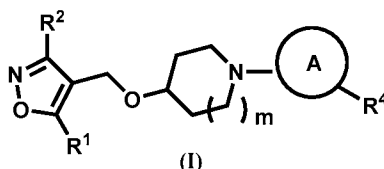
Small molecule compounds which act as FXR modulators have been disclosed in the following publications: WO 2000/037077, WO 2002/072598, WO 2003/015771, WO 2003/099821, WO 2004/00752, WO 2004/048349, WO 2005/009387, WO 2005/082925, US 2005/0054634, WO 2007/052843, WO 5 2007/070796, WO 2007/076260, WO 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 10 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 15 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; Xu, Y., *J. Med. Chem.* **DOI**: 10.1021/acs.jmedchem.5b00342).

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

SUMMARY OF THE INVENTION

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



wherein:

m is 0, 1, or 2;

R¹ is hydrogen, halogen, cyano, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted

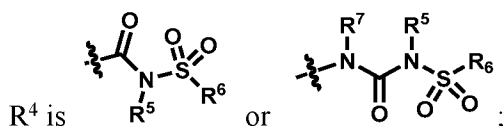
C₃-C₆ cycloalkyl or optionally substituted 3- to 6- membered heterocycloalkyl.

Preferably, R¹ is isopropyl, *tert*-butyl or cyclopropyl;

R² is an optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, or optionally substituted cycloalkyl;



is optionally substituted aryl or optionally substituted heteroaryl containing 1, 2 or 3 heteroatoms independently selected from N, O and S;



R⁵ and R⁷ are independently selected from the group consisting of:

- 1) Hydrogen;
- 2) Optionally substituted -C₁-C₈ alkyl;
- 3) Optionally substituted -C₂-C₈ alkenyl;
- 4) Optionally substituted -C₂-C₈ alkynyl; and
- 5) Optionally substituted -C₃-C₈ cycloalkyl;

R⁶ is selected from the group consisting of:

- 1) Optionally substituted -C₁-C₈ alkyl;
- 2) Optionally substituted -C₂-C₈ alkenyl;
- 3) Optionally substituted -C₂-C₈ alkynyl;
- 4) Optionally substituted -C₃-C₈ cycloalkyl;
- 5) Optionally substituted aryl;
- 6) Optionally substituted arylalkyl;
- 7) Optionally substituted heterocycloalkyl;
- 8) Optionally substituted heteroaryl;
- 9) Optionally substituted heteroarylalkyl; and

10) NR⁸R⁹; wherein R⁸ and R⁹ are each independently selected from hydrogen, optionally substituted -C₁-C₈ alkyl, optionally substituted -C₂-C₈ alkenyl, optionally substituted -C₂-C₈ alkynyl, optionally substituted -C₃-C₈ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted

heteroarylalkyl, or R⁸ and R⁹ are taken together with the nitrogen atom to which they are attached to form an optionally substituted heterocyclic ring.

In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or
 5 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.

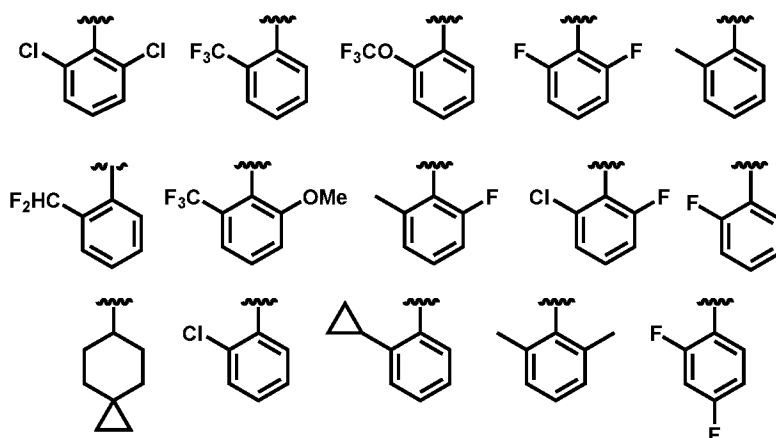
In another embodiment, the present invention provides a method for the prevention or treatment of an FXR mediated disease or condition. The method
 10 comprises administering a therapeutically effective amount of a compound of Formula (I). The present invention also provides the use of a compound of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

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

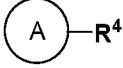
In certain embodiments, the present invention relates to compounds of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R¹ is isopropyl, *tert*-butyl or cyclopropyl.

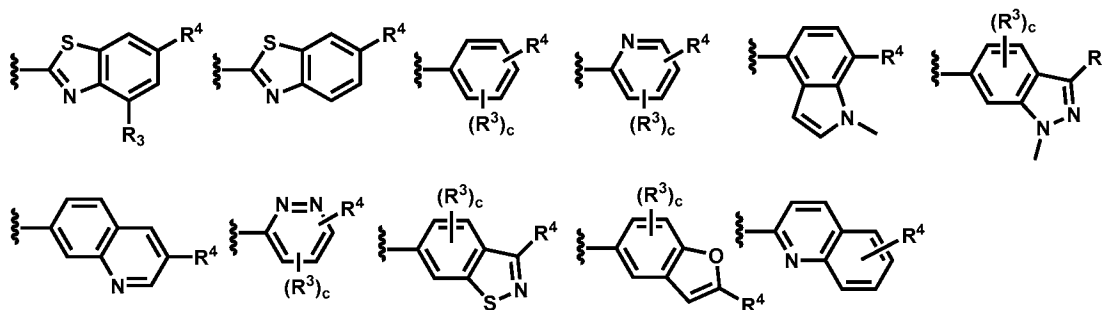
20 In certain embodiments, the present invention relates to compounds of Formula (I), or a pharmaceutically acceptable salt thereof, where R² is selected from the group below:



In certain embodiments, the present invention relates to compounds of
 25 Formula (I), or a pharmaceutically acceptable salt thereof, wherein m is 1.

In certain embodiments, the present invention relates to compounds of

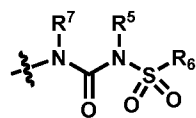
Formula (I), or a pharmaceutically acceptable salt thereof,  is selected from the group consisting of:



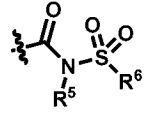
- 5 c is 0, 1 or 2; each R^3 is independently selected from the group consisting of hydroxy, OMe, OCH_2F , OCF_3 , $\text{C}_2\text{-C}_6\text{-alkoxy}$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{ haloalkyl}$, halo, $\text{C}_2\text{-C}_6\text{ alkenyl}$, $\text{C}_2\text{-C}_6\text{ alkynyl}$, $\text{C}_3\text{-C}_6\text{ cycloalkyl}$, $\text{O-C}_1\text{-C}_2\text{ alkylphenyl}$, cyano, CH_2F , CHF_2 , CF_3 , SCF_3 , NH_2 , NHMe , and NMe_2 .

In certain embodiments, the present invention relates to compounds of

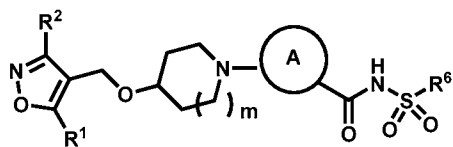
- 10 Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^4 is



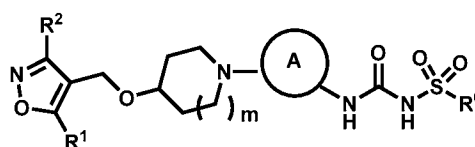
, where in R^5 , R^6 , and R^7 are previously defined. In another embodiment, the present invention relates to compounds of Formula (I), or a

pharmaceutically acceptable salt thereof, wherein R^4 is , where R^5 and R^6 are as previously defined.

- 15 In certain embodiments, the compounds of the invention are represented by Formula II or III and pharmaceutically acceptable salts thereof:



II

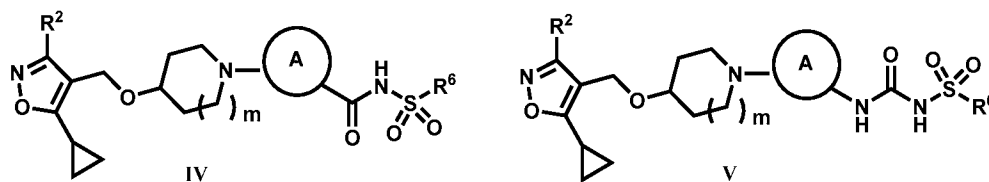


III

wherein R^1 , R^2 , m , , and R^6 are as previously defined.

In certain embodiments, the compounds of the invention are represented by

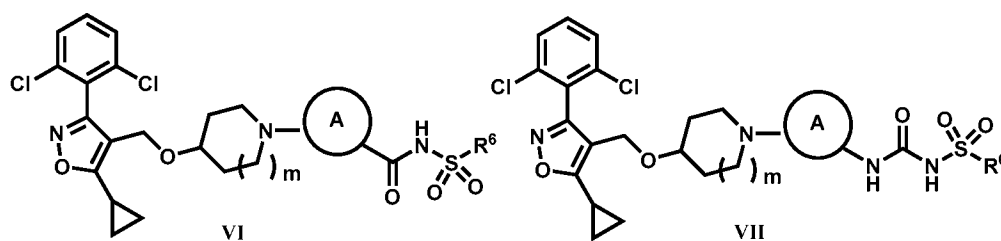
- 20 Formula IV or V and pharmaceutically acceptable salts thereof:



wherein R^2 , m , (A) , and R^6 are as previously defined.

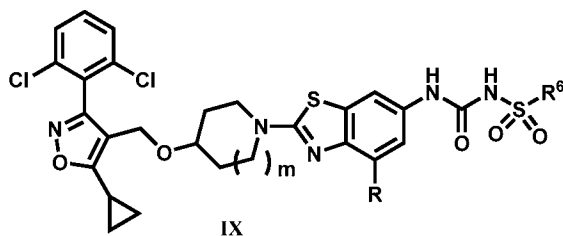
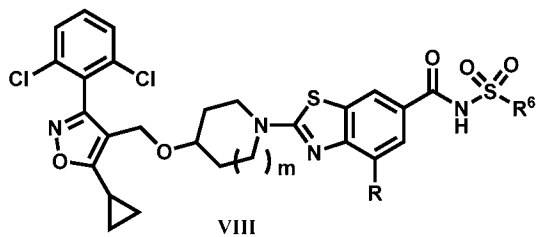
In certain embodiments, the compounds of the invention are represented by Formula VI or VII and pharmaceutically acceptable salts thereof:

5



wherein m , (A) , and R^6 are as previously defined.

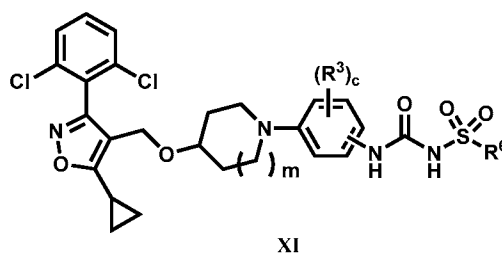
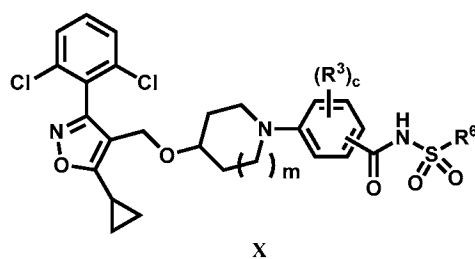
In certain embodiments, the compounds of the invention are represented by Formula VIII or IX and pharmaceutically acceptable salts thereof:



10

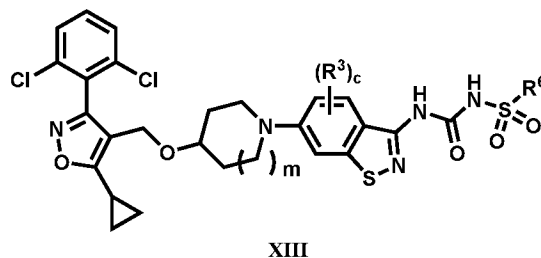
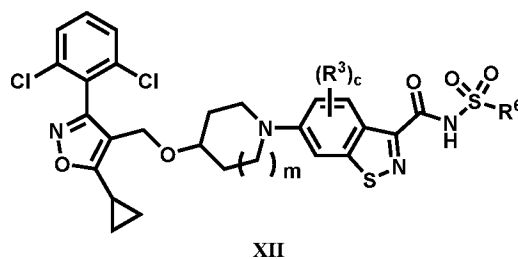
wherein R is hydrogen or R^3 , m , R^3 , and R^6 are as previously defined.

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



wherein m , R^3 , c , and R^6 are as previously defined.

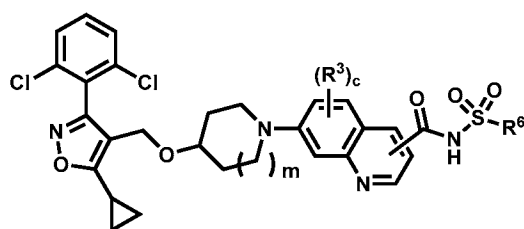
In certain embodiments, the compounds of the invention are represented by Formula XII or XIII and pharmaceutically acceptable salts thereof:



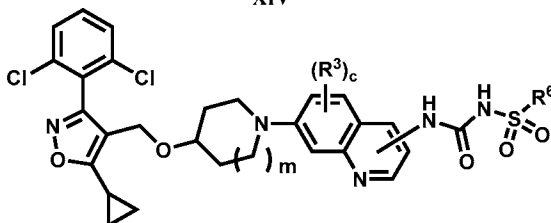
5

wherein m , R^3 , c , and R^6 are as previously defined.

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



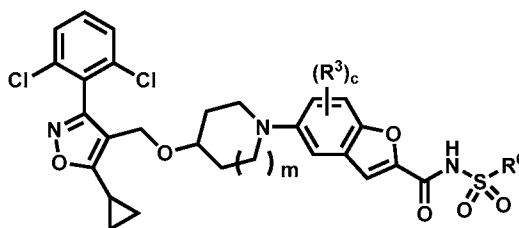
XIV



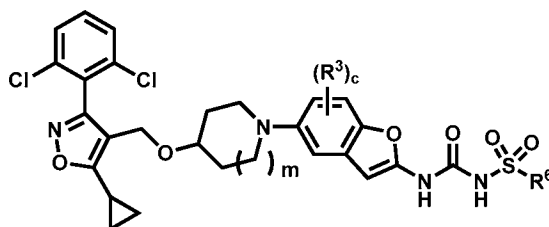
XV

wherein m , R^3 , c , and R^6 are as previously defined.

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



XVI

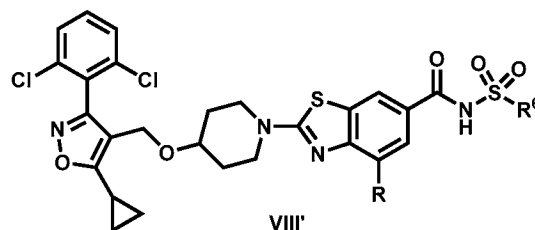


XVII

5

wherein, m , R^3 , c , and R^6 are as previously defined.

In certain embodiment, the compounds of the invention are represented by Formula VIII':

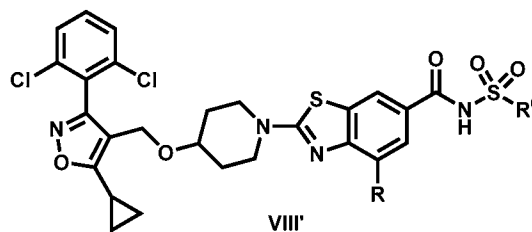


VIII'

10 and pharmaceutically acceptable salts thereof, where R is hydrogen or R^3 , and R^3 and R^6 are as previously defined. Compounds of Formula VIII' include, but are not

limited to, the following compounds (Compound 1 to Compound 87 in Table 1)

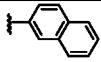
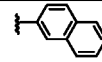
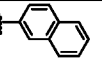
wherein R and R⁶ are delineated for each compound in Table 1.



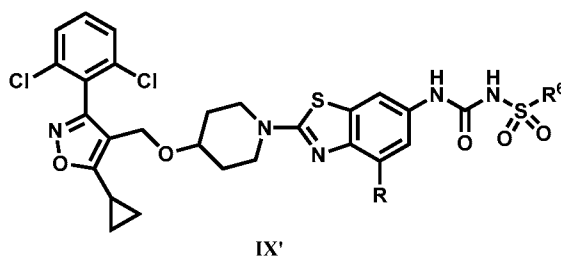
5

Table 1

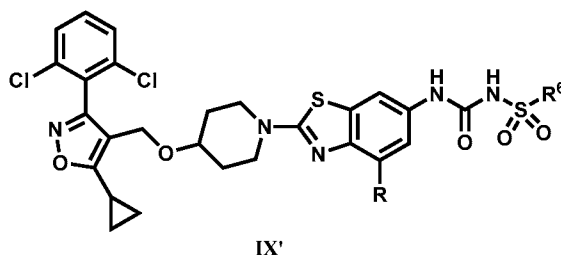
Compound	R	R ⁶	Compound	R	R ⁶	Compound	R	R ⁶
1	H	Methyl	30	F	Methyl	59	OMe	Methyl
2	H	Ethyl	31	F	Ethyl	60	OMe	Ethyl
3	H	Isopropyl	32	F	Isopropyl	61	OMe	Isopropyl
4	H	Butyl	33	F	Butyl	62	OMe	Butyl
5	H	t-Butyl	34	F	t-Butyl	63	OMe	t-Butyl
6	H	Propyl	35	F	Propyl	64	OMe	Propyl
7	H	Benzyl	36	F	Benzyl	65	OMe	Benzyl
8	H	Vinyl	37	F	Vinyl	66	OMe	Vinyl
9	H	Allyl	38	F	Allyl	67	OMe	Allyl
10	H	-CF ₃	39	F	-CF ₃	68	OMe	-CF ₃
11	H		40	F		69	OMe	
12	H		41	F		70	OMe	
13	H		42	F		71	OMe	
14	H		43	F		72	OMe	
15	H		44	F		73	OMe	
16	H		45	F		74	OMe	
17	H		46	F		75	OMe	
18	H		47	F		76	OMe	
19	H		48	F		77	OMe	
20	H		49	F		78	OMe	
21	H		50	F		79	OMe	
22	H		51	F		80	OMe	

23	H		52	F		81	OMe	
24	H	-NH ₂	53	F	-NH ₂	82	OMe	-NH ₂
25	H	-NHCH ₃	54	F	-NHCH ₃	83	OMe	-NHCH ₃
26	H	-N(CH ₃) ₂	55	F	-N(CH ₃) ₂	84	OMe	-N(CH ₃) ₂
27	H		56	F		85	OMe	
28	H		57	F		86	OMe	
29	H		58	F		87	OMe	

In certain embodiments, the compounds of the invention are represented by Formula IX':



- 5 and pharmaceutically acceptable salts thereof, where R is hydrogen or R³, and R³ and R⁶ are as previously defined. Representative compounds of Formula IX' include, but are not limited to, the following compounds (Compound 88 to Compound 174 in Table 2) wherein R and R⁶ are delineated for each compound in Table 2.



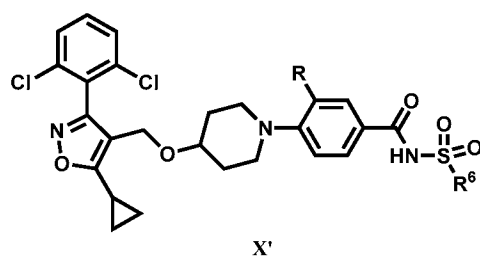
10

Table 2

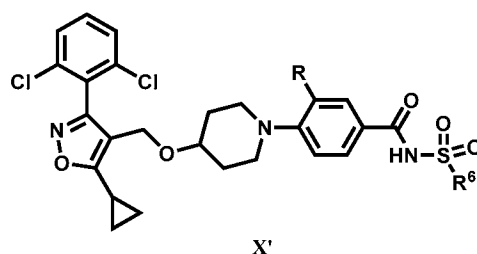
Compound	R	R ⁶	Compound	R	R ⁶	Compound	R	R ⁶
88	H	Methyl	117	F	Methyl	146	OMe	Methyl
89	H	Ethyl	118	F	Ethyl	147	OMe	Ethyl
90	H	Isopropyl	119	F	Isopropyl	148	OMe	Isopropyl
91	H	Butyl	120	F	Butyl	149	OMe	Butyl
92	H	t-Butyl	121	F	t-Butyl	150	OMe	t-Butyl
93	H	Propyl	122	F	Propyl	151	OMe	Propyl

94	H	Benzyl	123	F	Benzyl	152	OMe	Benzyl
95	H	Vinyl	124	F	Vinyl	153	OMe	Vinyl
96	H	Allyl	125	F	Allyl	154	OMe	Allyl
97	H	-CF ₃	126	F	-CF ₃	155	OMe	-CF ₃
98	H		127	F		156	OMe	
99	H		128	F		157	OMe	
100	H		129	F		158	OMe	
101	H		130	F		159	OMe	
102	H		131	F		160	OMe	
103	H		132	F		161	OMe	
104	H		133	F		162	OMe	
105	H		134	F		163	OMe	
106	H		135	F		164	OMe	
107	H		136	F		165	OMe	
108	H		137	F		166	OMe	
109	H		138	F		167	OMe	
110	H		139	F		168	OMe	
111	H	-NH ₂	140	F	-NH ₂	169	OMe	-NH ₂
112	H	-NHCH ₃	141	F	-NHCH ₃	170	OMe	-NHCH ₃
113	H	-N(CH ₃) ₂	142	F	-N(CH ₃) ₂	171	OMe	-N(CH ₃) ₂
114	H		143	F		172	OMe	
115	H		144	F		173	OMe	
116	H		145	F		174	OMe	

In certain embodiments, the compounds of the invention are represented by
Formula X':



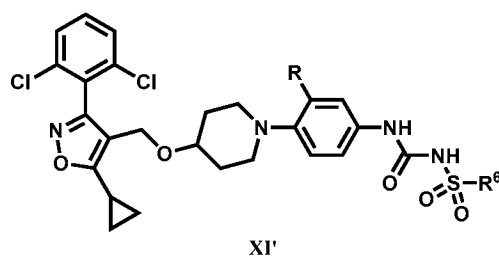
and pharmaceutically acceptable salts thereof, wherein R is hydrogen or R³, R³ and R⁶ are as previously defined. Representative compounds of Formula X' include, but are not limited to, the following compounds (Compound 175 to Compound 232 in Table 3) according to Formula X', wherein R and R⁶ are delineated for each compound in Table 3.

**Table 3**

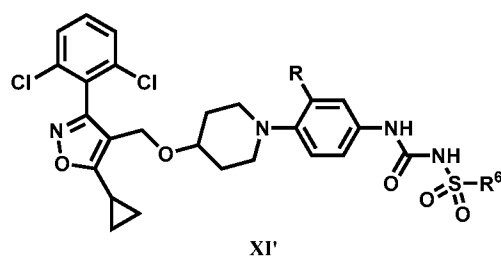
Compound	R	R ⁶	Compound	R	R ⁶
175	H	Methyl	204	F	Methyl
176	H	Ethyl	205	F	Ethyl
177	H	Isopropyl	206	F	Isopropyl
178	H	Butyl	207	F	Butyl
179	H	t-Butyl	208	F	t-Butyl
180	H	Propyl	209	F	Propyl
181	H	Benzyl	210	F	Benzyl
182	H	Vinyl	211	F	Vinyl
183	H	Allyl	212	F	Allyl
184	H	-CF ₃	213	F	-CF ₃
185	H		214	F	
186	H		215	F	
187	H		216	F	
188	H		217	F	

189	H		218	F	
190	H		219	F	
191	H		220	F	
192	H		221	F	
193	H		222	F	
194	H		223	F	
195	H		224	F	
196	H		225	F	
197	H		226	F	
198	H	-NH ₂	227	F	-NH ₂
199	H	-NHCH ₃	228	F	-NHCH ₃
200	H	-N(CH ₃) ₂	229	F	-N(CH ₃) ₂
201	H		230	F	
202	H		231	F	
203	H		232	F	

In certain embodiments, the compounds of the invention are represented by Formula XI':



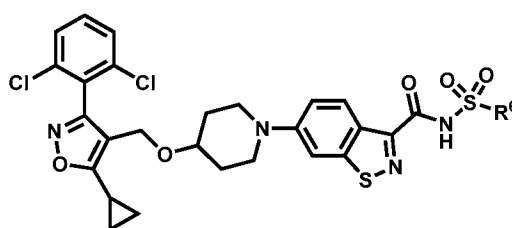
- 5 and pharmaceutically acceptable salts thereof, wherein R is hydrogen or R³, R³ and R⁶ are as previously defined. Representative compounds of Formula XI' include, but are not limited to, the following compounds (Compound 233 to Compound 290 in Table 4) wherein R and R⁶ are delineated for each compound in Table 4.

**Table 4**

Compound	R	R ⁶	Compound	R	R ⁶
233	H	Methyl	262	F	Methyl
234	H	Ethyl	263	F	Ethyl
235	H	Isopropyl	264	F	Isopropyl
236	H	Butyl	265	F	Butyl
237	H	t-Butyl	266	F	t-Butyl
238	H	Propyl	267	F	Propyl
239	H	Benzyl	268	F	Benzyl
240	H	Vinyl	269	F	Vinyl
241	H	Allyl	270	F	Allyl
242	H	-CF ₃	271	F	-CF ₃
243	H		272	F	
244	H		273	F	
245	H		274	F	
246	H		275	F	
247	H		276	F	
248	H		277	F	
249	H		278	F	
250	H		279	F	
251	H		280	F	
252	H		281	F	
253	H		282	F	
254	H		283	F	

255	H		284	F	
256	H	-NH ₂	285	F	-NH ₂
257	H	-NHCH ₃	286	F	-NHCH ₃
258	H	-N(CH ₃) ₂	287	F	-N(CH ₃) ₂
259	H		288	F	
260	H		289	F	
261	H		290	F	

In certain embodiments, the compounds of the invention are represented by Formula XII':



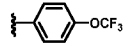
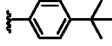
XII'

- 5 and pharmaceutically acceptable salts thereof, wherein R⁶ is as previously defined. Representative compounds of Formula XII' include, but are not limited to, the following compounds (Compound 291 to Compound 319 in Table 5) wherein R⁶ is delineated for each compound in Table 5.

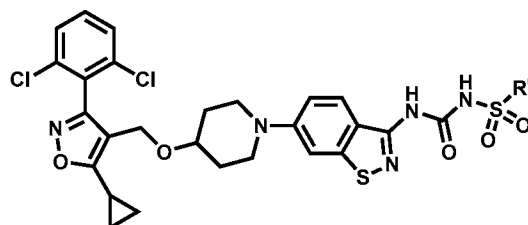
10

Table 5

Compound	R ⁶	Compound	R ⁶	Compound	R ⁶
291	Methyl	301		311	
292	Ethyl	302		312	
293	Isopropyl	303		313	
294	Butyl	304		314	-NH ₂
295	t-Butyl	305		315	-NHCH ₃
296	Propyl	306		316	-N(CH ₃) ₂
297	Benzyl	307		317	

298	Vinyl	308		318	
299	Allyl	309		319	
300	-CF ₃	310			

In certain embodiments, the compounds of the invention are represented by Formula XIII':

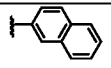
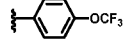
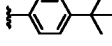


XIII'

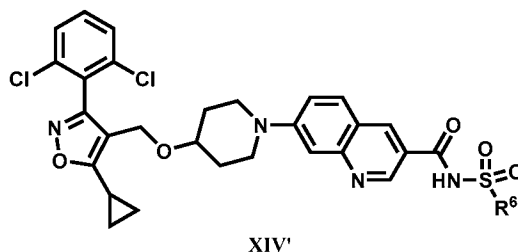
- 5 and pharmaceutically acceptable salts thereof, wherein R⁶ is as previously defined. Representative compounds of Formula XIII' include, but are not limited to, the following compounds (Compound 320 to Compound 348 in Table 6), wherein R⁶ is delineated for each compound in Table 6.

10

Table 6

Compound	R ⁶	Compound	R ⁶	Compound	R ⁶
320	Methyl	330		340	
321	Ethyl	331		341	
322	Isopropyl	332		342	
323	Butyl	333		343	-NH ₂
324	t-Butyl	334		344	-NHCH ₃
325	Propyl	335		345	-N(CH ₃) ₂
326	Benzyl	336		346	
327	Vinyl	337		347	
328	Allyl	338		348	
329	-CF ₃	339			

In certain embodiments, the compounds of the invention are represented by Formula XIV':



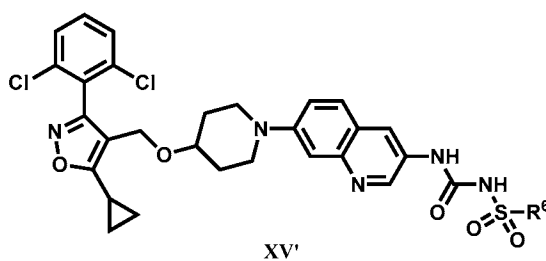
and pharmaceutically acceptable salts thereof, wherein R⁶ is as previously defined.

- 5 Representative compounds of Formula XIV' include, but are not limited to, the following compounds (Compound 349 to Compound 377 in Table 7), wherein R⁶ is delineated for each compound in Table 7.

Table 7

Compound	R ⁶	Compound	R ⁶	Compound	R ⁶
349	Methyl	359		369	
350	Ethyl	360		370	
351	Isopropyl	361		371	
352	Butyl	362		372	-NH ₂
353	t-Butyl	363		373	-NHCH ₃
354	Propyl	364		374	-N(CH ₃) ₂
355	Benzyl	365		375	
356	Vinyl	366		376	
357	Allyl	367		377	
358	-CF ₃	368			

- 10 In certain embodiments, the compounds of the invention are represented by Formula XV':

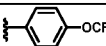
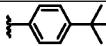


and pharmaceutically acceptable salts thereof, wherein R⁶ is as previously defined.

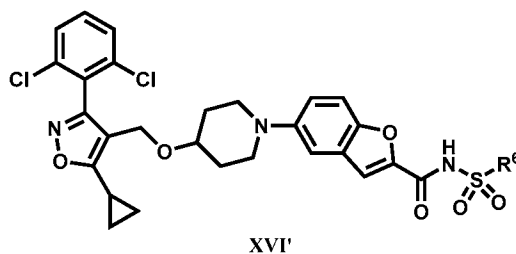
Representative compounds of Formula XV' include, but are not limited to, the following compounds (Compound 378 to Compound 406 in Table 8), wherein R⁶ is

5 delineated for each compound in Table 8.

Table 8

Compound	R ⁶	Compound	R ⁶	Compound	R ⁶
378	Methyl	388		398	
379	Ethyl	389		399	
380	Isopropyl	390		400	
381	Butyl	391		401	-NH ₂
382	t-Butyl	392		402	-NHCH ₃
383	Propyl	393		403	-N(CH ₃) ₂
384	Benzyl	394		404	
385	Vinyl	395		405	
386	Allyl	396		406	
387	-CF ₃	397			

In certain embodiments, the compounds of the invention are represented by Formula XVI':



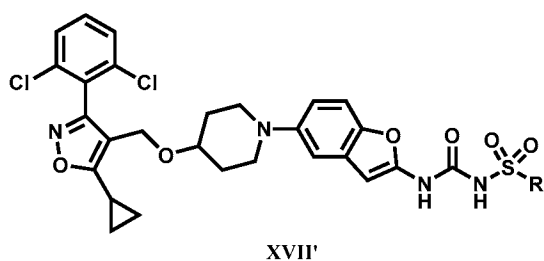
and pharmaceutically acceptable salts thereof, wherein R⁶ is as previously defined. Representative compounds of Formula XVI' include, but are not limited to, the following compounds (Compound 407 to Compound 435 in Table 9), wherein R⁶ is delineated for each compound in Table 9.

5

Table 9

Compound	R ⁶	Compound	R ⁶	Compound	R ⁶
407	Methyl	417		427	
408	Ethyl	418		428	
409	Isopropyl	419		429	
410	Butyl	420		430	-NH ₂
411	t-Butyl	421		431	-NHCH ₃
412	Propyl	422		432	-N(CH ₃) ₂
413	Benzyl	423		433	
414	Vinyl	424		434	
415	Allyl	425		435	
416	-CF ₃	426			

In certain embodiments, the compounds of the invention are represented by Formula XVII':



10 and pharmaceutically acceptable salts thereof, wherein R⁶ is as previously defined. Representative compounds of Formula XVII' include, but are not limited to, the following compounds (Compound 436 to Compound 464 in Table 10), wherein R⁶ is delineated for each compound in Table 10.

15

Table 10

Compound	R ⁶	Compound	R ⁶	Compound	R ⁶
436	Methyl	446		456	
437	Ethyl	447		457	
438	Isopropyl	448		458	
439	Butyl	449		459	-NH ₂
440	t-Butyl	450		460	-NHCH ₃
441	Propyl	451		461	-N(CH ₃) ₂
442	Benzyl	452		462	
443	Vinyl	453		463	
444	Allyl	454		464	
445	-CF ₃	455			

In certain embodiments, 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.

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
5 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
10 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
15 Type II diabetes, or obesity.

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

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.

20

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
25 a larger group.

The term "alkyl", as used herein, refers to a saturated, monovalent straight- or branched-chain hydrocarbon group. Preferred alkyl groups include C₁-C₆ alkyl and C₁-C₈ alkyl groups. Examples of C₁-C₆ alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl groups; and
30 examples of C₁-C₈ 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 C₂-C₆ alkenyl and C₂-C₈ 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.

5 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 C₂-C₆ alkynyl and C₂-C₈ alkynyl groups. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butyne, heptynyl, octynyl and the like.

10 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 C₃-C₈ cycloalkyl and C₃-C₁₂ cycloalkyl groups. Examples of C₃-C₈-cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and examples of C₃-C₁₂-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.

20 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 C₃-C₈ cycloalkenyl and C₃-C₁₂ cycloalkenyl groups. Examples of C₃-C₈-cycloalkenyl include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C₃-C₁₂-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.

30 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 C₁–C₃ alkyl or C₁–C₆ 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, quinoliny, isoquinoliny, benzimidazolyl, benzooxazolyl, quinoxaliny, and the like.

The term “heteroarylalkyl,” as used herein, refers to a C₁–C₃ alkyl or C₁–C₆ alkyl residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

The term “substituted” as used herein, refers to independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited to, deuterium, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -NH₂, N₃, protected amino, alkoxy, thioalkoxy, oxo, C₁–C₁₂-alkyl, C₂–C₁₂-alkenyl, C₂–C₁₂-alkynyl, C₃–C₁₂-cycloalkyl, -halo- C₁–C₁₂-alkyl, -halo- C₂–C₁₂-alkenyl, -halo- C₂–C₁₂-alkynyl, -halo-C₃–C₁₂-cycloalkyl, -NH -C₁–C₁₂-alkyl, -NH -C₂–C₁₂-alkenyl, -NH -C₂–C₁₂-alkynyl, -NH -C₃–C₁₂-cycloalkyl, -NH -aryl, -NH -heteroaryl, -NH -heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁–C₁₂-alkyl, -O-C₂–C₁₂-alkenyl, -O-C₂–C₁₂-alkynyl, -O-C₃–C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)- C₁–C₁₂-alkyl, -C(O)- C₂–C₁₂-alkenyl, -C(O)- C₂–C₁₂-alkynyl, -C(O)-C₃–C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH- C₁–C₁₂-alkyl, -CONH- C₂–C₁₂-alkenyl, -CONH- C₂–C₁₂-alkynyl, -CONH-C₃–C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂- C₁–C₁₂-alkyl, -OCO₂- C₂–C₁₂-alkenyl, -OCO₂- C₂–C₁₂-alkynyl, -OCO₂-C₃–C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH- C₁–C₁₂-alkyl, -OCONH- C₂–C₁₂-alkenyl, -OCONH- C₂–C₁₂-alkynyl, -OCONH- C₃–C₁₂-cycloalkyl, -OCONH- aryl, -OCONH-heteroaryl, -OCONH- heterocycloalkyl, -OCON(C₁–C₁₂-alkyl)₂, -NHC(O)- C₁–C₁₂-alkyl, -NHC(O)-C₂–C₁₂-alkenyl, -NHC(O)-C₂–C₁₂-alkynyl, -NHC(O)-C₃–C₁₂-

- cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -
 NHCO₂- C₁-C₁₂-alkyl, -NHCO₂- C₂-C₁₂-alkenyl, -NHCO₂- C₂-C₁₂-alkynyl, -NHCO₂-
 C₃-C₁₂-cycloalkyl, -NHCO₂- aryl, -NHCO₂- heteroaryl, -NHCO₂- heterocycloalkyl, -
 NHC(O)NH₂, -NHC(O)NH- C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -
 5 NHC(O)NH-C₂-C₁₂-alkynyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -
 NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, -NHC(S)NH-
 C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkynyl, -
 NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -
 NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, -NHC(NH)NH- C₁-C₁₂-alkyl, -
 10 NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkynyl, -NHC(NH)NH-C₃-
 C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-
 heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-
 C₂-C₁₂-alkynyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-
 heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-
 15 C₁₂-alkenyl, -C(NH)NH-C₂-C₁₂-alkynyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-
 aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, - S(O)-
 C₂-C₁₂-alkenyl, - S(O)-C₂-C₁₂-alkynyl, - S(O)-C₃-C₁₂-cycloalkyl, - S(O)-aryl, - S(O)-
 heteroaryl, - S(O)-heterocycloalkyl -SO₂NH₂, -SO₂NH- C₁-C₁₂-alkyl, -SO₂NH- C₂-
 C₁₂-alkenyl, -SO₂NH- C₂-C₁₂-alkynyl, -SO₂NH- C₃-C₁₂-cycloalkyl, -SO₂NH- aryl, -
 20 SO₂NH- heteroaryl, -SO₂NH- heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-
 C₁₂-alkenyl, - NHSO₂-C₂-C₁₂-alkynyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -
 NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -
 arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl,
 polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-
 25 alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkynyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-
 heteroaryl, -S-heterocycloalkyl, methylthiomethyl, or -L'-R', wherein L' is C₁-
 C₆alkylene, C₂-C₆alkenylene or C₂-C₆alkynylene, and R' is aryl, heteroaryl,
 heterocyclic, C₃-C₁₂cycloalkyl or C₃-C₁₂cycloalkenyl. It is understood that the aryls,
 heteroaryls, alkyls, and the like can be further substituted. In some cases, each
 30 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, -
 NO₂, -CN, or -NH₂.

In accordance with the invention, any of the aryls, substituted aryls, heteroaryl and substituted heteroaryl 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, cycloalkylene, 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 synthesize using methods known in the art, for example by employing deuterated starting materials. Unless stated to the contrary, isotopically labelled compounds are pharmaceutically acceptable.

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

- 5 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
- 10 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

15 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

20 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

25 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,

30 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 are described generally in T.H. Greene and P.G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, *t*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl, and the like.

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 alkanolic, alkenolic, 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.),
5 *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
10 (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
15 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
20 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
25 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
30 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 H₂O, 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
5 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
10 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)
15 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.,
20 *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),
25 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
30 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.

5 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
10 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.

15 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
20 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
25 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
30 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.

5 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,
10 carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, 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,
15 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.

20 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,
25 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 as magnesium stearate
30 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;

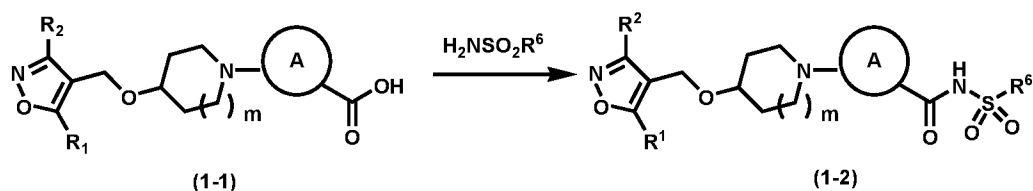
DCC for *N,N*-dicyclohexylcarbodiimide;

- DCM for dichloromethane;
 DMAP for *N,N*-dimethylaminopyridine;
 DMF for *N,N*-dimethyl formamide;
 DPPA for diphenylphosphoryl azide;
 5 EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
 Et₃N for triethylamine;
 EtOAc for ethyl acetate;
 HATU for 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-
 b]pyridinium 3-oxid hexafluorophosphate;
 10 HCl for hydrochloric acid;
 PyAOP for 7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium
 hexafluorophosphate;
 PyBOP for benzotriazol-1-yl-oxytripyrrolidinophosphonium
 hexafluorophosphate;
 15 TFFH for tetramethylfluoroformamidium hexafluorophosphate;
 THF for tetrahydrofuran.

SYNTHETIC METHODS

- The compounds and processes of the present invention will be better
 20 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,
 25 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



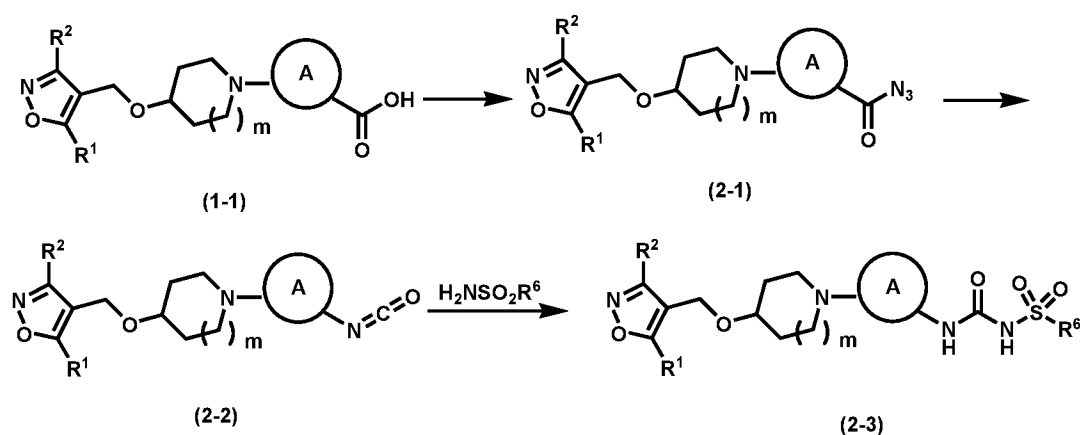
- 30 As shown in Scheme 1, novel isoxazole acylsulfonamide analogs of the
 compound of Formula (1-2) are prepared from the compound of Formula (1-1), wherein

R^1 , R^2 , m , and $\textcircled{A}$ are as previously defined. For the preparation of carboxylic acids of Formula (1-1), see WO 2009/012125 and WO 2012/087520. The compound of Formula (1-1) is coupled with a sulfonamide using suitable coupling conditions to give

the compound of Formula (1-2), wherein R^1 , R^2 , m , $\textcircled{A}$, and R^6 , 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 about 50 °C.

Scheme 2



As shown in Scheme 2, novel isoxazole sulfonyl urea analogs of the compound of Formula (2-3) are prepared from the compound of Formula (1-1),

wherein R^1 , R^2 , m , and $\textcircled{A}$ are as previously defined. The compound of Formula (1-1) is converted to the acyl azide compound of Formula (2-1) 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 preferred solvent is toluene. Suitable bases include, but are not limited to, triethylamine or diisopropylethylamine. The reaction temperature is from -20°C to 40°C. Further Curtius rearrangement of the compound of Formula (2-1) at elevated temperature provides the isocyanate compound of Formula (2-2), and reacting of compound (2-2) with a sulfonamide under basic conditions affords the

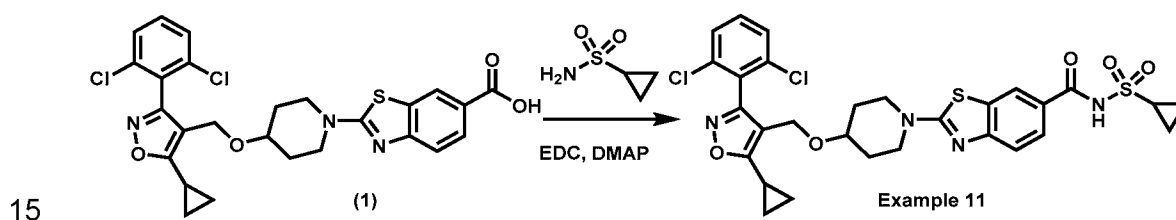
sulfonylurea compound of Formula (2-3), wherein R^1 , R^2 , m , $\textcircled{A}$, and R^6 are as previously defined. A more detailed discussion of the procedures, reagents and conditions for Curtius rearrangement is described in literature, for example, by Jerry March in "Advanced Organic Chemistry" 4th ed, John Wiley & Son, Inc., 1992.

5

Examples

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

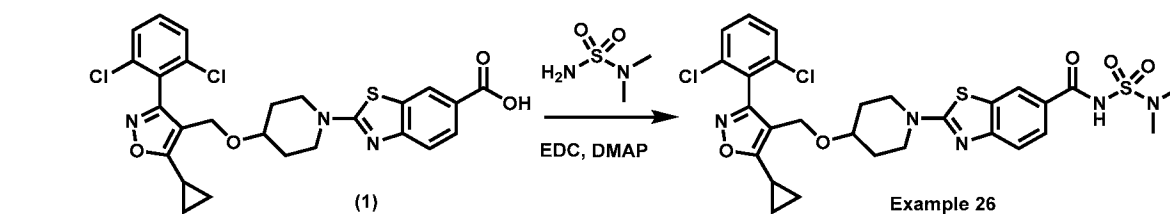
Example 11:



For the preparation of carboxylic acid (1), see WO 2012/087520. To a solution of acid (1) (16 mg, 0.029 mmol) in DCM was added cyclopropanesulfonamide (5.34 mg, 0.044 mmol), DMAP (5.39 mg, 0.044 mmol) and EDCI (8.45 mg, 0.044 mmol). The mixture was stirred at 23 °C for 15 h, quenched with 1 M HCl, and extracted with EtOAc (3 x). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue on silica gel column with 0 - 50 % of acetone/hexane provided **Example 11** (5 mg). LC/MS observed $[\text{M}+\text{H}]^+$, 647.20.

20

Example 26:

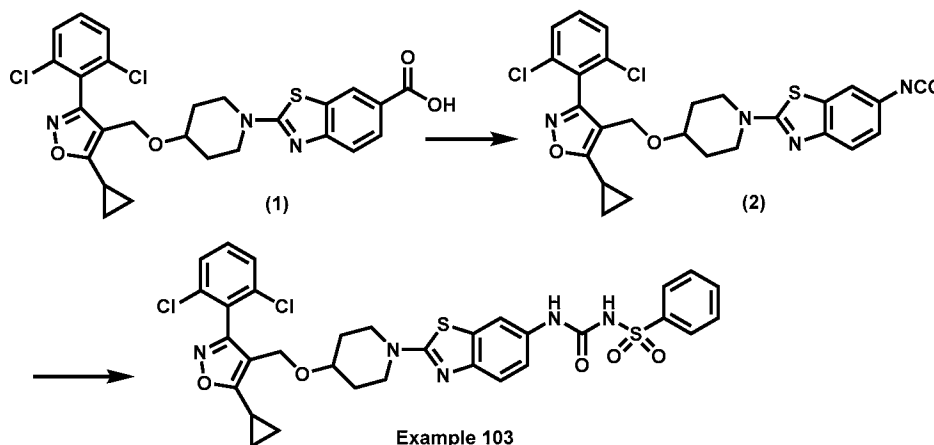


To a solution of acid (1) (16 mg, 0.029 mmol) in DCM was added N,N-dimethylsulfamide (5.47 mg, 0.044 mmol), DMAP (5.39 mg, 0.044 mmol) and EDCI

(8.45 mg, 0.044 mmol). The mixture was stirred at 23 °C for 15 h, quenched with 1 M HCl, and extracted with EtOAc (3 x). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo. Purification of the residue on silica gel column with 0 - 50 % of acetone/hexane provided **Example 26** (6.1 mg). LC/MS observed

5 [M+H]⁺, 650.10.

Example 103:



To a solution of compound (1) (200 mg, 0.37 mmol) in toluene (3 ml) is added triethylamine (0.10 ml, 0.74 mmol) and diphenyl phosphorazidate (0.087 ml, 0.40 mmol) dropwise. The mixture is stirred at 23°C for 1 h, at 85 °C for 3.5 h, and cooled to 23°C. A solution of benzenesulfamide (86 mg, 0.55 mmol) in THF (0.5 mL) and DBU (83 µl, 0.55 mmol) is added. The mixture is stirred at 23 °C for 14 h, quenched with 1 M HCl, and extracted with EtOAc (2 x). The combined organic layer is dried

10 over Na₂SO₄, and concentrated in vacuo. Purification of the residue on silica gel column with 0 - 30 % acetone provides **Example 103**.

15

ASSAYS

Human FXR (NR1H4) Assay

Determination of a ligand mediated Gal4 promoter driven transactivation to

20 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,

25 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. EC₅₀ 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. EC₅₀ 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 the reference compound (1), potency ranges were determined in the Human FXR (NR1H4) Assay as listed below in Table 7. The efficacy was normalized to CDCA set

as 100%. (A=EC50 < 0.1 μ M; B= 0.1 μ M < EC50 < 1.0 μ M; C=1.0 μ M < EC50 < 10 μ M; D= EC50 > 10 μ M)

Table 11

Example	EC50	Efficacy (%)
CDCA	D	100
Compound (1)	A	304
11	B	122
26	A	129

5

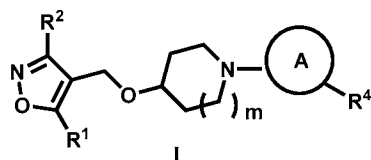
While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended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

10

CLAIMS

WHAT IS CLAIMED IS:

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

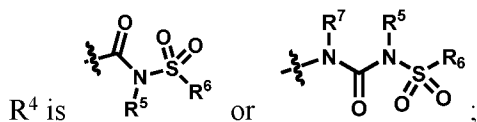


wherein:

m is 0, 1, or 2;

- 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 an optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, optionally substituted heteroarylalkyl, or optionally substituted cycloalkyl;

- 15 $\textcircled{A}$ is optionally substituted aryl or optionally substituted heteroaryl containing 1, 2 or 3 heteroatoms selected from N, O and S;



R^5 and R^7 are independently selected from the group consisting of:

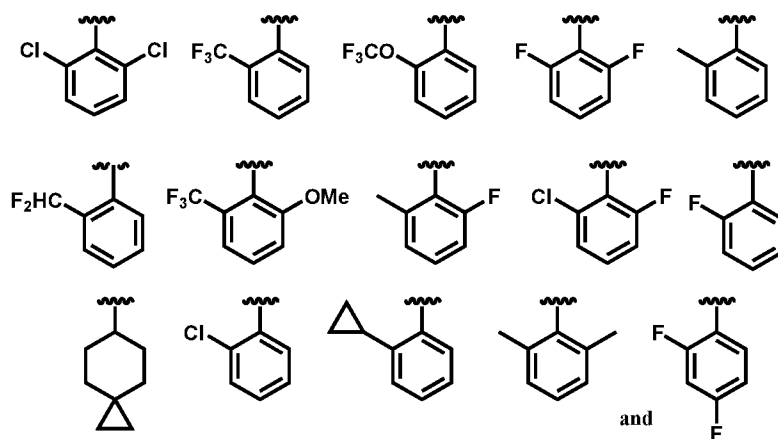
- 1) Hydrogen;
- 20 2) Optionally substituted $-C_1$ - C_8 alkyl;
- 3) Optionally substituted $-C_2$ - C_8 alkenyl;
- 4) Optionally substituted $-C_2$ - C_8 alkynyl; and
- 5) Optionally substituted $-C_3$ - C_8 cycloalkyl; and

R^6 is selected from the group consisting of:

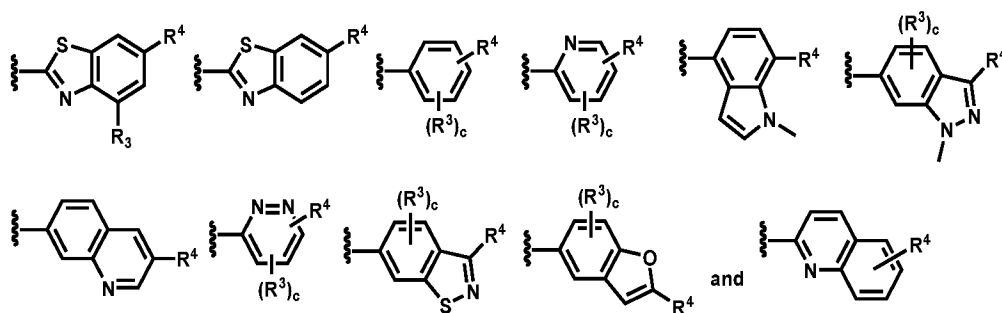
- 25 1) Optionally substituted $-C_1$ - C_8 alkyl;
- 2) Optionally substituted $-C_2$ - C_8 alkenyl;
- 3) Optionally substituted $-C_2$ - C_8 alkynyl;
- 4) Optionally substituted $-C_3$ - C_8 cycloalkyl;

- 5) Optionally substituted aryl;
 6) Optionally substituted arylalkyl;
 7) Optionally substituted heterocycloalkyl;
 8) Optionally substituted heteroaryl; and
 5 9) Optionally substituted heteroarylalkyl;
 10) NR^8R^9 ; wherein R^8 and R^9 are each independently selected from hydrogen, substituted or unsubstituted $-\text{C}_1-\text{C}_8$ alkyl, substituted or unsubstituted $-\text{C}_2-\text{C}_8$ alkenyl, substituted or unsubstituted $-\text{C}_2-\text{C}_8$ alkynyl, substituted or unsubstituted $-\text{C}_3-\text{C}_8$ cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, or R^8 and R^9 are taken together with the nitrogen atom they attached to form a heterocyclic ring.

2. The compound of claim 1, wherein R^2 is selected from the group consisting of:

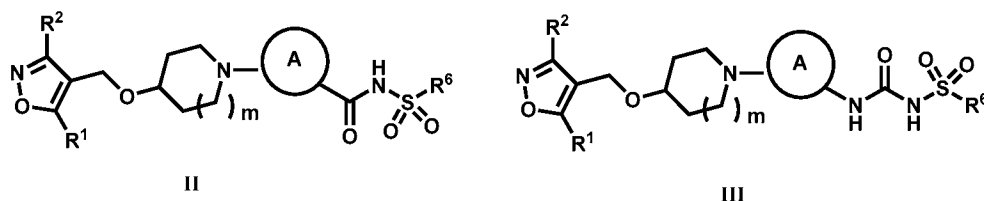


3. The compound of claim 1, wherein $\text{A}-\text{R}^4$ is selected from the group consisting of:



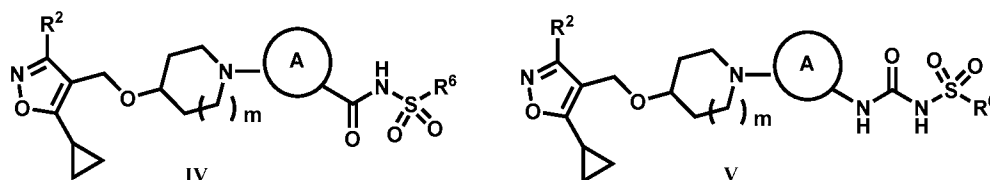
- wherein c is 0, 1 or 2; and each R^3 is independently selected from the group consisting of hydroxy, OMe, OCH_2F , OCF_3 , C_2 - C_6 -alkoxy, C_1 - C_6 -alkyl, C_1 - C_6 haloalkyl, halo, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, O - C_1 - C_2 alkylphenyl, cyano, CH_2F ,
 5 CHF_2 , CF_3 , SCF_3 , NH_2 , $NHMe$, and NMe_2 .

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



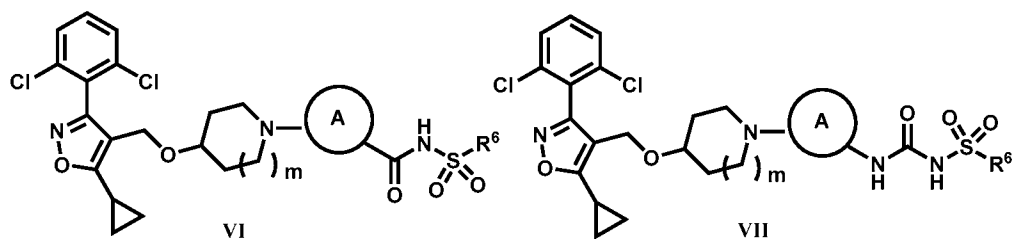
- 10 wherein R^1 , R^2 , m , $\textcircled{A}$, and R^6 are as defined in claim 1.

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



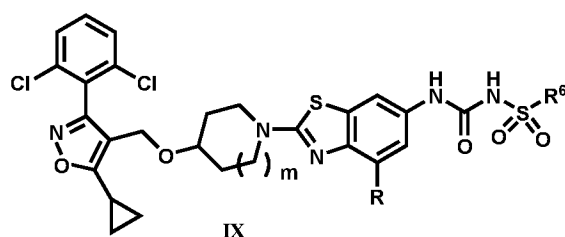
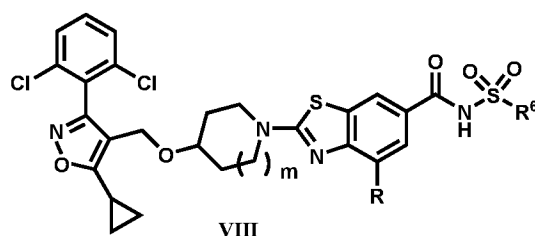
- 15 wherein R^2 , m , $\textcircled{A}$, and R^6 are as defined in claim 1.

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



wherein m, , and R⁶ are as defined in claim 1.

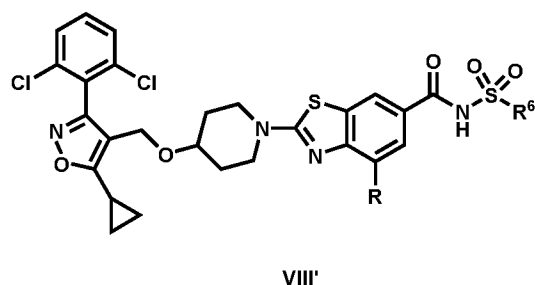
7. The compound of claim 1, represented by Formula VIII or Formula IX, or a
5 pharmaceutically acceptable salt thereof:



- wherein R is hydrogen or R³; R³ is independently selected from the group consisting
of hydroxy, OMe, OCH₂F, OCF₃, C₂-C₆-alkoxy, C₁-C₆-alkyl, C₁-C₆ haloalkyl, halo,
C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, O-C₁-C₂ alkylphenyl, cyano, CH₂F,
10 CHF₂, CF₃, SCF₃, NH₂, NHMe, and NMe₂; and m and R⁶ are as defined in claim 1.

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

(a) compounds of Formula VIII':



and pharmaceutically acceptable salts thereof, wherein R and R⁶ are delineated for each compound in Table 1,

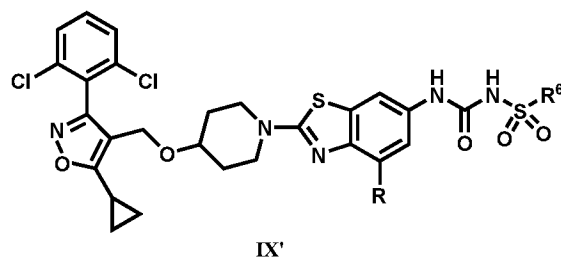
Table 1

Compound	R	R ⁶	Compound	R	R ⁶	Compound	R	R ⁶
1	H	Methyl	30	F	Methyl	59	OMe	Methyl
2	H	Ethyl	31	F	Ethyl	60	OMe	Ethyl
3	H	Isopropyl	32	F	Isopropyl	61	OMe	Isopropyl
4	H	Butyl	33	F	Butyl	62	OMe	Butyl
5	H	t-Butyl	34	F	t-Butyl	63	OMe	t-Butyl
6	H	Propyl	35	F	Propyl	64	OMe	Propyl
7	H	Benzyl	36	F	Benzyl	65	OMe	Benzyl
8	H	Vinyl	37	F	Vinyl	66	OMe	Vinyl
9	H	Allyl	38	F	Allyl	67	OMe	Allyl
10	H	-CF ₃	39	F	-CF ₃	68	OMe	-CF ₃
11	H		40	F		69	OMe	
12	H		41	F		70	OMe	
13	H		42	F		71	OMe	
14	H		43	F		72	OMe	
15	H		44	F		73	OMe	
16	H		45	F		74	OMe	
17	H		46	F		75	OMe	
18	H		47	F		76	OMe	
19	H		48	F		77	OMe	
20	H		49	F		78	OMe	
21	H		50	F		79	OMe	
22	H		51	F		80	OMe	
23	H		52	F		81	OMe	
24	H	-NH ₂	53	F	-NH ₂	82	OMe	-NH ₂

25	H	-NHCH ₃	54	F	-NHCH ₃	83	OMe	-NHCH ₃
26	H	-N(CH ₃) ₂	55	F	-N(CH ₃) ₂	84	OMe	-N(CH ₃) ₂
27	H		56	F		85	OMe	
28	H		57	F		86	OMe	
29	H		58	F		87	OMe	

and

(b) compounds of Formula IX':



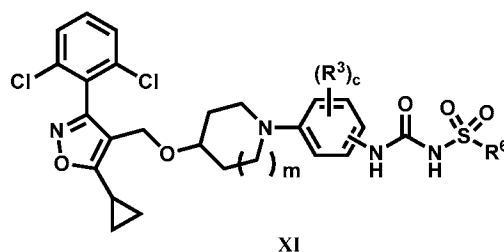
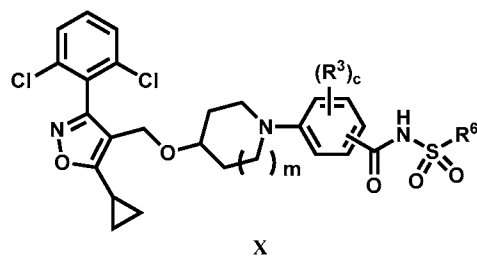
- 5 and pharmaceutically acceptable salts thereof, wherein R and R⁶ are delineated for each compound in Table 2,

Table 2

Compound	R	R ⁶	Compound	R	R ⁶	Compound	R	R ⁶
88	H	Methyl	117	F	Methyl	146	OMe	Methyl
89	H	Ethyl	118	F	Ethyl	147	OMe	Ethyl
90	H	Isopropyl	119	F	Isopropyl	148	OMe	Isopropyl
91	H	Butyl	120	F	Butyl	149	OMe	Butyl
92	H	t-Butyl	121	F	t-Butyl	150	OMe	t-Butyl
93	H	Propyl	122	F	Propyl	151	OMe	Propyl
94	H	Benzyl	123	F	Benzyl	152	OMe	Benzyl
95	H	Vinyl	124	F	Vinyl	153	OMe	Vinyl
96	H	Allyl	125	F	Allyl	154	OMe	Allyl
97	H	-CF ₃	126	F	-CF ₃	155	OMe	-CF ₃
98	H		127	F		156	OMe	
99	H		128	F		157	OMe	
100	H		129	F		158	OMe	
101	H		130	F		159	OMe	

102	H		131	F		160	OMe	
103	H		132	F		161	OMe	
104	H		133	F		162	OMe	
105	H		134	F		163	OMe	
106	H		135	F		164	OMe	
107	H		136	F		165	OMe	
108	H		137	F		166	OMe	
109	H		138	F		167	OMe	
110	H		139	F		168	OMe	
111	H	-NH ₂	140	F	-NH ₂	169	OMe	-NH ₂
112	H	-NHCH ₃	141	F	-NHCH ₃	170	OMe	-NHCH ₃
113	H	-N(CH ₃) ₂	142	F	-N(CH ₃) ₂	171	OMe	-N(CH ₃) ₂
114	H		143	F		172	OMe	
115	H		144	F		173	OMe	
116	H		145	F		174	OMe	

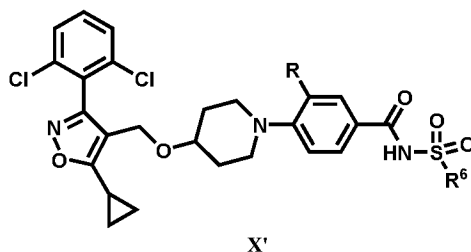
9. The compound of claim 1, represented by Formula X or Formula XI, or a pharmaceutically acceptable salt thereof:



wherein c is 0, 1 or 2; R³ is independently selected from the group consisting of hydroxy, OMe, OCH₂F, OCF₃, C₂-C₆-alkoxy, C₁-C₆-alkyl, C₁-C₆ haloalkyl, halo, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, O-C₁-C₂ alkylphenyl, cyano, CH₂F, CHF₂, CF₃, SCF₃, NH₂, NHMe, and NMe₂; and m and R⁶ are as defined in claim 1.

5

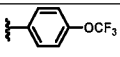
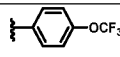
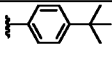
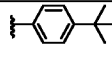
10. The compound of claim 1, which is selected from
(a) compounds of Formula X',



and pharmaceutically acceptable salts thereof, wherein R and R⁶ are delineated for
10 each compound in Table 3,

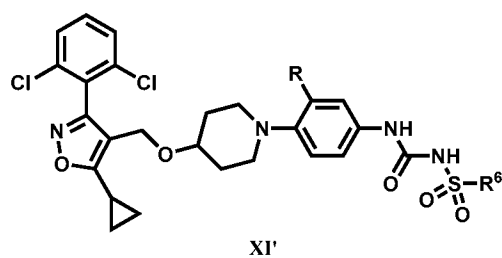
Table 3

Compound	R	R ⁶	Compound	R	R ⁶
175	H	Methyl	204	F	Methyl
176	H	Ethyl	205	F	Ethyl
177	H	Isopropyl	206	F	Isopropyl
178	H	Butyl	207	F	Butyl
179	H	t-Butyl	208	F	t-Butyl
180	H	Propyl	209	F	Propyl
181	H	Benzyl	210	F	Benzyl
182	H	Vinyl	211	F	Vinyl
183	H	Allyl	212	F	Allyl
184	H	-CF ₃	213	F	-CF ₃
185	H		214	F	
186	H		215	F	
187	H		216	F	
188	H		217	F	
189	H		218	F	

190	H		219	F	
191	H		220	F	
192	H		221	F	
193	H		222	F	
194	H		223	F	
195	H		224	F	
196	H		225	F	
197	H		226	F	
198	H	-NH ₂	227	F	-NH ₂
199	H	-NHCH ₃	228	F	-NHCH ₃
200	H	-N(CH ₃) ₂	229	F	-N(CH ₃) ₂
201	H		230	F	
202	H		231	F	
203	H		232	F	

and

(b) compounds of Formula XI':



5

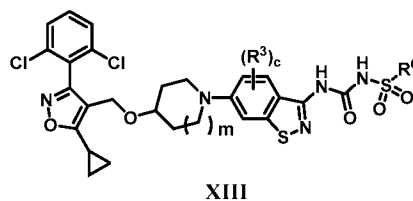
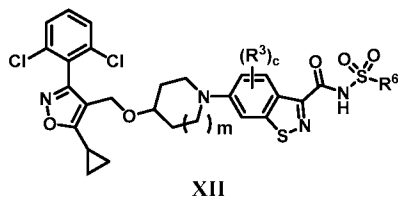
and pharmaceutically acceptable salts thereof, wherein R and R⁶ are delineated for each compound in Table 4,

Table 4

Compound	R	R ⁶	Compound	R	R ⁶
233	H	Methyl	262	F	Methyl

234	H	Ethyl	263	F	Ethyl
235	H	Isopropyl	264	F	Isopropyl
236	H	Butyl	265	F	Butyl
237	H	t-Butyl	266	F	t-Butyl
238	H	Propyl	267	F	Propyl
239	H	Benzyl	268	F	Benzyl
240	H	Vinyl	269	F	Vinyl
241	H	Allyl	270	F	Allyl
242	H	-CF ₃	271	F	-CF ₃
243	H		272	F	
244	H		273	F	
245	H		274	F	
246	H		275	F	
247	H		276	F	
248	H		277	F	
249	H		278	F	
250	H		279	F	
251	H		280	F	
252	H		281	F	
253	H		282	F	
254	H		283	F	
255	H		284	F	
256	H	-NH ₂	285	F	-NH ₂
257	H	-NHCH ₃	286	F	-NHCH ₃
258	H	-N(CH ₃) ₂	287	F	-N(CH ₃) ₂
259	H		288	F	
260	H		289	F	
261	H		290	F	

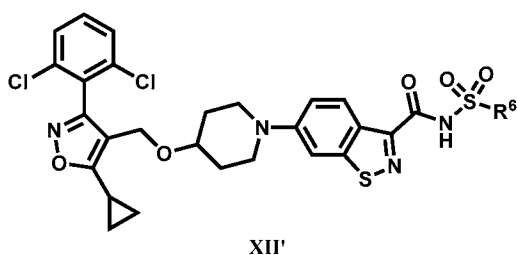
11. The compound of claim 1, represented by Formula XII or Formula XIII or a pharmaceutically acceptable salt thereof:



5 wherein c is 0, 1 or 2; each R³ is independently selected from the groups consisting of hydroxy, OMe, OCH₂F, OCF₃, C₂-C₆-alkoxy, C₁-C₆-alkyl, C₁-C₆ haloalkyl, halo, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, O-C₁-C₂ alkylphenyl, cyano, CH₂F, CHF₂, CF₃, SCF₃, NH₂, NHMe, and NMe₂; and m and R⁶ are as defined in claim 1.

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

(a) compounds of Formula XII':

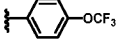
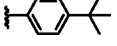


and pharmaceutically acceptable salts thereof, wherein R⁶ is delineated for each compound in Table 5,

15

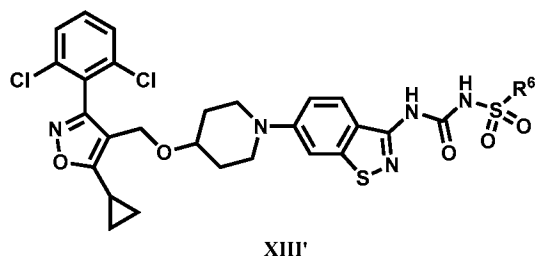
Table 5

Compound	R ⁶	Example	R ⁶	Compound	R ⁶
291	Methyl	301		311	
292	Ethyl	302		312	
293	Isopropyl	303		313	
294	Butyl	304		314	-NH ₂
295	t-Butyl	305		315	-NHCH ₃
296	Propyl	306		316	-N(CH ₃) ₂

297	Benzyl	307		317	
298	Vinyl	308		318	
299	Allyl	309		319	
300	-CF ₃	310			

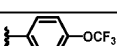
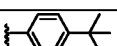
and

(b) compounds of Formula XIII':

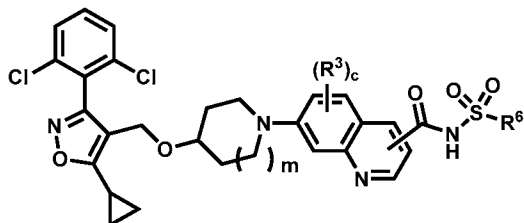


- 5 and pharmaceutically acceptable salts thereof, wherein R⁶ is delineated for each compound in Table 6,

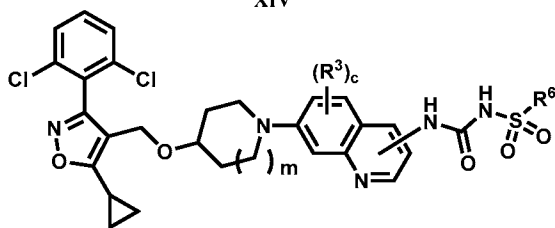
Table 6

Compound	R ⁶	Example	R ⁶	Compound	R ⁶
320	Methyl	330		340	
321	Ethyl	331		341	
322	Isopropyl	332		342	
323	Butyl	333		343	-NH ₂
324	t-Butyl	334		344	-NHCH ₃
325	Propyl	335		345	-N(CH ₃) ₂
326	Benzyl	336		346	
327	Vinyl	337		347	
328	Allyl	338		348	
329	-CF ₃	339			

13. The compound of claim 1, represented by Formula XIV or Formula XV or a pharmaceutically acceptable salt thereof:



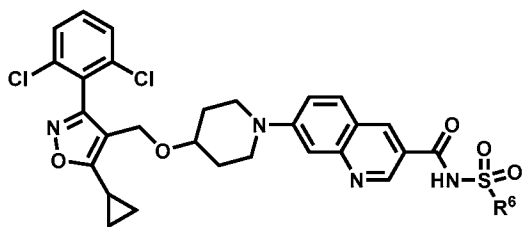
XIV



XV

5 wherein c is 0, 1 or 2; each R³ is independently selected from the groups consisting of hydroxy, OMe, OCH₂F, OCF₃, C₂-C₆-alkoxy, C₁-C₆-alkyl, C₁-C₆ haloalkyl, halo, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, O-C₁-C₂ alkylphenyl, cyano, CH₂F, CHF₂, CF₃, SCF₃, NH₂, NHMe, and NMe₂; and m and R⁶ are defined in claim 1.

10 14. The compound of claim 1, which is selected from (a) compounds of Formula XIV':



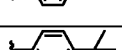
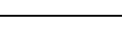
XIV'

and pharmaceutically acceptable salts thereof, wherein R⁶ is delineated for each compound in Table 7,

15

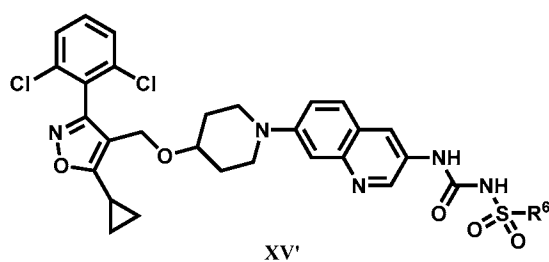
Table 7

Compound	R ⁶	Compound	R ⁶	Compound	R ⁶
349	Methyl	359		369	
350	Ethyl	360		370	

351	Isopropyl	361		371	
352	Butyl	362		372	-NH ₂
353	t-Butyl	363		373	-NHCH ₃
354	Propyl	364		374	-N(CH ₃) ₂
355	Benzyl	365		375	
356	Vinyl	366		376	
357	Allyl	367		377	
358	-CF ₃	368			

and

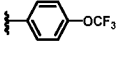
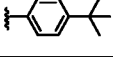
(b) compounds of Formula XV':



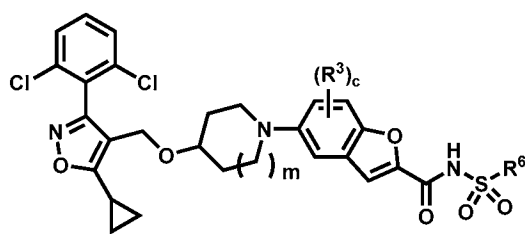
- 5 and pharmaceutically acceptable salts thereof, wherein R⁶ is delineated for each compound in Table 8,

Table 8

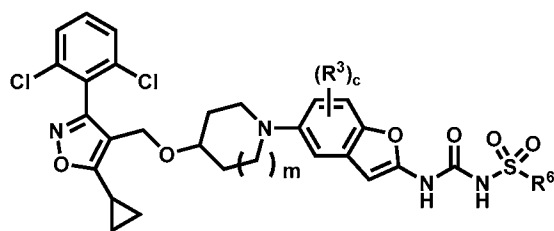
Compound	R ⁶	Compound	R ⁶	Compound	R ⁶
378	Methyl	388		398	
379	Ethyl	389		399	
380	Isopropyl	390		400	
381	Butyl	391		401	-NH ₂
382	t-Butyl	392		402	-NHCH ₃
383	Propyl	393		403	-N(CH ₃) ₂
384	Benzyl	394		404	

385	Vinyl	395		405	
386	Allyl	396		406	
387	-CF ₃	397			

15. The compound of claim 1, represented by Formula XVI or Formula XVII or a pharmaceutically acceptable salt thereof:



XVI



XVII

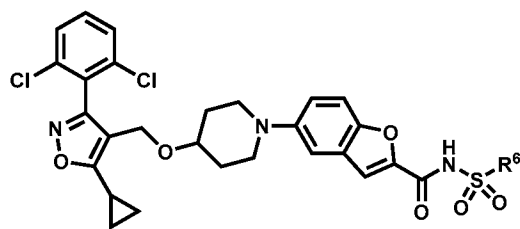
5

wherein c is 0, 1 or 2; R³ is independently selected from the groups consisting of hydroxy, OMe, OCH₂F, OCF₃, C₂-C₆-alkoxy, C₁-C₆-alkyl, C₁-C₆ haloalkyl, halo, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, O-C₁-C₂ alkylphenyl, cyano, CH₂F, CHF₂, CF₃, SCF₃, NH₂, NHMe, and NMe₂; and m and R⁶ are as defined in claim 1.

10

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

(a) compounds of Formula XVI':

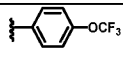
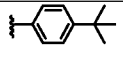


XVI'

and pharmaceutically acceptable salts thereof, wherein R⁶ is delineated for each compound in Table 9,

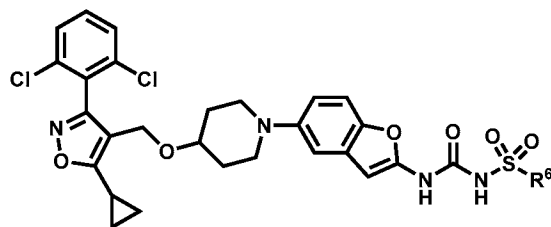
15

Table 9

Compound	R ⁶	Compound	R ⁶	Compound	R ⁶
407	Methyl	417		427	
408	Ethyl	418		428	
409	Isopropyl	419		429	
410	Butyl	420		430	-NH ₂
411	t-Butyl	421		431	-NHCH ₃
412	Propyl	422		432	-N(CH ₃) ₂
413	Benzyl	423		433	
414	Vinyl	424		434	
415	Allyl	425		435	
416	-CF ₃	426			

and

(b) compounds of Formula XVII':



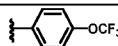
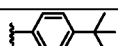
5

XVII'

and pharmaceutically acceptable salts thereof, wherein R⁶ is delineated for each compound in Table 10,

Table 10

Compound	R ⁶	Compound	R ⁶	Compound	R ⁶
436	Methyl	446		456	
437	Ethyl	447		457	
438	Isopropyl	448		458	

439	Butyl	449		459	-NH ₂
440	t-Butyl	450		460	-NHCH ₃
441	Propyl	451		461	-N(CH ₃) ₂
442	Benzyl	452		462	
443	Vinyl	453		463	
444	Allyl	454		464	
445	-CF ₃	455			

17. 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 1-16.

18. The method according to claim 17, 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.

19. The method according to claim 18, wherein the fibrotic disease is selected from primary biliary cirrhosis, primary sclerosing cholangitis, pulmonary fibrosis, renal fibrosis, and liver fibrosis.

20. The method according to claim 18, 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.

21. The method according to claim 18, wherein the renal disease is selected from
5 the group consisting of diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, and polycystic kidney disease.

22. The method according to claim 18, wherein the cardiovascular disease is
10 selected from the group consisting of atherosclerosis, arteriosclerosis, dyslipidemia, hypercholesterolemia, and hypertriglyceridemia.

23. The method according to claim 18, wherein the metabolic disease is selected
15 from the group consisting of insulin resistance, Type I and Type II diabetes, and obesity.

24. A pharmaceutical composition comprising a compound of any one of claims 1-16 and a pharmaceutically acceptable carrier.

20 25. Use of a compound of any one of claims 1-16 for the preparation of pharmaceutical compositions for the prevention or treatment of FXR-mediated diseases or conditions.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/29518

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/454, 31/55; C07D 417/14 (2017.01)

CPC - A61K 31/454, 31/55; C07D 417/14

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 2013/0261108 A1 (TULLY, DC et al.) 03 October 2013; abstract, paragraphs [0008], [0010], [0017], [0089], [0101], [0119], [0121], [0162], [0168], [0181], [0274]	1-8, 17/1-8, 18/17/1-8, 19/18/17/1-8, 20/18/17/1-8, 21/18/17/1-8, 22/18/17/1-8, 23/18/17/1-8, 24/1-8, 25/1-8
Y	US 2014/0221659 A1 (KINZEL, O et al.) 07 August 2014; abstract, paragraphs [0008], [0011]-[0013]	1-8, 17/1-8, 18/17/1-8, 19/18/17/1-8, 20/18/17/1-8, 21/18/17/1-8, 22/18/17/1-8, 23/18/17/1-8, 24/1-8, 25/1-8
A	US 2010/0152166 A1 (GENIN, MJ et al.) 17 June 2010; entire document	1-8, 17/1-8, 18/17/1-8, 19/18/17/1-8, 20/18/17/1-8, 21/18/17/1-8, 22/18/17/1-8, 23/18/17/1-8, 24/1-8, 25/1-8

☐ 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

23 June 2017 (23.06.2017)

Date of mailing of the international search report

14 SEP 2017

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/29518

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

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

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

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

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

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

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

---Continued Within the Next Supplemental Box---

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-8, 17-25

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US17/29518

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

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid. Groups I+, Claims 1-25 (in-part); compound of Formula (I), wherein m is 1; R1 is C3-C6 cycloalkyl; R2 is optionally substituted aryl; A is optionally substituted benzothiazole; R4 is -CON(R5)SO2R6 wherein R5 is hydrogen and R6 is C1-C8 alkyl (exemplary compound structure), and methods associated therewith.

The compound, compositions and methods will be searched to the extent the compound encompasses a compound of Formula (I), wherein m is 1; R1 is C3-C6 cycloalkyl; R2 is optionally substituted aryl; A is optionally substituted benzothiazole; R4 is -CON(R5)SO2R6 wherein R5 is hydrogen and R6 is C1-C8 alkyl (exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure (e.g. no optional or variable atoms or substituents) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), 3 (in-part), 4 (in-part), 5 (in-part), 6 (in-part), 7 (in-part), 8 (in-part), 17 (in-part), 18 (in-part), 19 (in-part), 20 (in-part), 21 (in-part), 22 (in-part), 23 (in-part), 24 (in-part), and 25 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula (I), wherein m is 1; R1 is C3-C6 cycloalkyl; R2 is optionally substituted aryl; A is optionally substituted benzothiazole; R4 is -CON(R5)SO2R6 wherein R5 is hydrogen and R6 is C1-C8 alkyl (exemplary compound structure). Applicants must specify the claims that encompass any additionally elected compound structure(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound of Formula (I), wherein m is 1; R1 is C3-C6 cycloalkyl; R2 is optionally substituted aryl; A is optionally substituted benzothiazole; R4 is -CON(R5)SO2R6 wherein R5 is hydrogen and R6 is C1-C8 alkyl (exemplary elected compound structure).

Groups I+ share the technical features including: a compound of Formula (I), wherein m is 1; R1 is C3-C6 cycloalkyl; R2 is optionally substituted aryl; A is optionally substituted benzothiazole; R4 is -CON(R5)SO2R6 wherein R5 is hydrogen and R6 is C1-C8 alkyl, for use in the treatment of an FXR-mediated disease or condition.

However, these shared technical features are previously disclosed by US 2013/0261108 A1 to Tully, et al. (hereinafter 'Tully') in view of US 2014/0221659 A1 to Kinzel, et al. (hereinafter 'Kinzel').

Tully discloses a compound of Formula (I) (compound of formula II; paragraph [0017]), wherein m is 1 (formula II (m is 1); paragraph [0017]); R1 is C3-C6 cycloalkyl (formula II wherein R2 (R1) is cyclopropyl; paragraph [0010]); R2 is optionally substituted aryl (formula II wherein L is a bond and R1 (R2) is optionally substituted phenyl; paragraph [0008]); and A is optionally substituted benzothiazole (formula II (A is optionally substituted benzothiazole); paragraph [0017]), for use in the treatment of an FXR-mediated disease or condition (method for treating a condition mediated by FXR in a subject in need thereof; paragraphs [0089], [0171]), but Tully does not disclose wherein R4 is -CON(R5)SO2R6 wherein R5 is hydrogen and R6 is C1-C8 alkyl. However, Kinzel discloses wherein R4 is -CON(R5)SO2R6 wherein R5 is hydrogen and R6 is C1-C8 alkyl (formula I wherein A is a heteroaryl group and R (R4) is CONR7R8 wherein R7 (R5) is H and R8 is SO2-C1 alkyl (R6 is C1 alkyl); paragraphs [0011]-[0013]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by Tully, in order to have provided wherein R4 is -CON(R5)SO2R6 wherein R5 is hydrogen and R6 is C1-C8 alkyl, as previously disclosed by Kinzel, for providing heterocyclic compounds useful in the modulation of Farnesoid X receptors and treatment of related disorders (Tully; abstract; Kinzel; abstract).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Tully and Kinzel references, unity of invention is lacking.