

BILE ACID ANALOGS AS FXR/TGR5 AGONISTS AND METHODS OF USE THEREOF

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5 RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/084,769, filed on November 26, 2014. The entire teachings of the above application are incorporated herein by reference.

TECHNICAL FIELD

10 The present invention relates generally to compounds and pharmaceutical compositions useful as FXR/TGR5 modulators. Specifically, the present invention relates to bile acid derivatives and methods for their preparation and use.

BACKGROUND OF THE INVENTION

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

Small molecule compounds which act as FXR modulators have been disclosed in the following publications: WO 2000/037077, WO 2003/015771, WO 2004/048349, WO

2007/076260, WO 2007/092751, WO 2007/140174, WO 2007/140183, WO 2008/051942, WO 2008/157270, WO 2009/005998, WO 2009/012125, WO 2008/025539, WO 2008/025540, WO 2011/020615, and WO 2013/007387.

Further small molecule FXR modulators have been recently reviewed (R. C. Buijsman et al. *Curr. Med. Chem.* **2005**, *12*, 1017-1075).

TGR5 receptor is a G-protein-coupled receptor that has been identified as a cell-surface receptor that is responsive to bile acids (BAs). The primary structure of TGR5 and its responsiveness to bile acids has been found to be highly conserved in TGR5 among human, bovine, rabbit, rat, and mouse, and thus suggests that TGR5 has important physiological functions. TGR5 has been found to be widely distributed in not only lymphoid tissues but also in other tissues. High levels of TGR5 mRNA have been detected in placenta, spleen, and monocytes/macrophages. Bile acids have been shown to induce internalization of the TGR5 fusion protein from the cell membrane to the cytoplasm (Kawamata et al., *J. Bio. Chem.*, **2003**, *278*, 9435). TGR5 has been found to be identical to hGPCR19 reported by Takeda et al., *FEBS Lett.* **2002**, *520*, 97-101.

TGR5 is associated with the intracellular accumulation of cAMP, which is widely expressed in diverse cell types. While the activation of this membrane receptor in macrophages decreases pro-inflammatory cytokine production, (Kawamata, Y., et al., *J. Biol. Chem.* **2003**, *278*, 9435-9440) the stimulation of TGR5 by BAs in adipocytes and myocytes enhances energy expenditure (Watanabe, M., et al. *Nature.* **2006**, *439*, 484-489). This latter effect involves the cAMP-dependent induction of type 2 iodothyronine deiodinase (D2), which by, locally converting T4 into T3, gives rise to increased thyroid hormone activity. Consistent with the role of TGR5 in the control of energy metabolism, female TGR5 knock-out mice show a significant fat accumulation with body weight gain when challenged with a high fat diet, indicating that the lack of TGR5 decreases energy expenditure and elicits obesity (Maruyama, T., et al., *J. Endocrinol.* **2006**, *191*, 197-205). In addition and in line with the involvement of TGR5 in energy homeostasis, bile acid activation of the membrane receptor has also been reported to promote the production of glucagon-like peptide 1 (GLP-1) in murine enteroendocrine cell lines (Katsuma, S., *Biochem. Biophys. Res. Commun.*, **2005**, *329*, 386-390). On the basis of all the above observations, TGR5 is an attractive target for the treatment of disease e.g., obesity, diabetes and metabolic syndrome.

In addition to the use of TGR5 agonists for the treatment and prevention of metabolic diseases, compounds that modulate TGR5 modulators are also useful for the

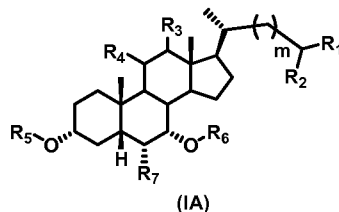
treatment of other diseases *e.g.*, central nervous diseases as well as inflammatory diseases (WO 01/77325 and WO 02/84286). Modulators of TGR5 also provide methods of regulating bile acid and cholesterol homeostasis, fatty acid absorption, and protein and carbohydrate digestion.

- 5 There is a need for the development of FXR and/or TGR5 modulators for the treatment and prevention of disease.

SUMMARY OF THE INVENTION

- 10 The present invention relates to compounds which modulate FXR and/or TGR activity as well as methods of using these compounds to treat disease.

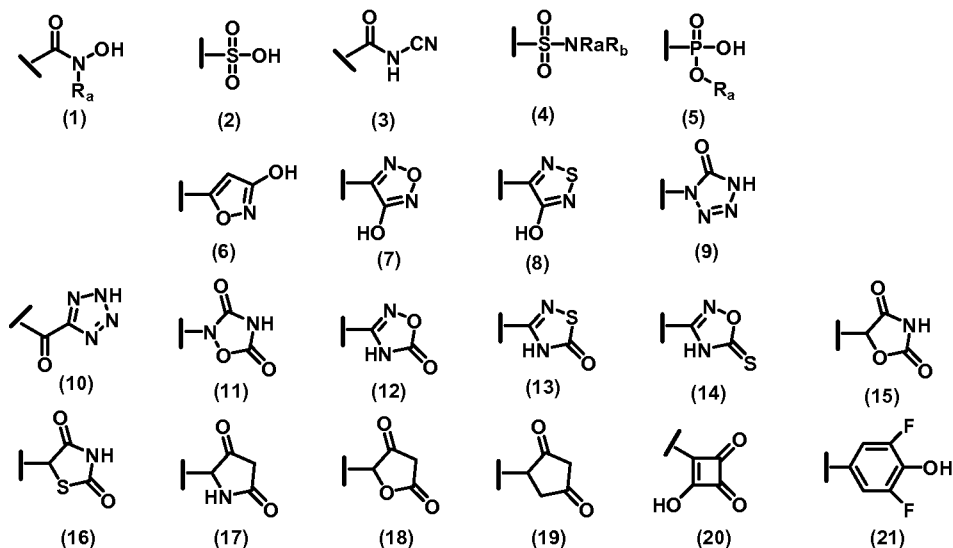
In one aspect, the invention provides compounds represented by Formula IA, or pharmaceutically acceptable salts, stereoisomer, solvate, hydrate or combination thereof:



wherein:

15

R₁ is selected from:



wherein,

R_a is hydrogen, substituted or unsubstituted C₃-C₈-cycloalkyl or substituted or unsubstituted C₁-C₈ alkyl;

R_b is selected from the group consisting of:

- 1) Halogen;
- 2) Hydroxyl;
- 3) Substituted or unsubstituted -C₁-C₈ alkyl;
- 4) Substituted or unsubstituted -C₂-C₈ alkenyl;
- 5) Substituted or unsubstituted -C₂-C₈ alkynyl;
- 6) Substituted or unsubstituted -C₃-C₈ cycloalkyl;
- 7) Substituted or unsubstituted aryl;
- 8) Substituted or unsubstituted alkylaryl;
- 9) Substituted or unsubstituted heterocycloalkyl;
- 10) Substituted or unsubstituted heteroaryl;
- 11) Substituted or unsubstituted alkylheteroaryl; and
- 12) -NR₁₀R₁₁; wherein R₁₀ and R₁₁ are each independently selected from hydrogen, substituted or unsubstituted -C₁-C₈ alkyl, substituted or unsubstituted -C₂-C₈ alkenyl, Substituted or unsubstituted -C₂-C₈ alkynyl, substituted or unsubstituted -C₃-C₈ cycloalkyl, or R₁₀ and R₁₁, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring.

R₂ is selected from the group consisting of:

- 1) Hydrogen;
- 2) Substituted or unsubstituted –C₁-C₈ alkyl;
- 3) Substituted or unsubstituted –C₂-C₈ alkenyl;
- 5 4) Substituted or unsubstituted –C₂-C₈ alkynyl;
- 5) Substituted or unsubstituted alkylaryl; and
- 6) Substituted or unsubstituted aryl.

In certain embodiments R₂ is hydrogen or methyl.

m is 0, 1, 2 or 3; in certain embodiments, m is 0, 1 or 2.

- 10 R₃ is hydrogen, hydroxyl, –OSO₃H, –OSO₃[–], –OAc, –OPO₃H₂ or –OPO₃^{2–}; in certain embodiments, R₃ is hydrogen or hydroxyl.

R₄ is hydrogen, halogen, CN, N₃, hydroxyl, –OSO₃H, –OSO₃[–], –OAc, –OPO₃H₂, –OPO₃^{2–}, –SR₂ or –NHR₁₂, wherein R₁₂ is hydrogen; substituted or unsubstituted –C₁-C₈ alkyl; substituted or unsubstituted –C₂-C₈ alkenyl; substituted or unsubstituted –C₂-C₈ alkynyl;

- 15 substituted or unsubstituted alkylaryl; or substituted or unsubstituted aryl; in certain embodiments, R₄ is hydrogen.

Alternatively, R₃ and R₄ are taken together with the carbon atoms to which they are attached to form –CH=CH–, a cycloalkyl ring or a heterocycloalkyl ring such as, but not limited to, cyclopropyl or epoxide.

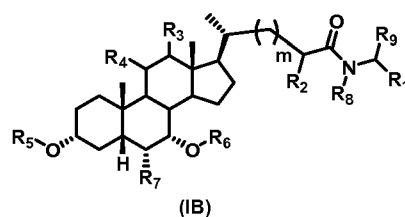
- 20 R₅ and R₆ are independently selected from hydrogen or a hydroxyl protecting group such as, but not limited to, acetyl, trimethylsilyl, or benzyl; in certain embodiments, both R₅ and R₆ are hydrogen.

R₇ is selected from the group consisting of:

- 1) Hydrogen;
- 25 2) Halogen;
- 3) Substituted or unsubstituted –C₁-C₈ alkyl;
- 4) Substituted or unsubstituted –C₂-C₈ alkenyl;
- 5) Substituted or unsubstituted –C₂-C₈ alkynyl; and
- 6) Substituted or unsubstituted –C₃-C₈ cycloalkyl.

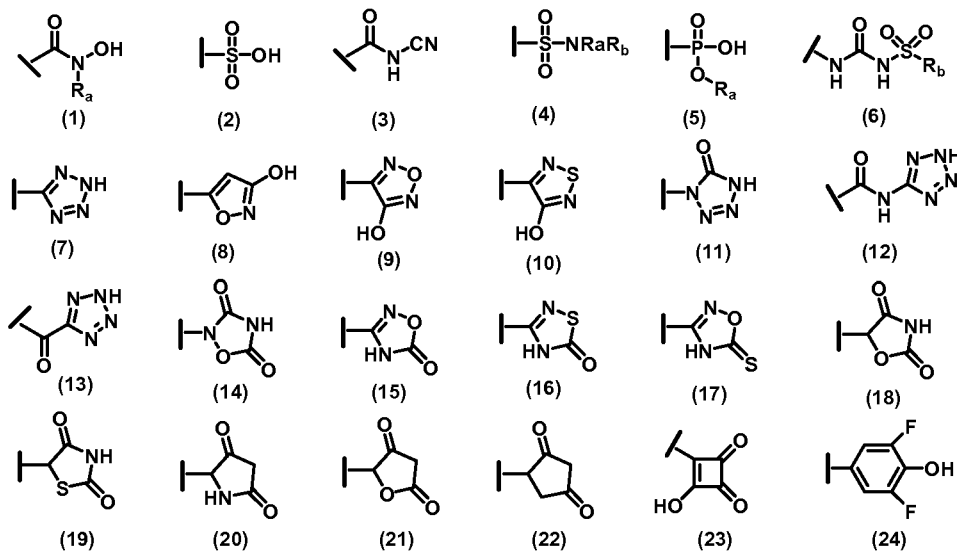
- 30 In certain embodiments, R₇ is C₁-C₄-alkyl, preferably ethyl.

In another aspect, the invention provides compounds represented by Formula IB, or pharmaceutically acceptable salts, stereoisomer, solvate, hydrate or combination thereof:



wherein:

R₁ is selected from:



5 wherein,

R_a is hydrogen, substituted or unsubstituted C₃-C₈-cycloalkyl or substituted or unsubstituted C₁-C₈ alkyl;

R_b is selected from the group consisting of:

- 1) hydrogen
- 2) Halogen;
- 3) Hydroxyl;
- 4) Substituted or unsubstituted -C₁-C₈ alkyl;
- 5) Substituted or unsubstituted -C₂-C₈ alkenyl;
- 6) Substituted or unsubstituted -C₂-C₈ alkynyl;
- 7) Substituted or unsubstituted -C₃-C₈ cycloalkyl;
- 8) Substituted or unsubstituted aryl;
- 9) Substituted or unsubstituted alkylaryl;
- 10) Substituted or unsubstituted heterocycloalkyl;
- 11) Substituted or unsubstituted heteroaryl;
- 12) Substituted or unsubstituted alkylheteroaryl; and

- 13) $-NR_{10}R_{11}$; wherein R_{10} and R_{11} are each independently selected from hydrogen, substituted or unsubstituted $-C_1-C_8$ alkyl, substituted or unsubstituted $-C_2-C_8$ alkenyl, substituted or unsubstituted $-C_2-C_8$ alkynyl, substituted or unsubstituted $-C_3-C_8$ cycloalkyl, or R_{10} and R_{11} , taken together with the nitrogen atom to which they are attached, form a heterocyclic ring.

R_2 is selected from the group consisting of:

- 1) Hydrogen;
- 2) Substituted or unsubstituted $-C_1-C_8$ alkyl;
- 3) Substituted or unsubstituted $-C_2-C_8$ alkenyl;
- 4) Substituted or unsubstituted $-C_2-C_8$ alkynyl;
- 5) Substituted or unsubstituted alkylaryl; and
- 6) Substituted or unsubstituted aryl.

In certain embodiments R_2 is hydrogen or methyl.

m is 0, 1, 2 or 3; in certain embodiments, m is 0, 1 or 2.

- 15 R_3 is hydrogen, hydroxyl, $-OSO_3H$, $-OSO_3^-$, $-OAc$, $-OPO_3H_2$ or $-OPO_3^{2-}$; in certain embodiments, R_3 is hydrogen or hydroxyl.

- R_4 is hydrogen, halogen, CN, N_3 , hydroxyl, $-OSO_3H$, $-OSO_3^-$, $-OAc$, $-OPO_3H_2$, $-OPO_3^{2-}$, $-SR_2$ or $-NHR_{12}$, wherein R_{12} is hydrogen; substituted or unsubstituted $-C_1-C_8$ alkyl; substituted or unsubstituted $-C_2-C_8$ alkenyl; substituted or unsubstituted $-C_2-C_8$ alkynyl; substituted or unsubstituted alkylaryl; or substituted or unsubstituted aryl; in certain embodiments, R_4 is hydrogen.

Alternatively, R_3 and R_4 are taken together with the carbon atoms to which they are attached to form $-CH=CH-$, a cycloalkyl ring or a heterocycloalkyl ring such as, but not limited to, cyclopropyl or epoxide.

- 25 R_5 and R_6 are independently selected from hydrogen or a hydroxyl protecting group such as, but not limited to, acetyl, trimethylsilyl, or benzyl; in certain embodiments, both R_5 and R_6 are hydrogen.

R_7 is selected from the group consisting of:

- 1) Hydrogen;
- 2) Halogen;
- 3) Substituted or unsubstituted $-C_1-C_8$ alkyl;
- 4) Substituted or unsubstituted $-C_2-C_8$ alkenyl;
- 5) Substituted or unsubstituted $-C_2-C_8$ alkynyl; and

6) Substituted or unsubstituted $-C_3-C_8$ cycloalkyl.

In certain embodiments, R_7 is C_1-C_4 -alkyl, preferably ethyl.

R_8 and R_9 are independently selected from hydrogen; substituted or unsubstituted $-C_1-C_8$ alkyl; substituted or unsubstituted $-C_2-C_8$ alkenyl; substituted or unsubstituted $-C_2-C_8$ alkynyl; substituted or unsubstituted alkylaryl; or substituted or unsubstituted aryl; in certain embodiments, both R_8 and R_9 are hydrogen.

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

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

In yet another embodiment, the present invention provides a method for the prevention or treatment of a TGR5 mediated disease or condition. The method comprises administering a therapeutically effective amount of a compound of Formula (IA) or Formula (IB). The present invention also provides the use of a compound of Formula (IA) or Formula (IB) for the preparation of a medicament for the prevention or treatment of a TGR5 mediated disease or condition.

In certain embodiments, a disease that involves modulation of the TGR5 receptor is selected from metabolic disease, inflammatory disease, liver disease, autoimmune disease, cardiac disease, kidney disease, cancer, and gastrointestinal disease.

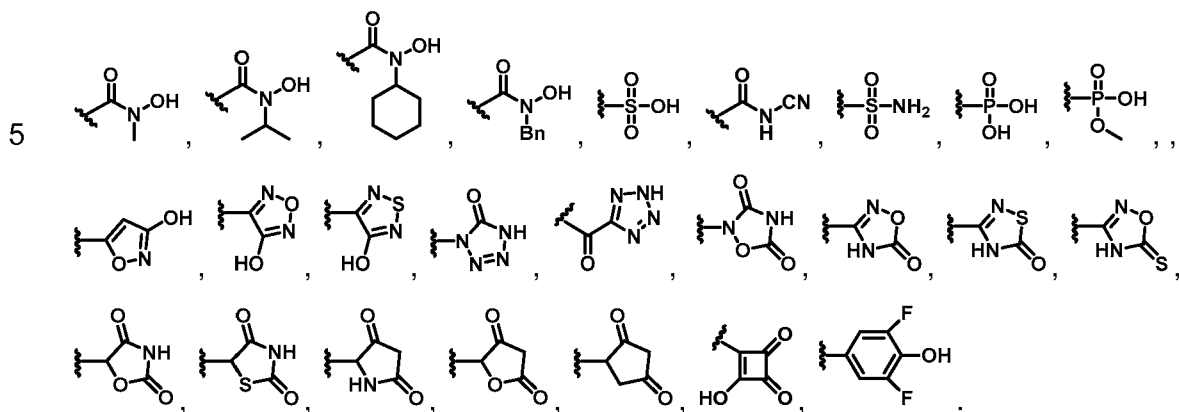
DETAILED DESCRIPTION OF THE INVENTION

A first embodiment of the invention is a compound represented by Formula IA or IB as described above, or a pharmaceutically acceptable salt, hydrate, solvate, ester or prodrug thereof.

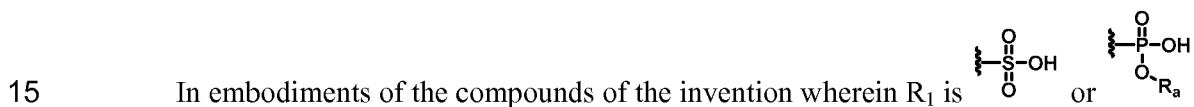
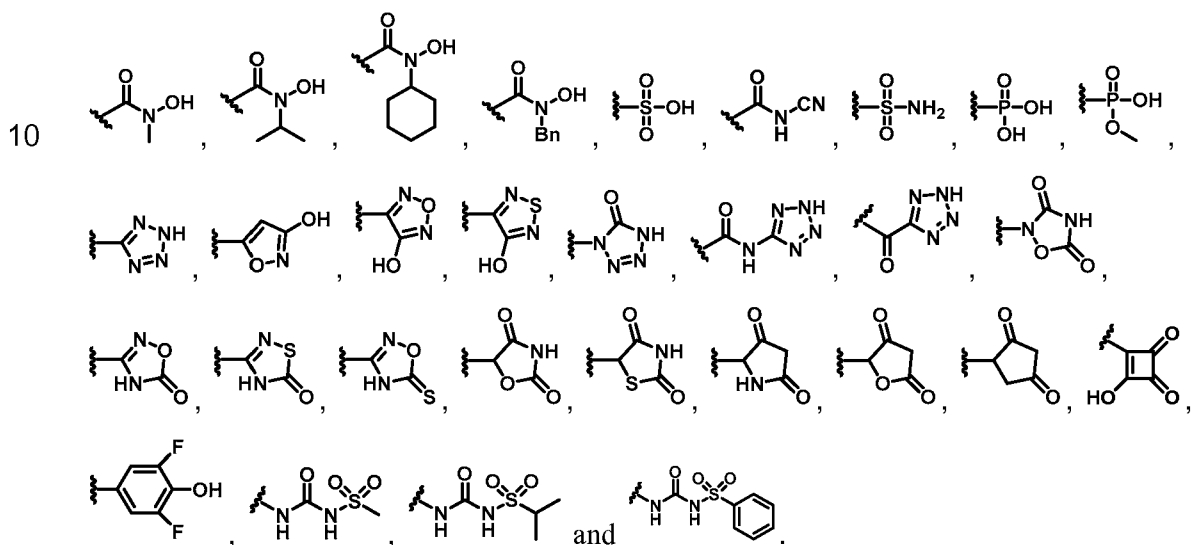
In certain embodiments of the invention, R_2 is hydrogen or methyl; m is 0, 1 or 2; R_3 is hydrogen or hydroxyl; R_4 is hydrogen; R_5 is hydrogen; R_6 is hydrogen; R_7 is ethyl; R_8 is hydrogen and R_9 is hydrogen.

In certain embodiments of the invention, R_a is hydrogen, C_4 - C_6 -cycloalkyl, phenyl- C_1 - C_4 -alkyl or C_1 - C_4 -alkyl, preferably benzyl, C_1 - C_3 -alkyl or C_4 - C_6 -cycloalkyl.

In certain embodiments of the invention, R_1 in Formula IA is selected from the group consisting of



In certain embodiments of the invention, R_1 in Formula IB is selected from the group consisting of



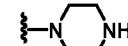
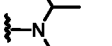
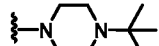
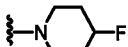
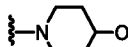
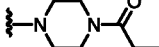
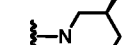
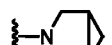
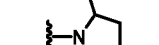
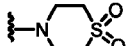
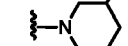
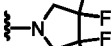
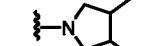
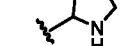
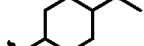
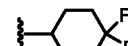
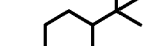
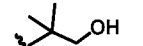
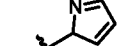
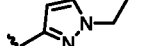
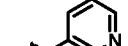
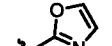
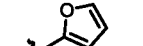
In embodiments of the compounds of the invention wherein R_1 is SO_3H or PO_3H_2 , this R_1 can be deprotonated to form the conjugate base of the parent compound which forms a salt with a pharmaceutically acceptable cation, such as ammonium, an alkali metal cation, including Li^+ , Na^+ , K^+ and Cs^+ , or an alkaline earth metal cation, such as Mg^{2+} or Ca^{2+} .

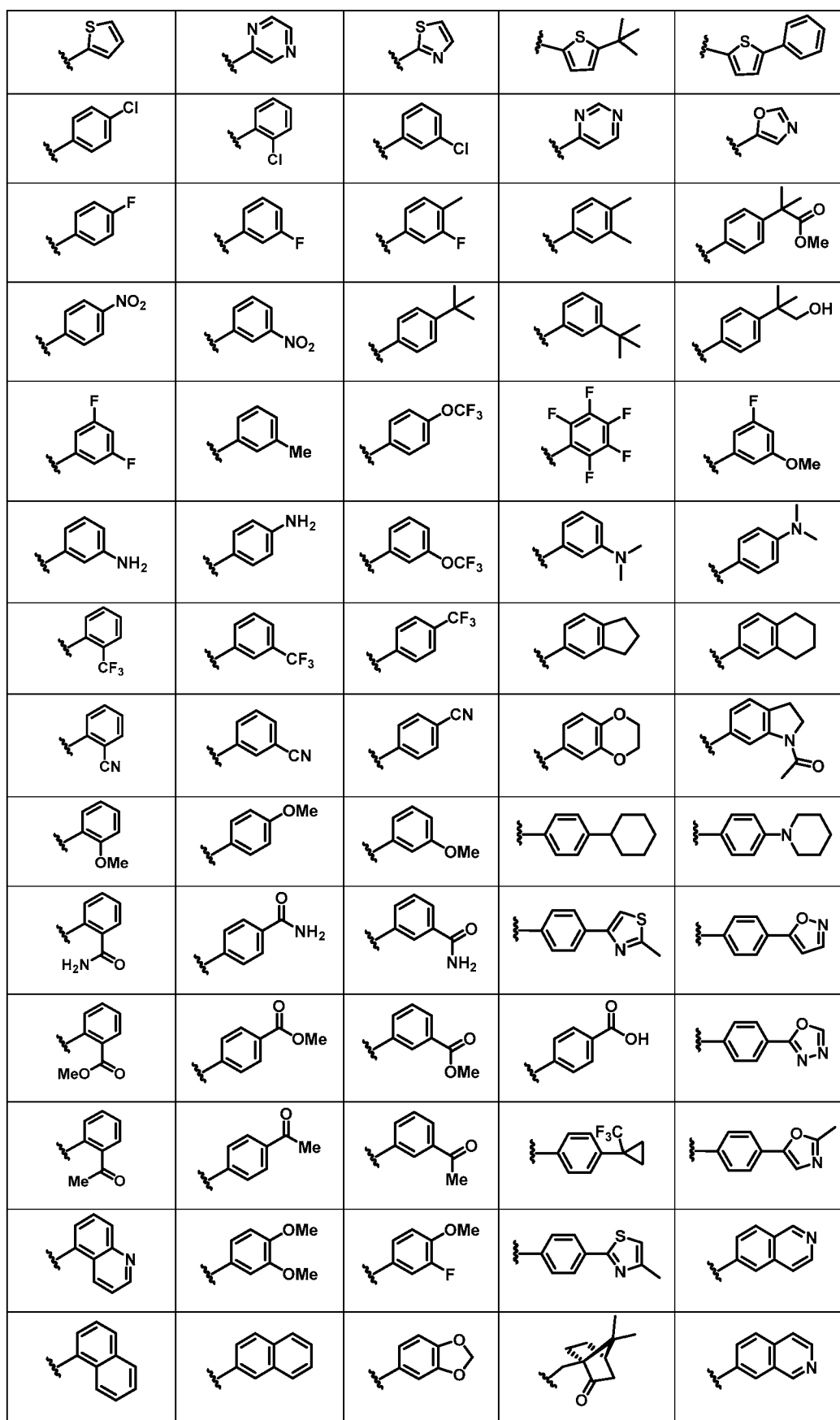
In certain embodiments of the compounds of the invention, R_1 is $-S(O)_2NR_aR_b$, wherein R_a and R_b are both hydrogen.

- In certain embodiments of the compounds of the invention, R_b is C_1 - C_4 -alkyl, halogenated C_1 - C_4 -alkyl, C_1 - C_4 -alkenyl, phenyl- C_1 - C_4 -alkyl, substituted or unsubstituted C_3 - C_6 -cycloalkyl, C_1 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, substituted or unsubstituted phenyl or halogen.

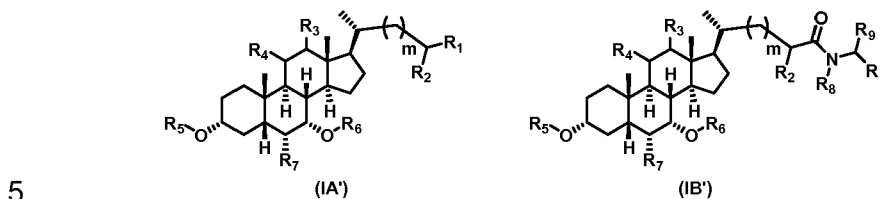
In certain embodiments of the compounds of the invention, R_b is methyl, ethyl, isopropyl, butyl, t-butyl, propyl, benzyl, vinyl, allyl, CF_3 , , , , , , , , , , ,  or fluoro.

- In certain embodiments of the compounds of the invention, R_b is selected from the groups set forth in the table below:

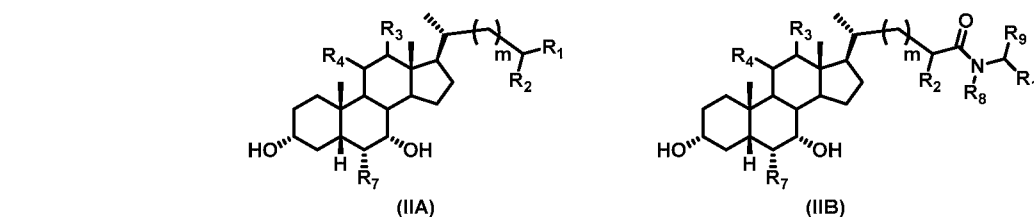
				
				
				
				
				
				
				
				
				
				



In certain embodiments, the compounds of the invention have the stereochemistry indicated in Formula (IA') and Formula (IB').

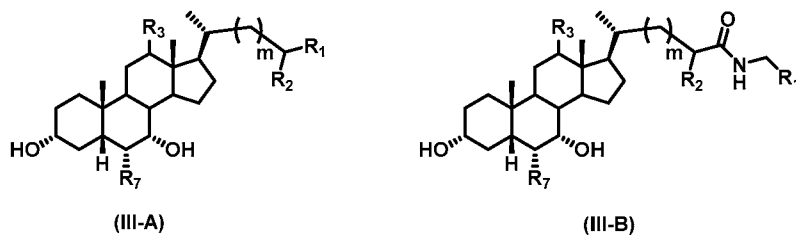


A second embodiment of the invention is a compound represented by Formula (IIA) or (IIB) or a pharmaceutically acceptable salt, hydrate, solvate, ester or prodrug thereof.



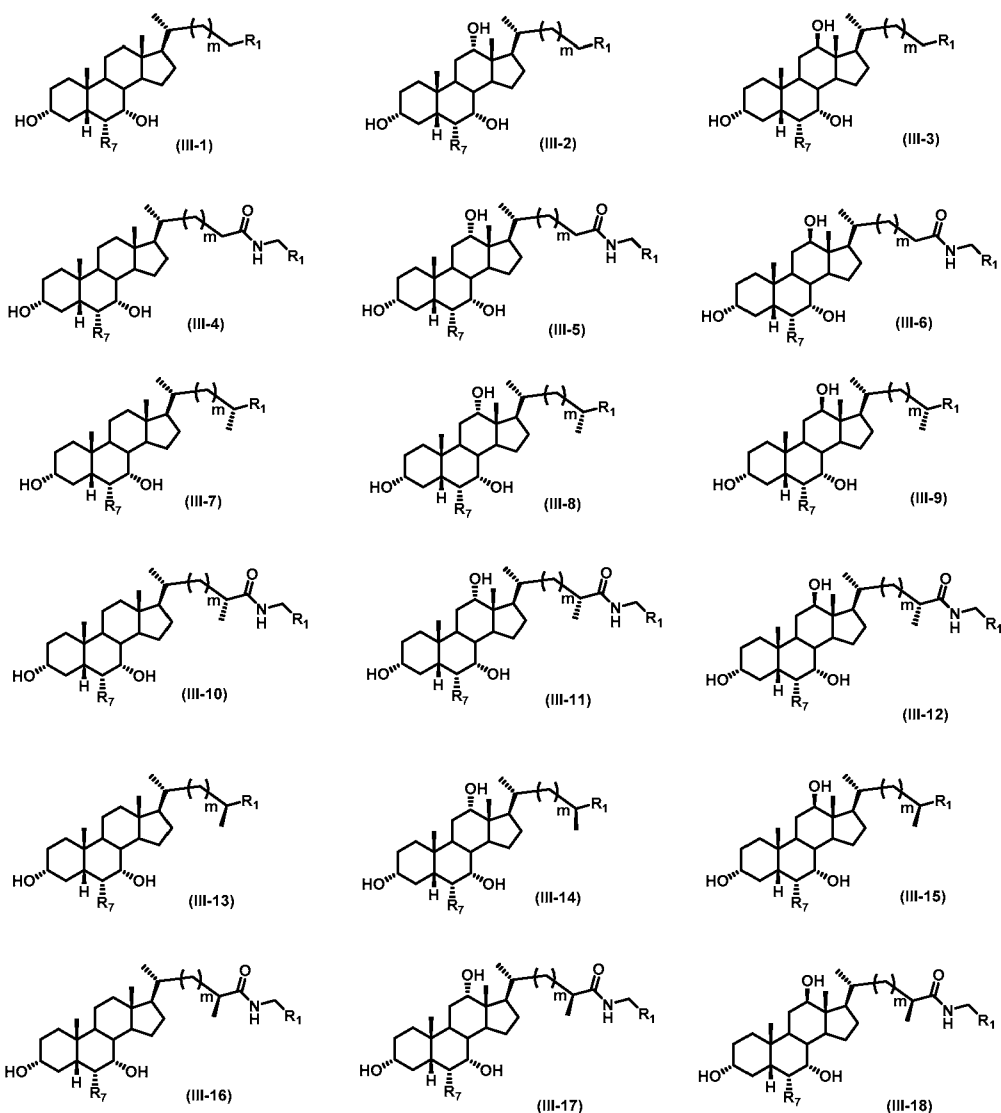
wherein R₁, R₂, R₃, R₄, R₇, R₈, R₉ and m are as previously defined.

A third embodiment of the invention is a compound represented by Formula (III-A) or (III-B) or a pharmaceutically acceptable salt, hydrate, solvate, ester or prodrug thereof.

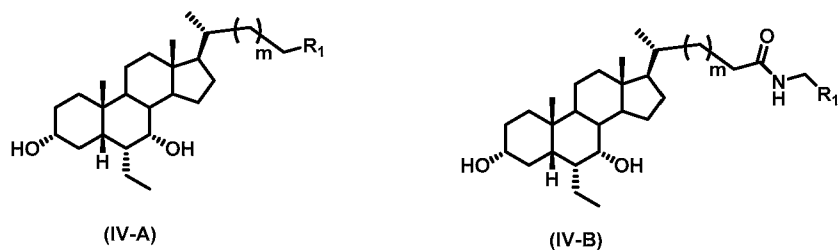


wherein, R₁, R₂, R₃, R₇ and m are as previously defined.

15 Illustrative structures of Formula (III-A) and Formula (III-B) can be represented, but are not limited, by Formula (III-1~III-18), where R₁, R₇ and m are as previously defined:



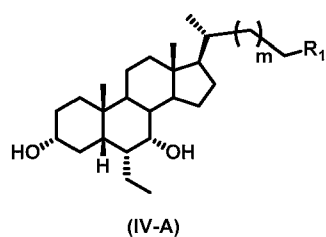
A fourth embodiment of the invention is a compound represented by Formula (IV-A) or (IV-B) or a pharmaceutically acceptable salt, solvate, hydrate, ester or prodrug thereof:



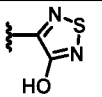
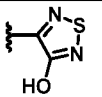
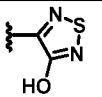
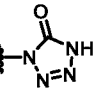
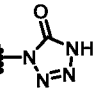
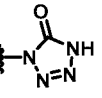
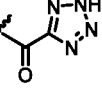
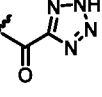
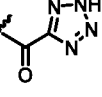
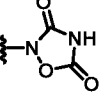
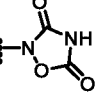
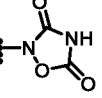
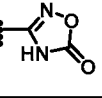
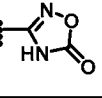
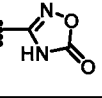
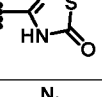
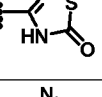
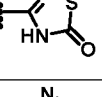
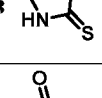
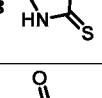
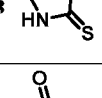
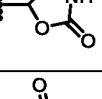
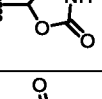
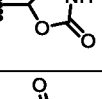
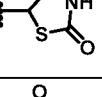
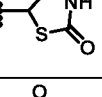
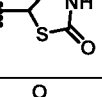
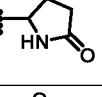
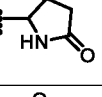
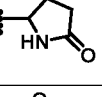
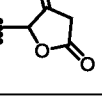
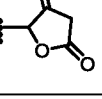
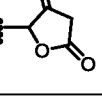
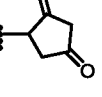
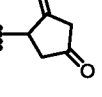
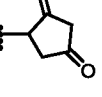
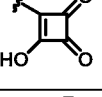
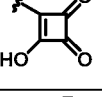
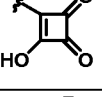
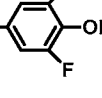
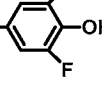
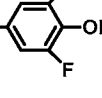
5

wherein R_1 and m are as previously defined.

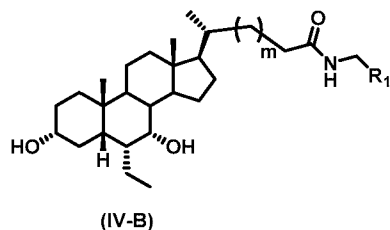
Representative compounds of the invention include, but are not limited to, the following compounds according to Formula (IV-A), wherein, R_1 and m are delineated for each compound in Table 1.

**Table 1**

Compound	m	R ₁	Compound	m	R ₁	Compound	m	R ₁
1	0		31	1		61	2	
2	0		32	1		62	2	
3	0		33	1		63	2	
4	0		34	1		64	2	
5	0		35	1		65	2	
6	0		36	1		66	2	
7	0		37	1		67	2	
8	0		38	1		68	2	
9	0		39	1		69	2	
11	0		41	1		71	2	
12	0		42	1		72	2	

13	0		43	1		73	2	
14	0		44	1		74	2	
16	0		46	1		76	2	
17	0		47	1		77	2	
18	0		48	1		78	2	
19	0		49	1		79	2	
20	0		50	1		80	2	
21	0		51	1		81	2	
22	0		52	1		82	2	
23	0		53	1		83	2	
24	0		54	1		84	2	
25	0		55	1		85	2	
26	0		56	1		86	2	
27	0		57	1		87	2	

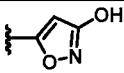
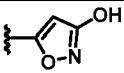
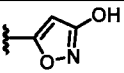
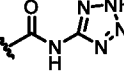
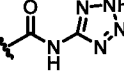
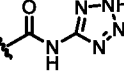
Representative compounds of the invention include, but are not limited to, the following compounds according to Formula (IV-B), wherein R₁ and m are delineated for each example in Table 2.



5

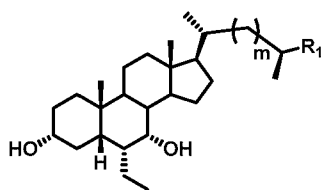
Table 2

Compound	m	R ₁	Compound	m	R ₁	Compound	m	R ₁
91	0		121	1		151	2	
92	0		122	1		152	2	
93	0		123	1		153	2	
94	0		124	1		154	2	
95	0		125	1		155	2	
96	0		126	1		156	2	
97	0		127	1		157	2	
98	0		128	1		158	2	
99	0		129	1		159	2	
100	0		130	1		160	2	

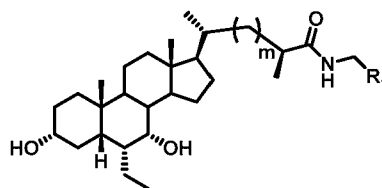
101	0		131	1		161	2	
102	0		132	1		162	2	
103	0		133	1		163	2	
104	0		134	1		164	2	
105	0		135	1		165	2	
106	0		136	1		166	2	
107	0		137	1		167	2	
108	0		138	1		168	2	
109	0		139	1		169	2	
110	0		140	1		170	2	
111	0		141	1		171	2	
112	0		142	1		172	2	
113	0		143	1		173	2	
114	0		144	1		174	2	
115	0		145	1		175	2	

116	0		146	1		176	2	
117	0		147	1		177	2	
118	0		148	1		178	2	
119	0		149	1		179	2	
120	0		150	1		180	2	

A fifth embodiment of the invention is a compound represented by Formula (V-A) or (V-B) or a pharmaceutically acceptable salt, solvate, hydrate, ester or prodrug thereof.



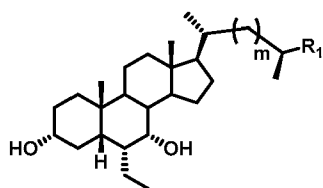
(V-A)



(V-B)

5 wherein R_1 and m are as previously defined.

Representative compounds of the invention include, but are not limited to, the following compounds according to Formula (V-A), wherein, R_1 and m are delineated for each compound in Table 3.

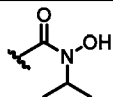
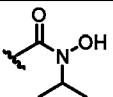
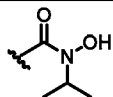
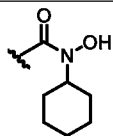
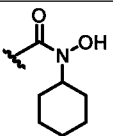
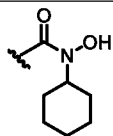
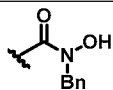
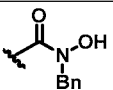
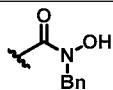
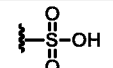
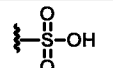
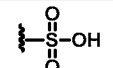
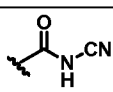
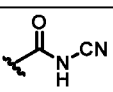
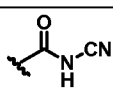
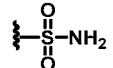
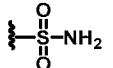
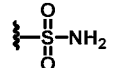
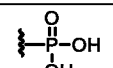
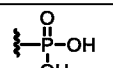
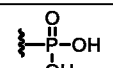
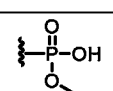
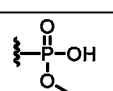
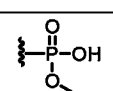
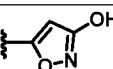
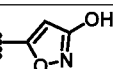
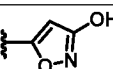
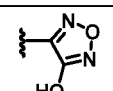
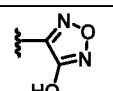
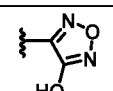
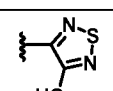
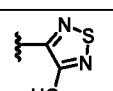
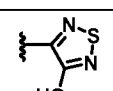
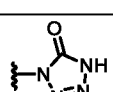
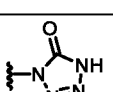
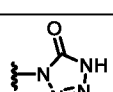
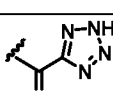
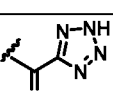
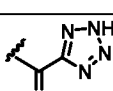
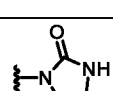
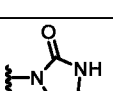
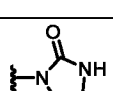
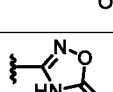
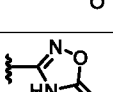
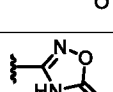


(V-A)

10

Table 3

Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
181	0		211	1		241	2	

182	0		212	1		242	2	
183	0		213	1		243	2	
184	0		214	1		244	2	
185	0		215	1		245	2	
186	0		216	1		246	2	
187	0		217	1		247	2	
188	0		218	1		248	2	
189	0		219	1		249	2	
191	0		221	1		251	2	
192	0		222	1		252	2	
193	0		223	1		253	2	
194	0		224	1		254	2	
196	0		226	1		256	2	
197	0		227	1		257	2	
198	0		228	1		258	2	

199	0		229	1		259	2	
200	0		230	1		260	2	
211	0		231	1		261	2	
212	0		232	1		262	2	
213	0		233	1		263	2	
214	0		234	1		264	2	
215	0		235	1		265	2	
216	0		236	1		266	2	
217	0		237	1		267	2	

Representative compounds of the invention include, but are not limited to, the following compounds according to Formula (V-B), wherein, R₁ and m are delineated for

5 each compound in Table 4.

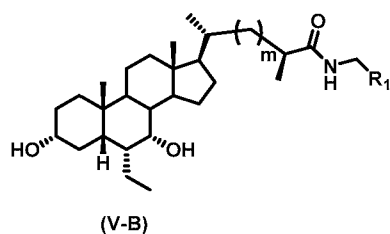
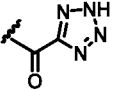
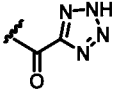
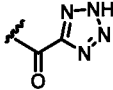
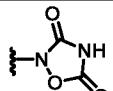
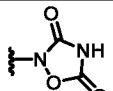
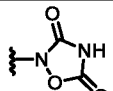
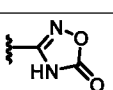
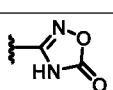
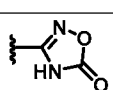
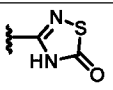
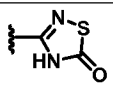
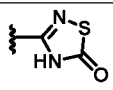
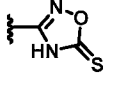
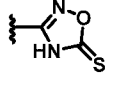
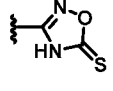
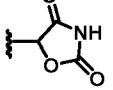
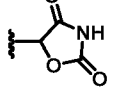
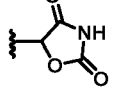
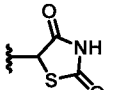
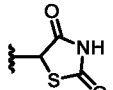
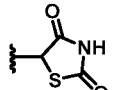
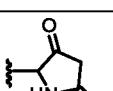
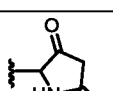
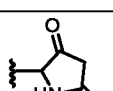
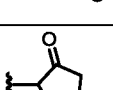
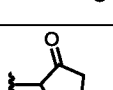
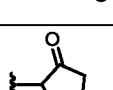
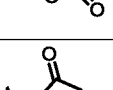
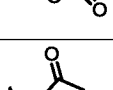
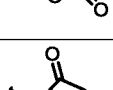
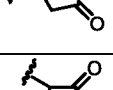
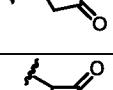
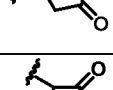
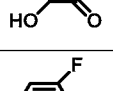
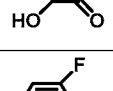
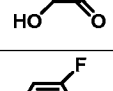
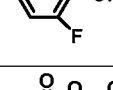
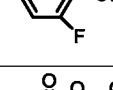
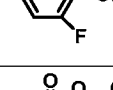
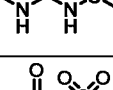
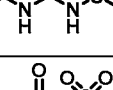
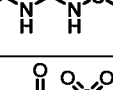
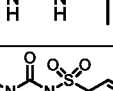
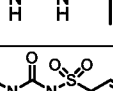
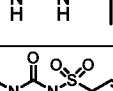


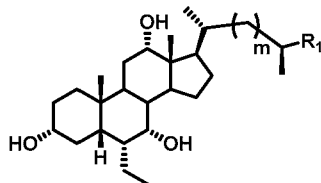
Table 4

Compound	m	R ₁	Compound	m	R ₁	Compound	m	R ₁
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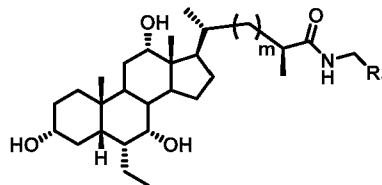
						d		
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273	0		303	1		333	2	
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275	0		305	1		335	2	
276	0		306	1		336	2	
277	0		307	1		337	2	
278	0		308	1		338	2	
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281	0		311	1		341	2	
282	0		312	1		342	2	
283	0		313	1		343	2	
284	0		314	1		344	2	
285	0		315	1		345	2	

286	0		316	1		346	2	
287	0		317	1		347	2	
288	0		318	1		348	2	
289	0		319	1		349	2	
290	0		320	1		350	2	
291	0		321	1		351	2	
292	0		322	1		352	2	
293	0		323	1		353	2	
294	0		324	1		354	2	
295	0		325	1		355	2	
296	0		326	1		356	2	
297	0		327	1		357	2	
298	0		328	1		358	2	
299	0		329	1		359	2	
300	0		330	1		360	2	

A sixth embodiment of the invention is a compound represented by Formula (VI-A) or (VI-B) or a pharmaceutically acceptable salt, solvate, hydrate, ester or prodrug thereof:



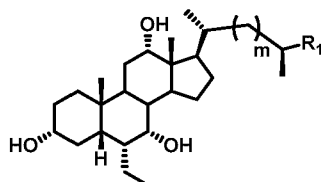
(VI-A)



(VI-B)

5 wherein, R_1 and m are as previously defined.

Representative compounds of the invention include, but are not limited to, the following compounds according to Formula (VI-A), wherein R_1 and m are delineated for each compound in Table 5.

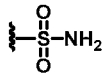
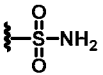
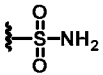
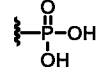
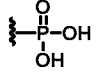
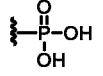
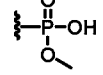
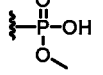
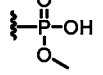
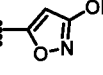
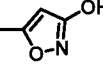
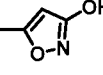
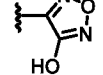
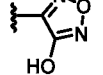
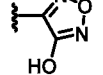
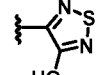
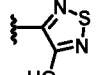
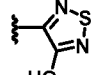
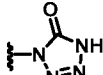
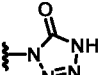
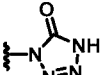
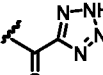
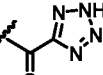
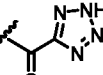
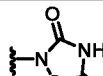
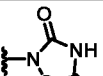
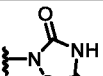
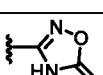
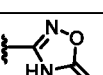
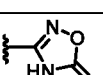
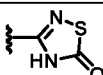
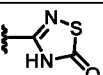
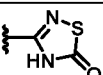
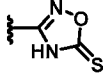
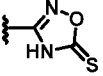
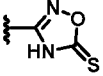
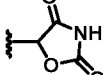
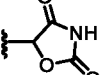
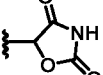
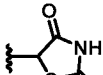
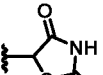
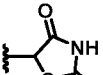
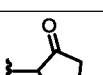
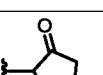
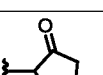


(VI-A)

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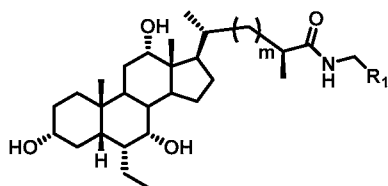
Table 5

Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
361	0		391	1		421	2	
362	0		392	1		422	2	
363	0		393	1		423	2	
364	0		394	1		424	2	
365	0		395	1		425	2	
366	0		396	1		426	2	

367	0		397	1		427	2	
368	0		398	1		428	2	
369	0		399	1		429	2	
371	0		401	1		431	2	
372	0		402	1		432	2	
373	0		403	1		433	2	
374	0		404	1		434	2	
376	0		406	1		436	2	
377	0		407	1		437	2	
378	0		408	1		438	2	
379	0		409	1		439	2	
380	0		410	1		440	2	
381	0		411	1		441	2	
382	0		412	1		442	2	
383	0		413	1		443	2	

384	0		414	1		444	2	
385	0		415	1		445	2	
386	0		416	1		446	2	
387	0		417	1		447	2	

Representative compounds of the invention include, but are not limited to, the following compounds according to Formula (VI-B), wherein R_1 and m are delineated for each compound in Table 6.

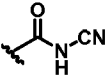
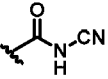
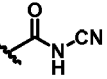
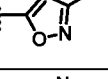
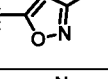
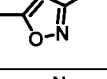
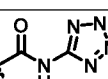
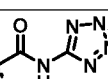
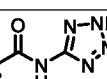
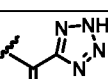
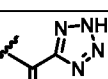
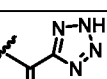


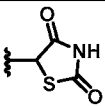
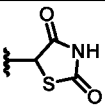
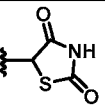
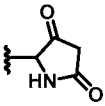
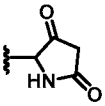
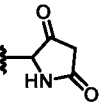
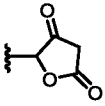
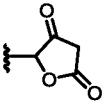
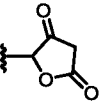
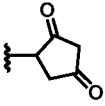
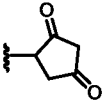
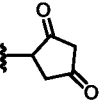
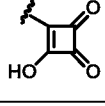
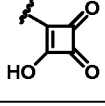
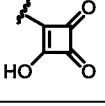
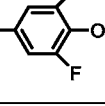
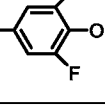
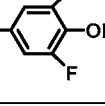
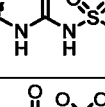
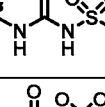
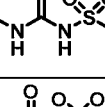
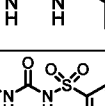
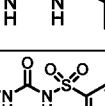
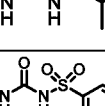
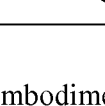
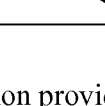
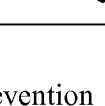
(VI-B)

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Table 6

Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
451	0		481	1		511	2	
452	0		482	1		512	2	
453	0		483	1		513	2	
454	0		484	1		514	2	
455	0		485	1		515	2	

456	0		486	1		516	2	
457	0		487	1		517	2	
458	0		488	1		518	2	
459	0		489	1		519	2	
460	0		490	1		520	2	
461	0		491	1		521	2	
462	0		492	1		522	2	
463	0		493	1		523	2	
464	0		494	1		524	2	
465	0		495	1		525	2	
466	0		496	1		526	2	
467	0		497	1		527	2	
468	0		498	1		528	2	
469	0		499	1		529	2	
470	0		500	1		530	2	
471	0		501	1		531	2	

472	0		502	1		532	2	
473	0		503	1		533	2	
474	0		504	1		534	2	
475	0		505	1		535	2	
476	0		506	1		536	2	
477	0		507	1		537	2	
478	0		508	1		538	2	
479	0		509	1		539	2	
480	0		510	1		540	2	

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 the invention. The present invention

5 also provides the use of a compound of the invention 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, hypercholesteremia, or hyperlipidemia chronic liver disease, gastrointestinal disease, renal disease, metabolic disease, cancer (i.e.,

10 colorectal cancer), or neurological indications such as stroke.

In certain embodiments, the chronic liver disease is primary biliary cirrhosis (PBC), cerebrotendinous xanthomatosis (CTX), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis

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

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

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

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

In yet another embodiment, the invention provides the use of the compound or pharmaceutical composition of the invention, in the manufacture of a medicament for a treating or preventing a disease in a subject that involves modulation of the TGR5 receptor. The invention includes a method of treating or preventing a disease that involves modulation of the TGR5 receptor in a subject by administering a compound or pharmaceutical composition of the invention.

In certain embodiments, a disease that involves modulation of the TGR5 receptor is selected from metabolic disease, inflammatory disease, liver disease, autoimmune disease, cardiac disease, kidney disease, cancer, and gastrointestinal disease.

In one aspect, the disease is an inflammatory disease selected from allergy, osteoarthritis, appendicitis, bronchial asthma, pancreatitis, allergic rash, and psoriasis. The invention includes a method of treating or preventing an inflammatory disease selected from allergy, osteoarthritis, appendicitis, bronchial asthma, pancreatitis, allergic rash, and psoriasis.

In one aspect, the disease is an autoimmune disease selected from rheumatoid arthritis, multiple sclerosis, and type I diabetes. The invention includes a method of treating

or preventing an autoimmune disease selected from rheumatoid arthritis, multiple sclerosis, and type I diabetes.

In one aspect, the disease is a gastrointestinal disease selected from inflammatory bowel disease (Crohn's disease, ulcerative colitis), short bowel syndrome (post-radiation colitis), microscopic colitis, irritable bowel syndrome (malabsorption), and bacterial overgrowth. The invention includes a method of treating or preventing a gastrointestinal disease selected from inflammatory bowel disease (Crohn's disease, ulcerative colitis), short bowel syndrome (post-radiation colitis), microscopic colitis, irritable bowel syndrome (malabsorption), and bacterial overgrowth.

In one aspect, the disease is kidney disease selected from diabetic nephropathy, chronic renal failure, hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, and polycystic kidney disease. The invention includes a method of treating or preventing kidney disease selected from diabetic nephropathy, chronic renal failure, hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, and polycystic kidney disease.

In one aspect, the disease is cancer selected from colorectal cancer, liver cancer, hepatocellular carcinoma, cholangio carcinoma, renal cancer, gastric cancer, pancreatic cancer, prostate cancer, and insulinoma. The invention includes a method of treating or preventing cancer selected from colorectal cancer, liver cancer, hepatocellular carcinoma, cholangio carcinoma, renal cancer, gastric cancer, pancreatic cancer, prostate cancer, and insulinoma.

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

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

In one aspect, the compound is a dual agonist for both FXR and TGR5.

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

DEFINITIONS

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

The term "alkyl", as used herein, refers to a saturated, monovalent straight- or branched-chain hydrocarbon group. Preferred alkyl radicals include C₁-C₆ alkyl and C₁-C₈ alkyl radicals. 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 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.

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-butynyl, heptynyl, octynyl and the like.

The term "carbocycle" refers to a saturated (e.g., "cycloalkyl"), partially saturated (e.g., "cycloalkenyl" or "cycloalkynyl") or completely unsaturated (e.g., "aryl") ring system containing zero heteroatom ring atom. "Ring atoms" or "ring members" are the atoms bound together to form the ring or rings. Where a carbocycle group is a divalent moiety linking two other elements in a depicted chemical structure (such as Z in Formula I_A), the carbocycle group can be attached to the two other elements through any two substitutable ring atoms. A C₄-C₆ carbocycle has 4-6 ring atoms.

The term "cycloalkyl", 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. 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, cyclopentyl and cyclooctyl; and examples

of C₃-C₁₂-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl.

The term "cycloalkenyl" as used herein, denote a monovalent group derived from a monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double bond by the removal of a single hydrogen atom. 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, and the like.

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

The term "arylalkyl," as used herein, refers to a 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, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl, 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, -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, -diaryl amino, -diheteroaryl amino, -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,
 5 -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, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl,
 10 -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, -NHC(O)NH-C₂-C₁₂-alkynyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-
 15 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, -NHC(NH)NH-C₂-C₁₂-alkenyl, -
 NHC(NH)NH-C₂-C₁₂-alkynyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -
 20 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-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)-
 25 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, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-
 C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkynyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-
 30 heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -
 heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl,
 polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-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 substituent in a substituted moiety is additionally optionally substituted with one or more groups, each group being independently selected
5 from -F, -Cl, -Br, -I, -OH, -NO₂, -CN, or -NH₂.

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

It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl moiety
10 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
15 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
20 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
25 groups may be further substituted.

The term "heterocycloalkyl" and "heterocyclic" can be used interchangeably and refer to a non-aromatic 3-, 4-, 5-, 6- or 7-membered ring or a bi- or tri-cyclic group fused 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
30 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, and tetrahydrofuryl. Such heterocyclic groups may be further substituted to give substituted heterocyclic.

5 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, cycloalkenylenes, cycloalkynylene, arylalkylene, heteroarylalkylene and heterocycloalkylene groups are to be included in the
10 above definitions, and are applicable to provide the formulas herein with proper valency.

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

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

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

 The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxy group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group
25 as described herein may be selectively removed. Hydroxy protecting groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxy protecting groups include benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, methoxycarbonyl, tert-butoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-furfuryloxycarbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, *t*-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl, para-

methoxybenzyl, diphenylmethyl, triphenylmethyl (trityl), tetrahydrofuryl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2,2,2-trichloroethoxymethyl 2-(trimethylsilyl)ethoxymethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, and the like. Preferred hydroxy protecting groups for the present invention are acetyl (Ac or $-\text{C}(\text{O})\text{CH}_3$), benzoyl (Bz or $-\text{C}(\text{O})\text{C}_6\text{H}_5$), and trimethylsilyl (TMS or $-\text{Si}(\text{CH}_3)_3$).

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

Pharmaceutically acceptable salts can also be prepared by deprotonation of the parent compound with a suitable base, thereby forming the anionic conjugate base of the parent compound. In such salts the counter ion is a cation. Suitable cations include ammonium and metal cations, such as alkali metal cations, including Li^+ , Na^+ , K^+ and Cs^+ , and alkaline earth metal cations, such as Mg^{2+} and Ca^{2+} .

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques, which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, *et al.*, Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

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

As used herein, the term "pharmaceutically acceptable salt" refers to those salts of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are
5 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 reacting the
10 free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts e.g., salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the
15 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-
20 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,
25 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
30 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.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed.), *Methods in Enzymology*, Vol. 4, Academic Press (1985); Krogsgaard-Larsen, *et al.*, (ed.), "Design and Application of Prodrugs, *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991); Bundgaard, *et al.*, *Journal of Drug Deliver Reviews*, 8:1-38(1992); Bundgaard, J. of *Pharmaceutical Sciences*, 77:285 et seq. (1988); Higuchi and Stella (eds.) *Prodrugs as Novel Drug Delivery Systems*, *American Chemical Society* (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

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

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

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

"Solvates" means solvent addition forms that contain either stoichiometric or non
10 stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H₂O, such
15 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
20 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
25 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
30 of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example, *Organic Solvents Physical Properties and Methods of Purification*, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the *Techniques of Chemistry Series*, John Wiley & Sons, NY, 1986.

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

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

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

The compounds of this invention may be modified by appending various functionalities via synthetic means delineated herein to enhance selective biological properties. Such modifications include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase

oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

PHARMACEUTICAL COMPOSITIONS

5 The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid
10 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
15 waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as 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
20 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.

25 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
30 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
5 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
10 such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

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

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

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn,
30 may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug

release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

5 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.

10 Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose,
15 alginate, 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, cetyl alcohol and glycerol monostearate, h) absorbents
20 such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

 Solid compositions of a similar type may also be employed as fillers in soft and
25 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, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release
30 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 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
5 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
10 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,
15 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.

20 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.

25 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.

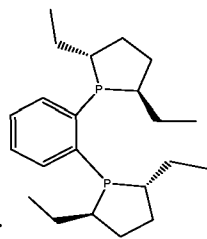
30 Abbreviations

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

ACN for acetonitrile;

BME for 2-mercaptoethanol;

- BOP for benzotriazol-1-yloxy-tris(dimethylamino)phosphonium
hexafluorophosphate;
- BzCl for benzoyl chloride;
- CDI for carbonyldiimidazole;
- 5 COD for cyclooctadiene;
- DABCO for 1,4-diazabicyclo[2.2.2]octane;
- DAST for diethylaminosulfur trifluoride;
- DABCYL for 6-(N-4'-carboxy-4-(dimethylamino)azobenzene)- aminoethyl-
1-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite;
- 10 DBU for 1, 8-Diazabicycloundec-7-ene;
- DCC for N, N'-dicyclohexylcarbodiimide;
- DCM for dichloromethane;
- DIAD for diisopropyl azodicarboxylate;
- DIBAL-H for diisobutylaluminum hydride;
- 15 DIPEA for diisopropyl ethylamine;
- DMAP for N,N-dimethylaminopyridine;
- DME for ethylene glycol dimethyl ether;
- DMEM for Dulbecco's Modified Eagles Media;
- DMF for N,N-dimethyl formamide;
- 20 DMSO for dimethylsulfoxide;
- DSC for N, N'-disuccinimidyl carbonate;



DUPHOS for

;

- EDANS for 5-(2-Amino-ethylamino)-naphthalene-1-sulfonic acid;
- EDCI or EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
- 25 EtOAc for ethyl acetate;
- EtOH for ethyl alcohol;
- HATU for O (7-Azabenzotriazole-1-yl)-N,N,N',N' – tetramethyluronium
hexafluorophosphate;
- HCl for hydrochloric acid;

Hoveyda's Cat. for Dichloro(*o*-isopropoxyphenylmethylene)
(tricyclohexylphosphine)ruthenium(II);

In for indium;

KHMDS is potassium bis(trimethylsilyl) amide;

5 Ms for mesyl;

NMM for N-4-methylmorpholine;

NMI for N-methylimidazole;

NMO for N-4-methylmorpholine-N-Oxide;

PyBrOP for Bromo-tri-pyrolidino-phosphonium hexafluorophosphate;

10 Ph for phenyl;

RCM for ring-closing metathesis;

RT for reverse transcription;

RT-PCR for reverse transcription-polymerase chain reaction;

TBME for tert-butyl methyl ether;

15 TEA for triethyl amine;

Tf₂O for trifluoromethanesulfonic anhydride;

TFA for trifluoroacetic acid;

THF for tetrahydrofuran;

TLC for thin layer chromatography;

20 (TMS)₂NH for hexamethyldisilazane;

TMSOTf for trimethylsilyl trifluoromethanesulfonate;

TBS for t-Butyldimethylsilyl;

TMS for trimethylsilyl;

TPAP tetrapropylammonium perruthenate;

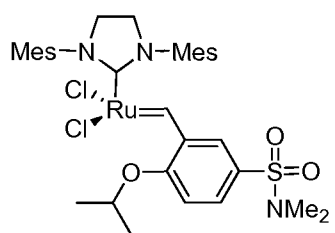
25 TPP or PPh₃ for triphenylphosphine;

TrCl for trityl chloride;

DMTrCl for 4,4'-dimethoxytrityl chloride;

tBOC or Boc for tert-butyloxy carbonyl;

Xantphos for 4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene; and



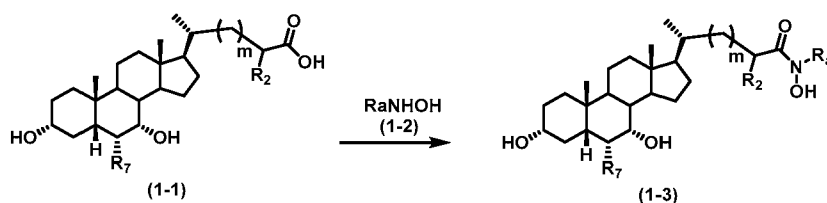
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Synthetic Methods

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

As shown in Scheme 1, novel bile acid analogs of the compound of formula (1-3) are prepared from the compound of formula (1-1), wherein R_2 , m , R_a , and R_7 are defined as previously. Thus, the compound of formula (1-1) is coupled with hydroxylamine compound of formula (1-2) using suitable coupling condition to give the compound of formula (1-3). 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, CH_2Cl_2 , DMF or THF. The reaction temperature can vary from $0^\circ C$ to about $50^\circ C$.

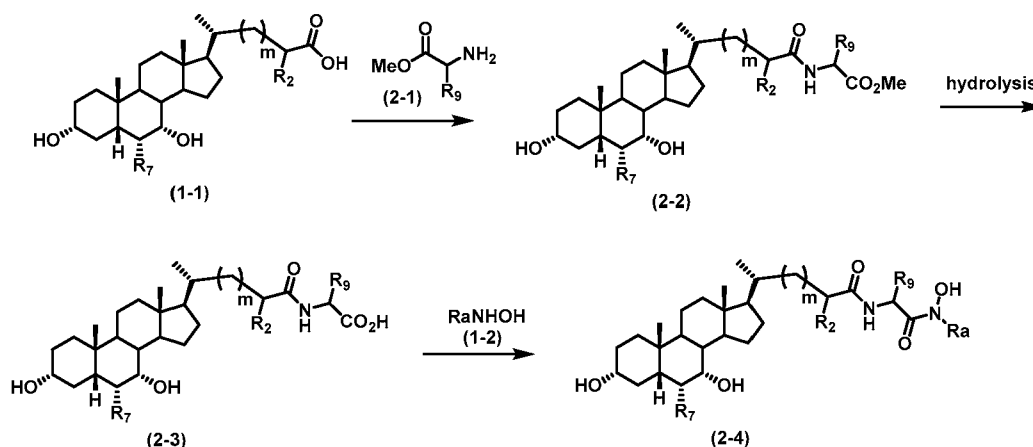
Scheme 1



Scheme 2 illustrates the preparation of the compound of formula (2-4) from the compound of formula (1-1), wherein R_2 , m , R_9 , R_a , and R_7 are defined as previously. Thus, the compound of formula (1-1) is coupled with an amino ester compound of formula (2-1) in suitable coupling condition to give the compound of formula (2-2). 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, CH_2Cl_2 , DMF or

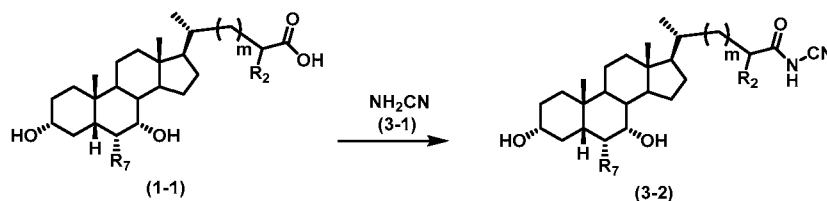
THF. The reaction temperature can vary from 0°C to about 50°C. Then, hydrolysis of methyl ester of compound of formula (2-2) gives the compound of formula (2-3). The reagent for hydrolysis can be, but not limited to LiOH, NaOH and KOH. The solvent can be, but not limited to THF, MeOH, EtOH, dioxane, water or mixture of above. The reaction temperature can vary from 0°C to about 80°C. Further coupling of the compound of formula (2-3) with the compound of formula (1-2) affords the compound of formula (2-4).

Scheme 2



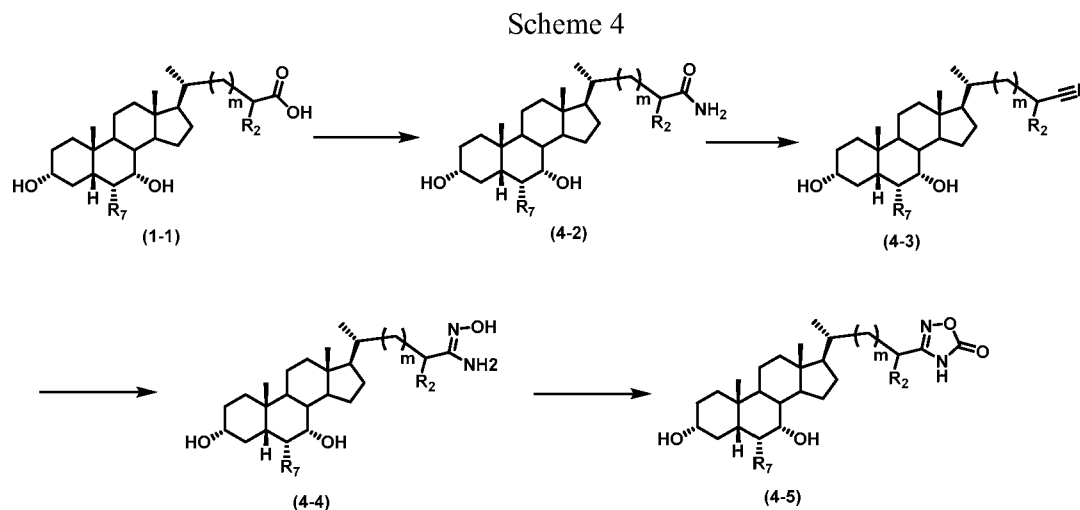
Scheme 3 illustrates the preparation of the compound of formula (3-2) from the compound of formula (1-1), wherein R_2 , m and R_7 are defined as previously. Thus, the compound of formula (1-1) is coupled with aminonitrile compound of formula (3-1) in suitable coupling condition to give the compound of formula (3-2). The coupling reagent can be selected from, but not limited to, DCC, EDC, CDI, di-isopropyl 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, CH_2Cl_2 , DMF or THF. The reaction temperature can vary from 0°C to about 50°C.

Scheme 3



As illustrated in scheme 4, novel bile acid analogs of the compound of formula (4-5) are prepared from the compound of formula (1-1), wherein R_2 , m and R_7 are defined as previously. The compound of formula (1-1) is coupled with ammonia using suitable coupling condition to give the compound of formula (4-2). The ammonia source can be selected from, but not limited to ammonium carbonate, ammonium hydroxide and ammonium bicarbonate. The coupling reagent can be selected from, but not limited to, DCC, EDC, CDI, di-isopropyl 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, CH_2Cl_2 , DMF or THF. The reaction temperature can vary from 0°C to about 50°C . The compound of formula (4-2) is treated with dehydration condition to give the compound of formula (4-3). The reagent can be selected from, but not limited to SOCl_2 , P_2O_5 , cyanuric trichloride and Burgess reagent. The dehydration reaction is carried out in aprotic solvent such as, but not limited to, CH_2Cl_2 , DMF or THF. The reaction temperature can vary from 0°C to about 100°C .

The compound of formula of (4-3) is treated with hydroxyl amine to give the compound of formula (4-4). Reagent also can be hydroxylamine salt with organic or inorganic base.

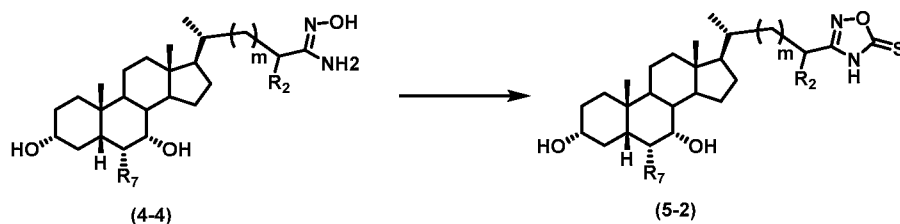


Suitable bases include, but not limited to LiOH, NaOH, KOH, triethylamine, diisopropylethylamine, DBU, N-methylmorpholine and DMAP. The dehydration reaction is carried out in solvent such as, but not limited to, MeOH, EtOH, iPr-OH, H₂O, CH₂Cl₂, DMF, DMSO or THF. The reaction temperature can vary from 0°C to about 100°C.

The compound of formula of (4-4) is treated with phosgene or phosgene alternative and base to give the compound of formula (4-5). Reagent can be selected from, but not limited to phosgene, diphosgene, triphosgene, carbonyl diimidazole and disuccinimidyl carbonate. Suitable bases include, but not limited to triethylamine, diisopropylethylamine, DBU, N-methylmorpholine and DMAP. The reaction is carried out in aprotic solvent such as, but not limited to, CH₂Cl₂, DMF, DMSO or THF. The reaction temperature can vary from 0°C to about 100°C.

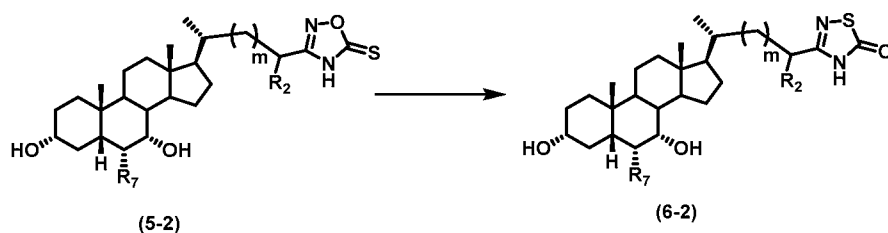
As illustrated in scheme 5, novel bile acid analogs of the compound of formula (5-2) are prepared from the compound of formula (4-4), wherein R₂, m and R₇ are defined as previously. The compound of formula (4-4) is treated with thiophosgene or thiophosgene alternative and base to give the compound of formula (5-2). Reagent can be selected from, but not limited to thiophosgene and di(1H-imidazol-1-yl)methanethione. Suitable bases include, but not limited to triethylamine, diisopropylethylamine, DBU, N-methylmorpholine and DMAP. The reaction is carried out in aprotic solvent such as, but not limited to, CH₂Cl₂, DMF, DMSO or THF. The reaction temperature can vary from 0°C to about 100°C.

Scheme 5



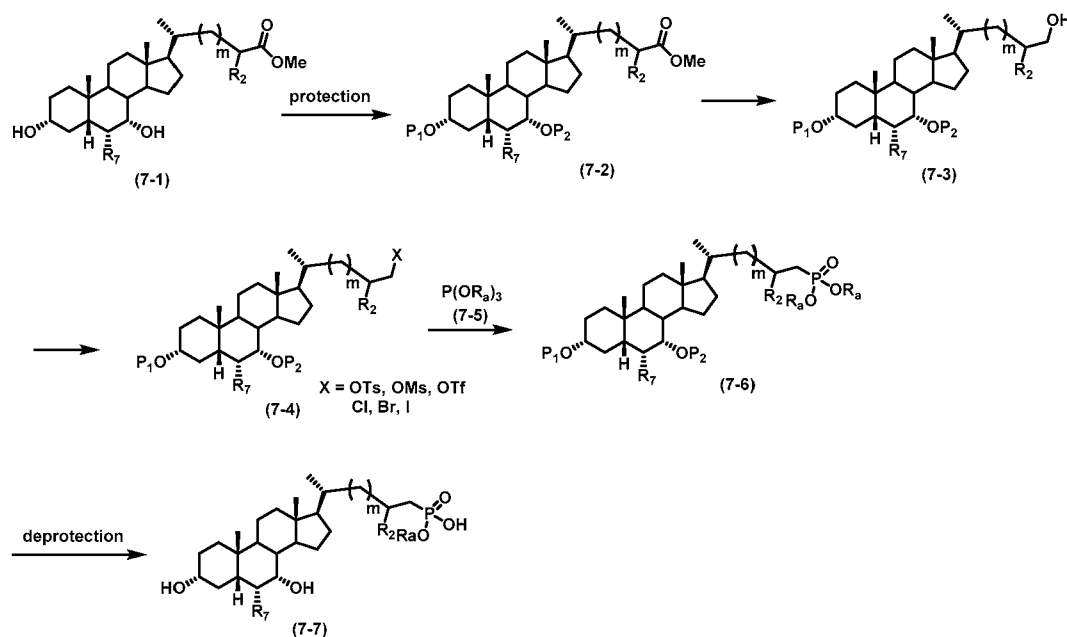
As illustrated in scheme 6, novel bile acid analogs of the compound of formula (6-2) are prepared from the compound of formula (5-2), wherein R_2 , m and R_7 are defined as previously. The compound of formula (5-2) is rearranged under acidic condition to give the compound of formula (6-2). The acid can be selected from, but not limited to $\text{BF}_3 \cdot \text{OEt}_2$, TMSOTf, $\text{Yb}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, H_2SO_4 , HCl, HBr and HClO_4 . The rearrangement reaction is carried out in solvent such as, but not limited to, CH_2Cl_2 , DMF, DMSO, or THF. The reaction temperature can vary from 0°C to about 100°C .

Scheme 6



As shown in Scheme 7, novel bile acid analogs of the compound of formula (7-7) are prepared from the compound of formula (7-1), wherein R_7 , R_2 , R_a and m are defined as previously, P_1 and P_2 are hydroxyl protecting groups. Thus, the two hydroxyl groups of the compound of formula (7-1) are protected with P_1 and P_2 groups. P_1 and P_2 can be same or different. P_1 and P_2 can be any hydroxyl protecting group such as, but not limited to Ac, Bz, chloroacetyl, TES, TBS, MOM and Bn. A more detailed discussion of the procedures, reagents and conditions for protection of hydroxyl group is described in literature, for example, by T.W. Greene and P.G.M. Wuts in "Protective Groups in Organic Synthesis" 3rd ed., John Wiley & Son, Inc., 1999.

Scheme 7

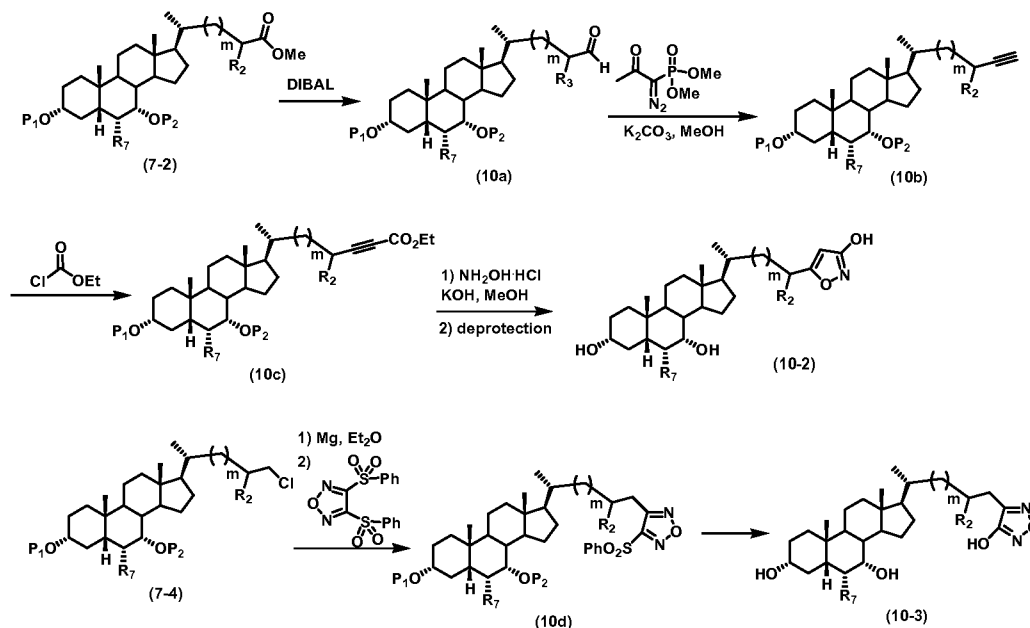


Then the hydroxyl protected compound of formula (7-2) is reduced to the primary alcohol compound of formula (7-3) using suitable reducing reagents which can be selected from, but not limited to, DIBAL-H, NaBH₄, LiBH₄, and LiAlH₄. The alcohol compound of formula (7-3) is transformed to compound of formula (7-4) where X is a leaving group such as OMs, OTs, OTf or halogen (Cl, Br, I), using suitable bases including but not limited to triethylamine, diisopropylethylamine, DBU, N-methylmorpholine and DMAP with acylation reagents such as MsCl, Ms₂O, TsCl and Tf₂O, or using suitable halogenation conditions which can be selected from, but not limited to Ph₃P/CBr₄, Ph₃P/I₂, and Ph₃P/Br₂. Treatment of compound (7-4) with trialkylphosphite of formula (7-5) at elevated temperatures provides the phosphate compound of formula (7-6). The R_a group in phosphate compound of formula (7-6) can be removed under acidic conditions (TMSBr/DCM) or partially removed under basic conditions (NaOH/MeOH). Deprotection of hydroxyl protecting groups of P₁ and P₂ of compound of formula (7-6) to give the compound of formula (7-7). More efficiently, the R_a group and the hydroxyl protecting group P₁/P₂ can be removed at the same time under suitable conditions. A more detailed discussion of the procedures, reagents and conditions for deprotection of hydroxyl protecting group is described in literature, for example, by T.W. Greene and P.G.M. Wuts in "Protective Groups in Organic Synthesis" 3rd ed., John Wiley & Son, Inc., 1999.

Scheme 8 illustrates the preparation of some other carboxylic acid isosteres of bile acid, such as the compound of formula (10-1), the compound of formula (10-2) and the compound of formula (10-3). R_7 , R_2 and m are defined as previously.

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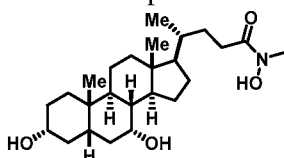
Scheme 8

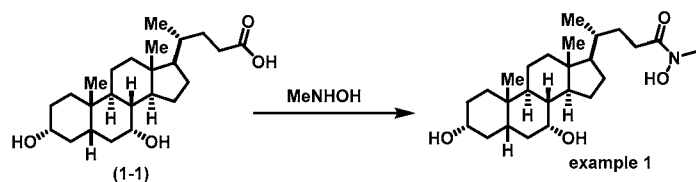


Examples

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

Example 1:





The bile acid analog (**1-1**, 0.3 mmol), HATU (0.3 mmol) and DIPEA (2.4 mmol) were first dissolved in DMF (5 mL). The solution was stirred at room temperature for 10 min., the methyl hydroxylamine was then added. The resulting mixture was stirred at room temperature for 2 h (monitored by TLC and LC/MS), then quenched with brine and 1 N HCl, and extracted with ethyl acetate. The combined organic layers were washed with brine and concentrated. The residue was purified by chromatography on silica gel using hexane/acetone (100/0 to 60/40, 10 min) to give the the compound of example 1 in 79% yield.

The examples 2 to 4 were prepared using same procedure as the one used in example preparation. The MS data is delineated in Table 7.

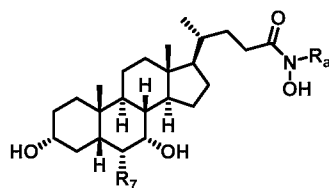
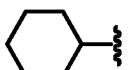
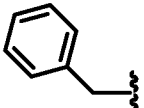
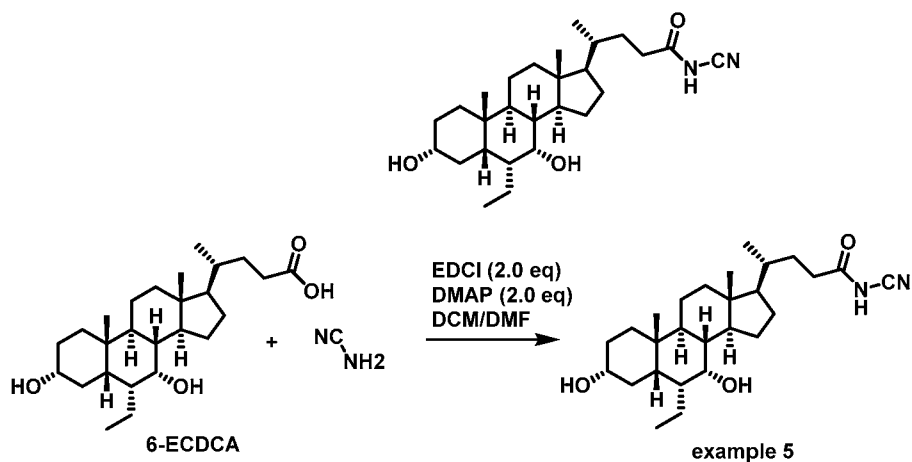


Table 7

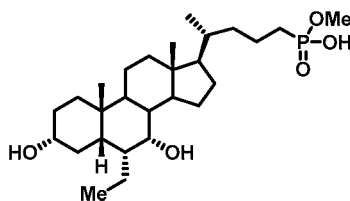
Example	R _a =	R ₇ =	Yield (%)	ESMS (M+1)
1	Me	H	79	422.33
2	<i>i</i> -Pr	H	77	450.46
3		H	60	490.60
4		Et	65	526.59

Example 5:

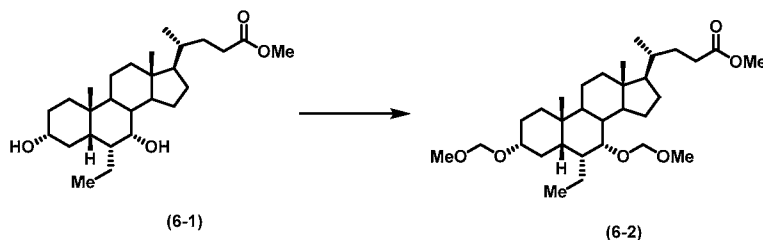


The bile acid analog (6-ECDCA, 0.15 mmol) is dissolved in DCM (2 mL)/DMF (0.5 mL). To the solution is added DMAP (0.3 mmol), EDCI (0.3 mmol) and cyanamide (0.45 mmol) sequentially. The mixture is stirred at room temperature for 2 h (reaction is monitored by TLC and LC/MS). The mixture is quenched with brine and extracted with ethyl acetate (2 ×). The combined organic layers are washed with 1 N HCl and sat. NaCl, dried over Na₂SO₄, and concentrated. The residue is purified by chromatography on silica gel using hexane/acetone (100/0 to 50/50, 10 min) to afford the compound of example 5.

Example 6

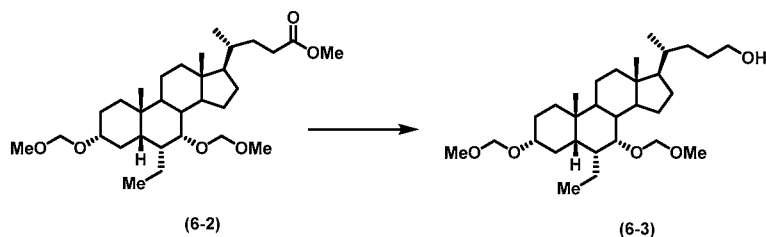


Step 6-1:



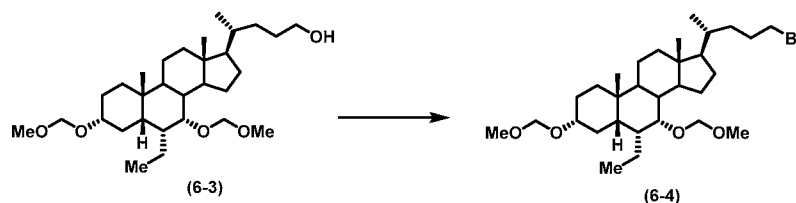
6-ECDCA methyl ester compound of formula (6-1) (J. Med. Chem. 2014, 57, 937-954) (0.23 mmol, 100 mg) is dissolved in DCM (2 mL) and cooled to 0°C. To the solution at 0°C is added DIPEA (0.69 mmol, 89 mg) and chloromethyl methyl ether (0.5 mmol, 40 mg). The resulting solution is stirred at 0°C to room temperature until TLC indicates the reaction is complete. The reaction is quenched by saturated NaHCO₃ and extracted with DCM. The combined organic layers is washed with 1 M HCl, dried over Na₂SO₄, and concentrated *in vacuo*. Purification of the residue by SiO₂ chromatography provides compound of formula (6-2).

Step 6-2:



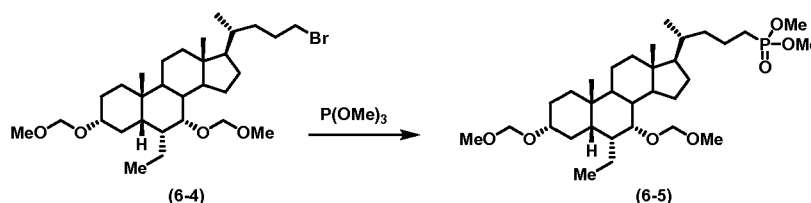
The ester compound of formula (6-2) (100 mg, 0.19 mmol) is dissolved in THF (2 mL). To the solution at 0°C is added dry MeOH (0.29 mmol) and LiBH₄ solution (2 M in THF, 0.15 mL, 0.3 mmol). The mixture is stirred at 0°C for 8 h or until TLC indicates the reaction is complete. The reaction is quenched with 1 M NaOH, warmed to room temperature, and extracted with EtOAc. The combined organic layer is washed with water, dried over Na₂SO₄, and concentrated *in vacuo*. Purification of the residue by SiO₂ chromatography provides compound of formula (6-3).

Step 6-3



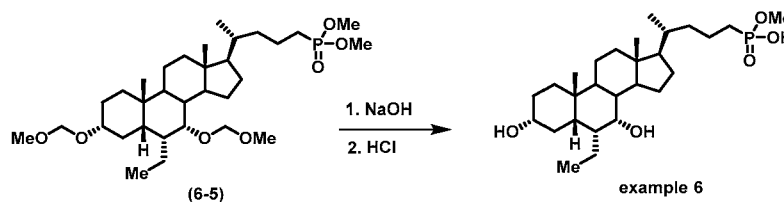
The alcohol compound of formula (6-3) (100 mg, 0.20 mmol) is dissolved in DCM (2 mL). To the solution at 0°C is added triphenylphosphine (0.20 mmol, 52 mg) and tetrabromomethane (0.20 mmol, 66 mg). The resulting mixture is stirred at 0°C for 40 min and then concentrated *in vacuo*. Purification of the residue by SiO₂ chromatography provides compound of formula (6-4).

Step 6-4:



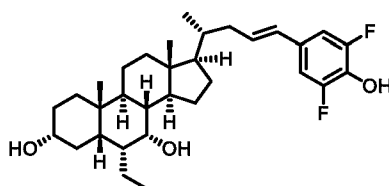
The bromide compound of formula (6-4) (100 mg, 0.18 mmol) is dissolved in trimethylphosphite (0.5 mL). The mixture is heated at 130°C for 4 h and cooled to room temperature. Purification of the residue with C18 chromatography provides compound of formula (6-5).

Step 6-5:

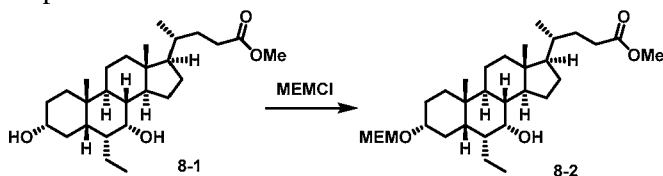


The phosphate compound of formula (6-5) (100 mg, 0.17 mmol) is dissolved in a solution of 1 M NaOH in MeOH (1.7 mL). The mixture is stirred at room temperature for 14 h. MeOH is removed *in vacuo* and the residue is dissolved in HCl/dioxane solution (4 M, 2 mL). The resulting mixture is stirred at room temperature for 2 h or until LC/MS indicates the completion of the reaction. Removal of the solvent and purification of the residue by C18 chromatography provides example 6.

Example 8:

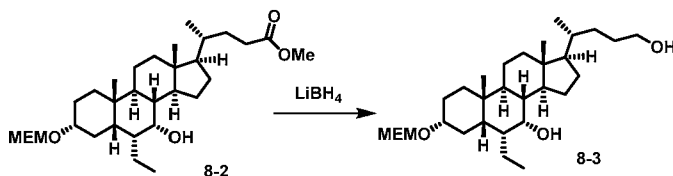


Step 8-1:



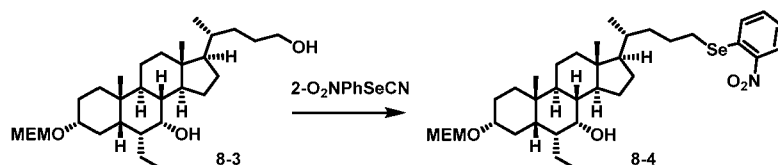
MEMCl (3.7 mL, 30 mmol) was added to a stirred solution of (**8-1**) (4.35 g, 10 mmol) (J. Med. Chem. 2014, 57, 937-954) and DIPEA (10.3 mL, 60 mmol) in DCM (100 mL) at 0 °C under N₂. The resulting reaction mixture was allowed to warm up to RT and stirred overnight, then quenched with water (50 mL) and 1 N HCl (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give 6.5 g of crude product (**8-2**), which was used directly for next step. LC-MS observed 2M+NH₄ = 1062.83 (Calcd. 1062.81).

Step 8-2:



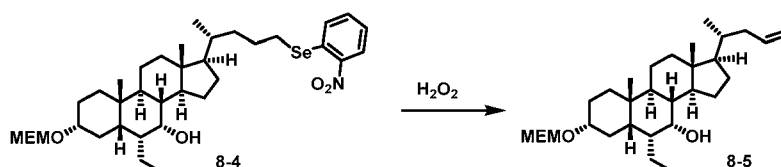
The above mentioned crude product (**8-2**) (4.18 g, 8.0 mmol) was first dissolved in THF (30 mL) at 0 °C under N₂, dry MeOH (1.28 mL, 32 mmol) was added, followed by slow addition of LiBH₄ (697 mg, 32 mmol). The mixture was stirred at 0 °C for 6h, TLC and LC-MS analysis showed partial conversion of the starting material, more LiBH₄ (348 mg, 16 mmol) was then added. The mixture was allowed to warm up to RT and stirred overnight, quenched with 1 M aq. NaOH (20 mL), and extracted with ethyl acetate. The combined organic layers were washed with brine and concentrated. The residue was purified by chromatography on silica gel using hexane/acetone (100/0 to 60/40, 10 min) to afford alcohol product (**8-3**) (3.2 g, 94% yield based on 86% conversion) as a white foam. LC-MS observed 2M+NH₄ = 1006.83 (Calcd. 1006.83).

Step 8-3:



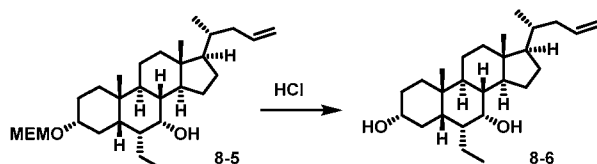
To a stirred solution of (**8-3**) (870 mg, 1.76 mmol) in THF (10 mL) at RT under N₂ was added 2-nitrophenyl selenocyanate (800 mg, 3.52 mmol), followed by PBu₃ (0.87 mL, 3.52 mmol). The reaction mixture was stirred at RT for 3h, and then concentrated. The residue was purified by chromatography on silica gel using hexane/EtOAc (100/0 to 60/40, 10 min) to give a product (**8-4**) as a yellow oil (1.14 g, 95% yield).

Step 8-4:



To a stirred solution of (**8-4**) (1.14g, 1.68 mmol) in THF (20 mL) at RT was added slowly H₂O₂ (30% in H₂O, 3.8 mL, 33.6 mmol). The reaction mixture was allowed to warm up to RT and stirred for 20h, quenched with H₂O/brine (1/1), and extracted with EtOAc. The combined organic layers were washed with brine and concentrated. DCM was added to the residue, and the solid was removed by filtration and washed with DCM. The filtrate was concentrated. The residue was purified by chromatography on silica gel using hexane/EtOAc (100/0 to 70/30, 10 min) to obtain a product (**8-5**) as a pale yellow oil (701 mg, 87% yield).

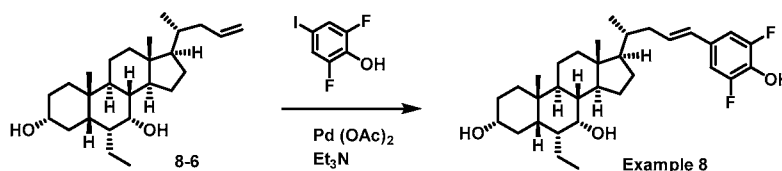
Step 8-5:



A solution of (**8-5**) (28 mg, 0.06 mmol) in THF (2 mL) at RT was treated with HCl (37%, 0.1 mL). The reaction mixture was stirred at RT for 2h, quenched with sat NaHCO₃, and extracted with EtOAc. The combined organic layers were washed with brine and concentrated. The residue was purified by chromatography on silica gel using hexane/EtOAc (100/0 to 60/40, 10 min) to afford a product as a white foam (**8-6**) (20 mg, 87% yield).

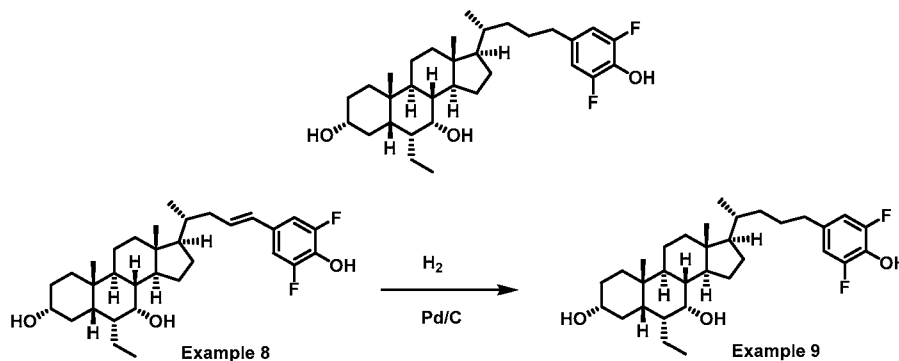
yield). LC-MS observed $2M+1 = 777.68$ (Calcd. 777.66). ^1H NMR (500 MHz, CDCl_3): δ 5.77 (1H, m), 4.90 (2H, d, $J = 11.5$ Hz), 3.71 (1H, s), 3.40 (1H, br s), 0.90 (6H, br s), 0.67 (3H, s).

5 Step 8-6:



A solution of (**8-6**) (58 mg, 0.15 mmol) and 2,6-difluoro-4-iodophenol (58 mg, 0.23 mmol) in DMF (1.5 mL) at RT was degassed with N_2 for 10 min, Et_3N (43 μl) and $\text{Pd}(\text{OAc})_2$ (4 mg) were added, and degassed for another 10 min. The reaction mixture was heated to 80 $^\circ\text{C}$ and stirred overnight, cooled down to RT, quenched with 3% citric acid and brine (1/1), and extracted with EtOAc. The combined organic layers were washed with brine and concentrated. The residue was purified by chromatography on silica gel using hexane/EtOAc (100/0 to 50/50, 10 min) to obtain example **8** as a white solid (64 mg, 83% yield). LC-MS observed $M+\text{HCO}_2\text{H}-1 = 561.34$ (Calcd. 561.37).

Example 9:

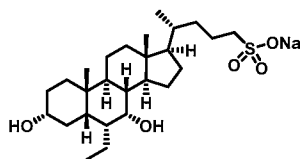


20

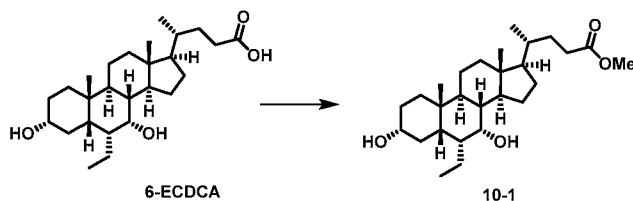
Pd/C (10%, 10 mg) was first added to a solution of example **8** (38 mg, 0.07 mmol) in MeOH/EtOAc (1/1, 2 mL). The mixture was first degassed with N_2 for 15 min and then stirred under H_2 for 16h, filtered through celite, and the solid was washed with MeOH and EtOAc. The filtrate was concentrated and dried to provide example **9** as a white solid (35 mg, 92% yield). LC-MS observed $M-1 = 517.35$ (Calcd. 517.36).

25

Example 10:



Step 10-1:

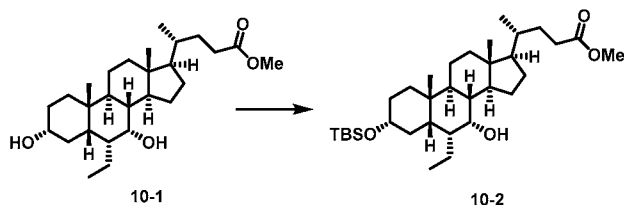


5

To a solution of 6 α -ethylchenodeoxycholic acid (6.5 g, 15.5 mmol) in MeOH (130 mL) was added sulfuric acid (98%, 0.13 mL). The solution was stirred at 23°C for 24 h, and concentrated *in vacuo*. Purification of the residue on silica gel (105 g) with 0 – 30% acetone in hexane provided compound **10-1** (6.6 g, 98% yield).

10

Step 10-2:

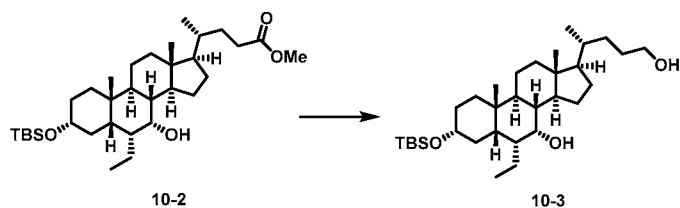


15

To a solution of compound **10-1** (6.39 g, 14.7 mmol) in DMF (30 mL) was added imidazole (2.20 g, 32.3 mmol) and TBSCl (2.33 g, 15.5 mmol). The mixture was stirred at 23°C for 20 h, quenched with pH 7 buffer, and extracted with MTBE. The organic layer was washed with sat. NaCl solution, dried over Na₂SO₄, and concentrated *in vacuo*. Purification of the residue on silica gel (105 g) with 0 – 50% EtOAc / hexane provided compound **10-2** (7.59 g, 94% yield).

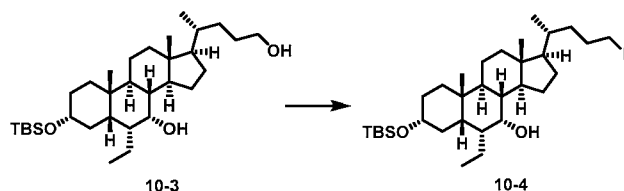
20

Step 10-3:



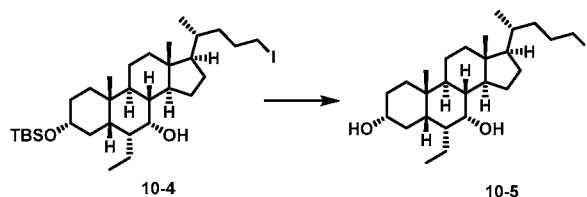
To a solution of **10-2** (7.59 g, 13.85 mmol) in THF was added LiBH₄ (2.0 M in THF, 41.6 mmol, 20.8 mL) and anhydrous MeOH (1.7 mL, 41.6 mmol) dropwise. The mixture was stirred at 23°C for 15 h, slowly quenched with water (100 mL), and extracted with EtOAc. The aqueous layer was acidified with 1 M HCl to pH 5 and extracted with EtOAc (2 x). The organic layers were combined, washed with 1 M HCl solution, sat. NaCl, dried over Na₂SO₄, and concentrated *in vacuo*. Purification of the residue on silic gel (105 g) with 0 – 30% EtOAc / hexane provided compound **10-3** (6.5 g) in 90% yield.

Step 10-4:



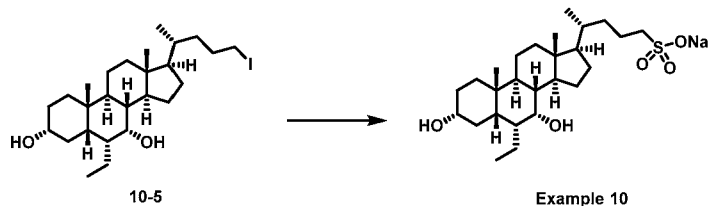
To a solution of **10-3** (200 mg, 0.38 mmol) in toluene (3 mL) was added PPh₃ (259 mg, 0.99 mmol) and imidazole (129 mg, 1.9 mmol). The mixture was stirred at RT for 5 min and iodine (193 mg, 1.52 mmol) was added. The reaction mixture was stirred at RT for 1.5 h, quenched with sat. Na₂S₂O₃ solution, and extracted with DCM (2 x). The organic layers were combined, dried over Na₂SO₄, and concentrated *in vacuo*. Purification of the residue on 12 g of silica with 0 – 20% EtOAc / hexane provided 240 mg of **10-4** (contains PPh₃).

Step 10-5:



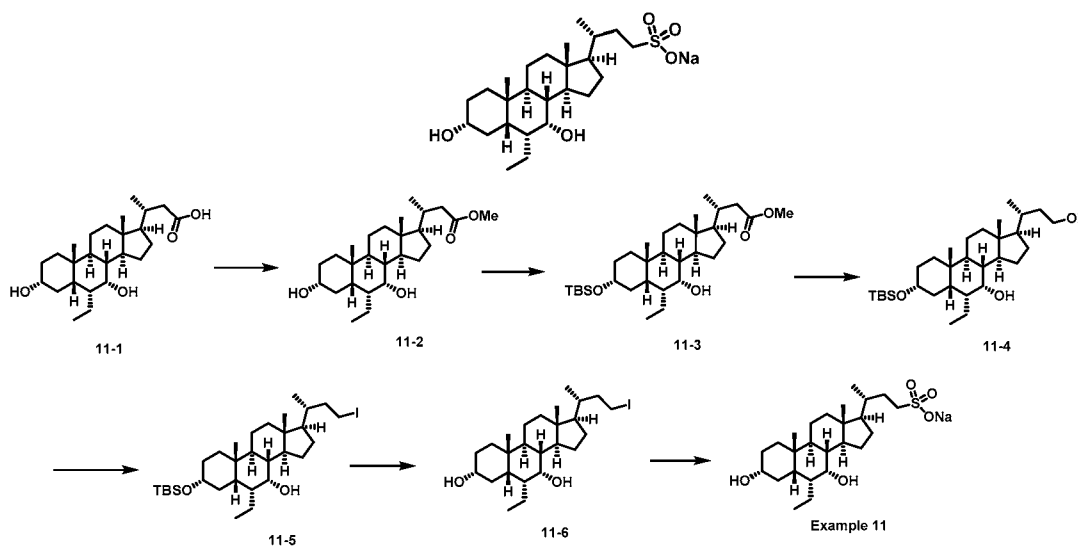
The above product **10-4** was dissolved in MeOH (15 mL) and treated with 37% HCl (0.03 mL). The solution was stirred at RT for 15 min and concentrated *in vacuo*. Purification of the residue on 12 g of silica with 0- 50% EtOAc in hexane provided **10-5** (165 mg) in 84% yield (2 steps). [2M+1]⁺, 1033.50.

Step 10-6:



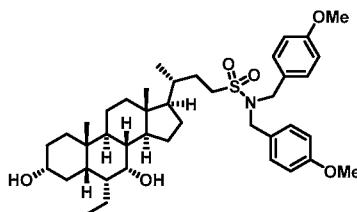
In a seal tube **10-5** (165 mg, 0.32 mmol) was dissolved in EtOH/THF/H₂O (2 mL/1 mL/2 mL). To the solution was added Na₂SO₃ (807 mg, 6.4 mmol). The tube was sealed and heated at 100°C for 5 h, cooled to RT, and diluted with water. The mixture was loaded on 34 g of C18 silica and eluted with 10 – 30% MeCN / H₂O. Example **6** (166 mg) was obtained as a sodium salt. [M+NH₄]⁺, 488.34.

Example 11:

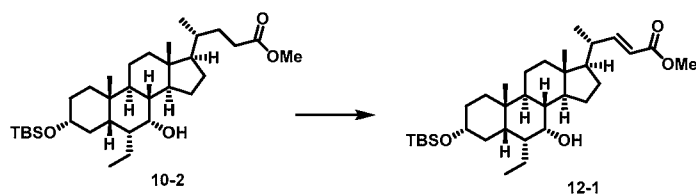


Example **11** was prepared from known acid **11-1** employing the same protocol as synthesis of Example **10**.

Example 12:

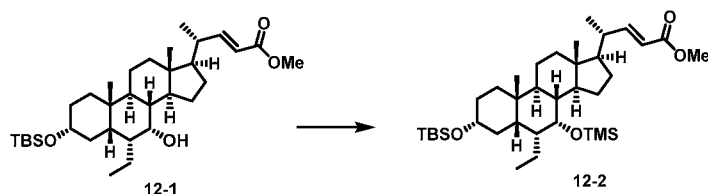


Step-12-1:



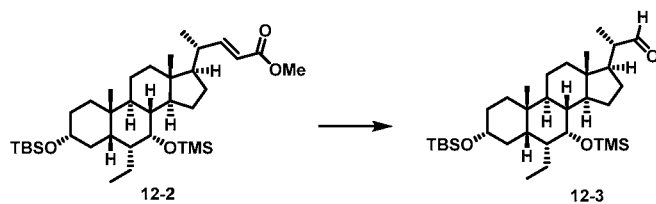
To a solution of **10-2** (7.13 g, 12.98 mmol) in THF (40 mL) at -78°C was added a solution of NaHMDS in THF (1.0 M, 27.3 mL) dropwise over 10 min. The mixture was stirred at -78°C for 1.5 h and a solution of PhSeBr (3.68 g, 15.6 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at at -78°C for 2.5 h and at RT for 30 min. The reaction was quenched at 0°C with sat. NH₄Cl solution and extracted with EtOAc (2 x). The combined organic layer was washed with sat. NaCl solution and concentrated *in vacuo*. The residue was dissolved in EtOAc (35 mL), cooled to 0°C, and treated with 30% H₂O₂ (7 mL). The resulting mixture was rigorously stirred for 40 min, diluted with EtOAc, and washed with sat. NaHCO₃ solution and sat. NaCl solution. The organic layer was concentrated and purified on 120 g of silica with 0 -20% acetone in hexane, which provided **12-1** (5.46 g) in 77% yield.

Step 12-1:



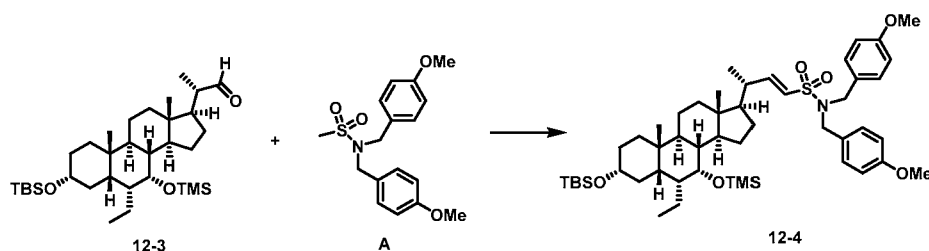
To a solution of **12-1** (2.0 g, 3.66 mmol) in DCM (12 mL) at 0°C was added 1-methylimidazole (0.58 mL, 7.32 mmol) and TMSCl (0.7 mL, 5.49 mmol). The mixture was stirred at 0°C for 2.5 h, quenched with 5% NaHCO₃, and extracted with DCM. The organic layer was dried over Na₂SO₄, and concentrated *in vacuo*. Purification of the residue on 50 g of silica with 0 -10% EtOAc / hexane provided **12-2** (2.1 g) in 93% yield.

Step 12-2:



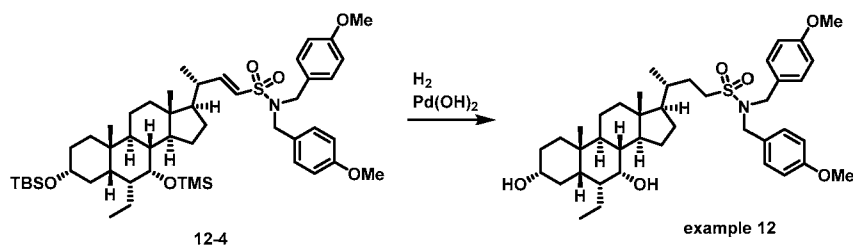
A solution of **12-2** (500 mg, 0.81 mmol) in DCM (20 mL) was cooled to -78°C. Ozone flow (3 psi) was passed through the reaction for 1 min or until the reaction turned blue. The solution was quenched with PPh₃ (276 mg), stirred at RT for 16 h, and concentrated *in vacuo*. Purification of the residue on 25 g of silica with 0 – 20% EtOAc / hexane provided **12-3** (313 mg).

Step 12-3:



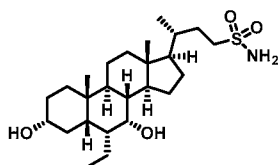
To a solution of sulfonamide A (195 mg, 0.58 mmol) in THF (3 mL) at -78°C was added LiHMDS solution (1.0 M in THF, 1.16 mL) dropwise. The solution was stirred at -78°C for 30 min and diethylchlorophosphate (0.084 mL, 0.58 mmol) was added. The mixture was stirred at -78°C for 1 h 20 min and a solution of **12-3** in THF (3 mL) was added dropwise. The reaction was stirred at at -78°C for 2 h, at 0°C for 2 h, and at RT for 30 min. The reaction was quenched with sat. NH₄Cl and extracted with EtOAc (3 x). The combined organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. Purification of the residue on 35 g of silica with 0 – 20% EtOAc in hexane provided **12-4** (209 mg) in 29% yield (2 steps).

Step 12-4:

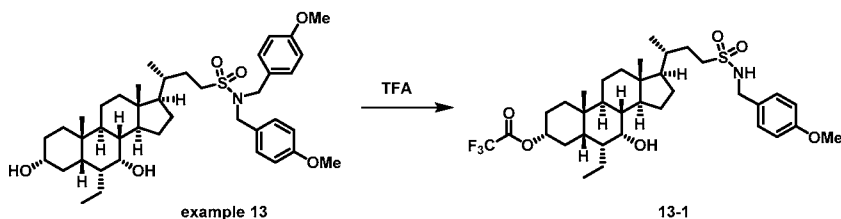


To a solution of **12-4** (50 mg, 0.057 mmol) in ethanol (5 ml) was added palladium hydroxide on carbon (10 mg). The mixture was stirred under hydrogen (120 psi) at RT for 15 h. The reaction was diluted with EtOAc (10 mL), filtered through 2.5 g of SiO₂ plug, and concentrated. The crude was purified on SiO₂ column with 0 - 50% EtOAc/hexane, which provided example **12** (40.5 mg). (2M+NH₄, 1410).

Example 13

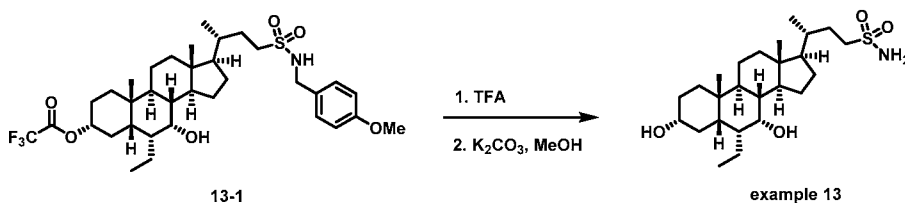


Step 13-1:



To a solution of example **12** (33 mg, 0.047 mmol) in CH_2Cl_2 (0.54 ml) at 0 °C was added trifluoroacetic acid (0.183 ml, 2.371 mmol) dropwise. The mixture was stirred at 0 °C for 4 h, and concentrated *in vacuo*. Purification of the residue on SiO_2 with 0 - 50% acetone/hexane provided **13-1** (18.4 mg) in 58% yield. $[\text{M}+\text{HCOOH}-1]^+$, 716.41.

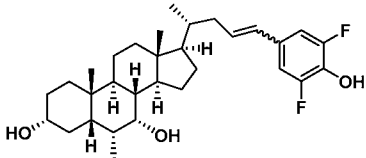
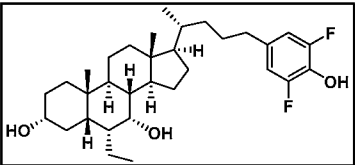
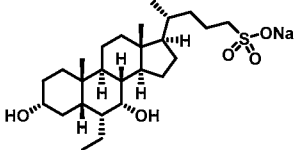
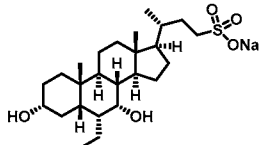
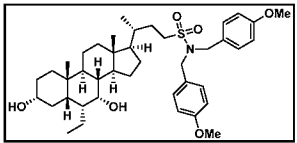
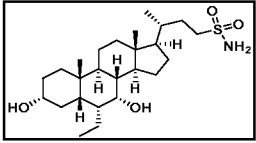
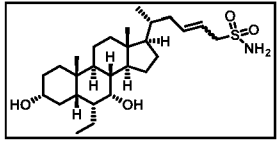
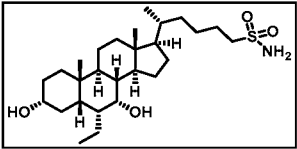
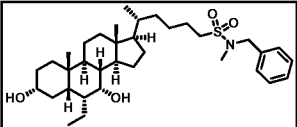
Step 13-2:

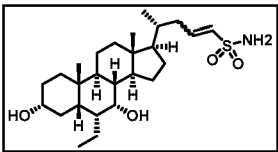
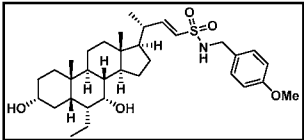
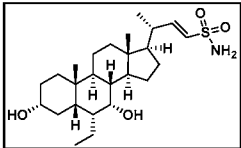
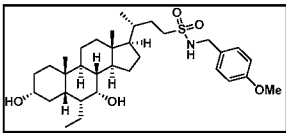
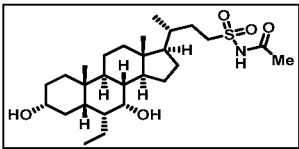
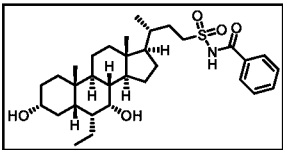
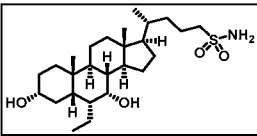
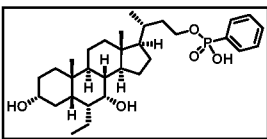
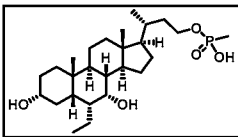
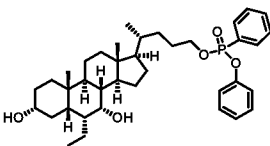


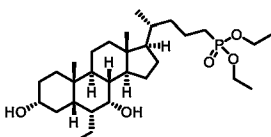
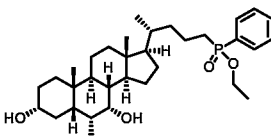
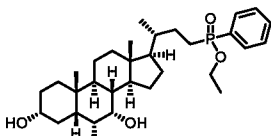
To a solution of **13-1** (18 mg, 0.027 mmol) in CH_2Cl_2 (0.3 ml) at 0 °C was added trifluoroacetic acid (0.103 ml, 1.34 mmol) dropwise. The mixture was stirred at 0 °C for 2 h, warmed to RT and stirred for 3 h, and concentrated *in vacuo*. The crude was dissolve in MeOH/EtOAc (5:1, 1 mL) and K_2CO_3 (37 mg, 0.268 mmol) was added. The mixture was stirred at RT for 2 h, filtered, and concentrated. Purification of the residue on silica gel with 0 - 50 acetone/hexane provided example **13** (5.4 mg). $[\text{M}+\text{HCOOH}-1]^+$, 500.30.

The example compounds 14 to 29 were prepared using similar procedures used above. The MS data is delineated in Table 8.

Table 8

Example	Structure	MS data (M-1) ⁻
8		561.34 (M-1+HCO ₂ H) ⁻
9		517.35
10		[M+HCOOH-1] ⁻ , 515.29
11		[M+HCOOH-1] ⁻ , 501
12		[M+NH ₄] ⁺ , 713.56
13		[M+HCOOH-1] ⁻ , 500.30
14		[M+NH ₄] ⁺ , 499
15		[M+NH ₄] ⁺ , 501.37
16		[M-2H ₂ O+1] ⁺ , 552.39

17		$[M-2H_2O+1]^+$, 432.30
18		$[2M+NH_4]^+$, 1164.88
19		$[2M+NH_4]^+$, 924.74
20		$[2M+NH_4]^+$, 1168.90
21		$[M-1]^-$, 496.31
22		$[M-1]^-$, 558.33
23		$[M+HCOOH-1]^-$, 514.32
24		$[M+HCOOH-1]^-$, 577.33
25		$[M+HCOOH-1]^-$, 515.32
26		$[2M+NH_4]^+$, 1262.79

27		$[M-2H_2O+1]^+$, 491
28		$[M+1]^+$, 559.39
29		$[M+1]^+$, 545.38

ASSAYS

Human FXR (NR1H4) Assay

Determination of a ligand mediated Gal4 promoter driven transactivation to quantify

5 ligand binding mediated activation of FXR. FXR Reporter Assay kit purchased from Indigo Bioscience (Catalogue number: IB00601) to determine the potency and efficacy of compound developed by Enanta that can induce FXR activation. The principle application of this reporter assay system is to quantify functional activity of human FXR. The assay utilizes non-human mammalian cells, CHO (Chinese hamster ovary) cells engineered to

10 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

15 reporter cells provides a sensitive surrogate measure of the changes in FXR activity. EC_{50} and efficacy (normalize to CDCA set as 100%) is determined by XLFit. The assay is according to the manufacturer's instructions. In brief, the assay was performed in white, 96 well plates using final volume of 100ul containing cells with different doses of compounds. Retrieve Reporter Cells from $-80^{\circ}C$ storage. Perform a rapid thaw of the frozen cells by

20 transferring a 10 ml volume of $37^{\circ}C$ cell recovery medium into the tube of frozen cells. Recap the tube of Reporter Cells and immediately place it in a $37^{\circ}C$ 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

5 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.

10 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

15 XLFit.

In vitro Human TGR5 (GPBAR1) activity assay

The potency and efficacy of the compounds of the invention on TGR5 receptor was evaluated using *in vitro* assays which carried out using the express kit from DiscoverX

20 (cAMP HUNTER™ eXpress GPBAR1 CHO-K1 GPCR Assay; Cataloguer number: 95-0049E2CP2S)GPBAR1 (G protein-coupled bile acid receptor 1) encodes a member of the G protein-coupled receptor (GPCR) superfamily. GPBAR1 activation following ligand binding initiates a series of second messenger cascades that result in a cellular response. Treatment of CHO cells expressing GPBAR1 with bile acids induces the production of

25 intracellular cAMP and internalization of the receptor. The potency and efficacy of compound for GPBAR1 activation by measuring cyclic adenosine monophosphate (cyclic AMP or cAMP) levels in live cells using a competitive immunoassay based on Enzyme Fragment Complementation (EFC).

In briefly, following seeding the cells into the white, 96 well microplate, place it in a 37°C,

30 5% CO₂ in a humidified incubator for 18-24 hours prior to testing. On second day, proceed to the appropriate cAMP Hunter eXpress Protocol according to the manufacturer's instructions. Dissolve agonist compound in DMSO at the desired stock concentration, and prepare 3-fold serial dilutions of agonist compound in Cell Assay Buffer. The concentration of each dilution should be prepared at 4X of the final screening concentration (i.e. 15 µL

- compound + 45 μ L Cell Assay Buffer/cAMP Antibody Reagent). For each dilution, the final concentration of solvent should remain constant. Transfer 15 μ L diluted compound the assay plate and incubate the plate for 30 minutes at 37°C. Following agonist incubation, add 60 μ L of working cAMP detection reagents/cAMP Solution mixture (cAMP Lysis Buffer, Substrate Reagent 1, cAMP Solution D) to the appropriate wells. Incubate for 1 hour at room temperature (23°C), protected from light. Add 60 μ L of cAMP Solution A to the appropriate wells. Incubate for 3 hours at room temperature (23°C), protected from light. Read samples on Envision standard luminescence plate reader. Calculate of average EC₅₀ after logarithm transformation.
- 10 To assess the FXR agonistic potency of the example compounds as well as for reference compound, potency ranges were determined in the Human FXR (NR1H4) Assay as listed below in Table 9. The efficacy was normalized to CDCA set as 100%. (A=EC₅₀ < 0.1 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 9

Example	EC ₅₀ (μ M)	Efficacy (%)
CDCA	D	100
6-ECDCA	B	223
1	D	11
2	D	13
3	D	2
4	C	270
8	B	298
9	C	271
10	C	4
11	n/a	1
12	C	1
13	C	118
14	B	167
15	B	195
16	C	97
17	B	147
18	C	16
19	C	3
20	D	60
21	C	74
22	C	249
23	C	202
24	C	75
25	C	5
26	C	129
27	C	246

28	B	265
29	C	49

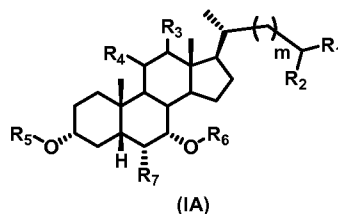
While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the

5 invention encompassed by the appended claims.

CLAIMS

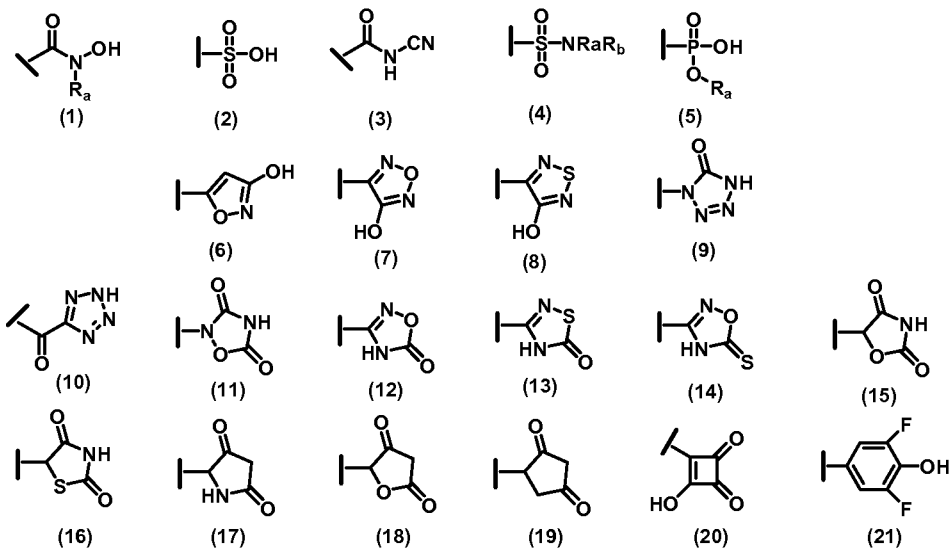
WHAT IS CLAIMED IS:

1. A compound represented by Formula IA, or pharmaceutically acceptable
 5 salts, stereoisomer, solvate, hydrate or combination thereof:



wherein:

R₁ is selected from:



wherein,

R_a is hydrogen, substituted or unsubstituted C₃-C₈-cycloalkyl or substituted or unsubstituted C₁-C₈ alkyl;

R_b is selected from the group consisting of:

- 15 1) hydrogen
 2) Halogen;
 3) Hydroxyl;
 4) Substituted or unsubstituted -C₁-C₈ alkyl;
 5) Substituted or unsubstituted -C₂-C₈ alkenyl;
 20 6) Substituted or unsubstituted -C₂-C₈ alkynyl;

- 7) Substituted or unsubstituted $-C_3-C_8$ cycloalkyl;
- 8) Substituted or unsubstituted aryl;
- 9) Substituted or unsubstituted alkylaryl;
- 10) Substituted or unsubstituted heterocycloalkyl;
- 5 11) Substituted or unsubstituted heteroaryl;
- 12) Substituted or unsubstituted alkylheteroaryl; and
- 13) $-NR_{10}R_{11}$; wherein R_{10} and R_{11} are each independently selected from hydrogen, substituted or unsubstituted $-C_1-C_8$ alkyl, substituted or unsubstituted $-C_2-C_8$ alkenyl, Substituted or unsubstituted $-C_2-C_8$ alkynyl, substituted or unsubstituted $-C_3-C_8$ cycloalkyl, or R_{10} and R_{11} , taken together with the nitrogen atom to which they are attached, form a heterocyclic ring.

R_2 is selected from the group consisting of:

- 1) Hydrogen;
- 2) Substituted or unsubstituted $-C_1-C_8$ alkyl;
- 15 3) Substituted or unsubstituted $-C_2-C_8$ alkenyl;
- 4) Substituted or unsubstituted $-C_2-C_8$ alkynyl;
- 5) Substituted or unsubstituted alkylaryl; and
- 6) Substituted or unsubstituted aryl.

m is 0, 1, 2 or 3;

- 20 R_3 is hydrogen, hydroxyl, $-\text{OSO}_3\text{H}$, $-\text{OSO}_3^-$, $-\text{OAc}$, $-\text{OPO}_3\text{H}_2$ or $-\text{OPO}_3^{2-}$;
- R_4 is hydrogen, halogen, CN, N_3 , hydroxyl, $-\text{OSO}_3\text{H}$, $-\text{OSO}_3^-$, $-\text{OAc}$, $-\text{OPO}_3\text{H}_2$, $-\text{OPO}_3^{2-}$, $-\text{SR}_2$ or $-\text{NHR}_{12}$, wherein R_{12} is hydrogen; substituted or unsubstituted $-C_1-C_8$ alkyl; substituted or unsubstituted $-C_2-C_8$ alkenyl; substituted or unsubstituted $-C_2-C_8$ alkynyl; substituted or unsubstituted alkylaryl; or substituted or unsubstituted aryl;

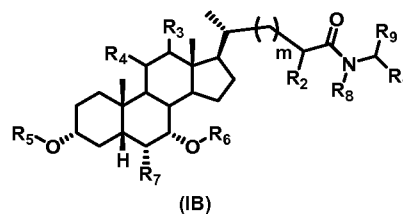
- 25 Alternatively, R_3 and R_4 are taken together with the carbon atoms to which they are attached to form $-\text{CH}=\text{CH}-$, a cycloalkyl ring or a heterocycloalkyl ring such as, but not limited to, cyclopropyl or epoxide;

R_5 and R_6 are independently selected from hydrogen or a hydroxyl protecting group;

R_7 is selected from the group consisting of:

- 30 1) Hydrogen;
- 2) Halogen;
- 3) Substituted or unsubstituted $-C_1-C_8$ alkyl;
- 4) Substituted or unsubstituted $-C_2-C_8$ alkenyl;

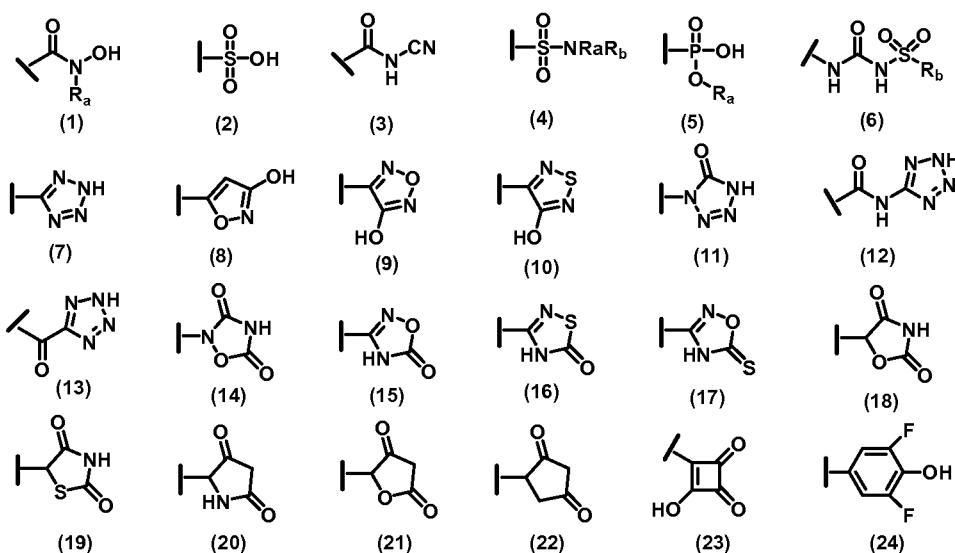
- 5) Substituted or unsubstituted $-C_2-C_8$ alkynyl; and
- 6) Substituted or unsubstituted $-C_3-C_8$ cycloalkyl; or
- (ii) a compound represented by Formula IB, or pharmaceutically acceptable salts, stereoisomer, solvate, hydrate or combination thereof:



5

wherein:

R_1 is selected from:



wherein,

- 10 R_a is hydrogen, substituted or unsubstituted C_3-C_8 -cycloalkyl or substituted or unsubstituted C_1-C_8 alkyl;

R_b is selected from the group consisting of:

- 1) hydrogen
- 2) Halogen;
- 15 3) Hydroxyl;
- 4) Substituted or unsubstituted $-C_1-C_8$ alkyl;
- 5) Substituted or unsubstituted $-C_2-C_8$ alkenyl;
- 6) Substituted or unsubstituted $-C_2-C_8$ alkynyl;
- 7) Substituted or unsubstituted $-C_3-C_8$ cycloalkyl;
- 20 8) Substituted or unsubstituted aryl;

- 9) Substituted or unsubstituted alkylaryl;
- 10) Substituted or unsubstituted heterocycloalkyl;
- 11) Substituted or unsubstituted heteroaryl;
- 12) Substituted or unsubstituted alkylheteroaryl; and
- 5 13) $-NR_{10}R_{11}$; wherein R_{10} and R_{11} are each independently selected from hydrogen, substituted or unsubstituted $-C_1-C_8$ alkyl, substituted or unsubstituted $-C_2-C_8$ alkenyl, Substituted or unsubstituted $-C_2-C_8$ alkynyl, substituted or unsubstituted $-C_3-C_8$ cycloalkyl, or R_{10} and R_{11} , taken together with the nitrogen atom to which they are attached, form a heterocyclic ring.
- 10 R_2 is selected from the group consisting of:
 - 1) Hydrogen;
 - 2) Substituted or unsubstituted $-C_1-C_8$ alkyl;
 - 3) Substituted or unsubstituted $-C_2-C_8$ alkenyl;
 - 4) Substituted or unsubstituted $-C_2-C_8$ alkynyl;
 - 15 5) Substituted or unsubstituted alkylaryl; and
 - 6) Substituted or unsubstituted aryl.

m is 0, 1, 2 or 3;

R_3 is hydrogen, hydroxyl, $-\text{OSO}_3\text{H}$, $-\text{OSO}_3^-$, $-\text{OAc}$, $-\text{OPO}_3\text{H}_2$ or $-\text{OPO}_3^{2-}$;

R_4 is hydrogen, halogen, CN, N_3 , hydroxyl, $-\text{OSO}_3\text{H}$, $-\text{OSO}_3^-$, $-\text{OAc}$, $-\text{OPO}_3\text{H}_2$, $-\text{OPO}_3^{2-}$, -

- 20 SR_2 or $-\text{NHR}_{12}$, wherein R_{12} is hydrogen; substituted or unsubstituted $-C_1-C_8$ alkyl; substituted or unsubstituted $-C_2-C_8$ alkenyl; substituted or unsubstituted $-C_2-C_8$ alkynyl; substituted or unsubstituted alkylaryl; or substituted or unsubstituted aryl;

Alternatively, R_3 and R_4 are taken together with the carbon atoms to which they are attached to form $-\text{CH}=\text{CH}-$, a cycloalkyl ring or a heterocycloalkyl ring;

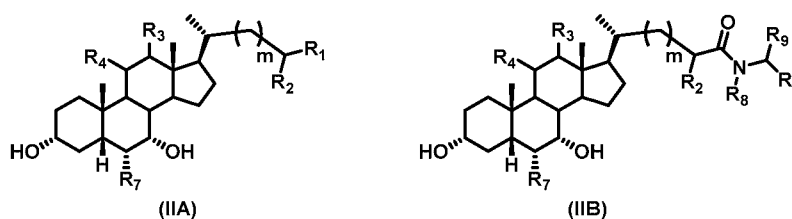
- 25 R_5 and R_6 are independently selected from hydrogen or a hydroxyl protecting group;

R_7 is selected from the group consisting of:

 - 1) Hydrogen;
 - 2) Halogen;
 - 3) Substituted or unsubstituted $-C_1-C_8$ alkyl;
 - 30 4) Substituted or unsubstituted $-C_2-C_8$ alkenyl;
 - 5) Substituted or unsubstituted $-C_2-C_8$ alkynyl; and
 - 6) Substituted or unsubstituted $-C_3-C_8$ cycloalkyl; and

R₈ and R₉ are independently selected from hydrogen; substituted or unsubstituted –C₁–C₈ alkyl; substituted or unsubstituted –C₂–C₈ alkenyl; substituted or unsubstituted –C₂–C₈ alkynyl; substituted or unsubstituted alkylaryl; or substituted or unsubstituted aryl.

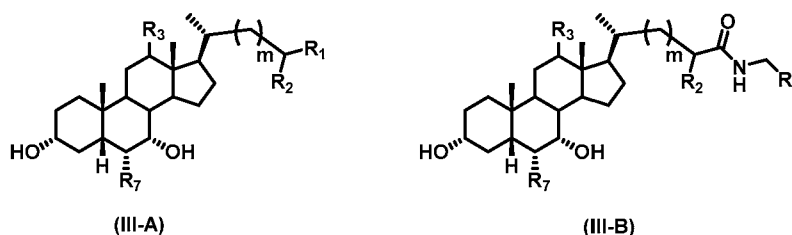
- 5 2. A compound of claim 1 represented by Formula II-A or Formula II-B or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, or combination thereof:



wherein, R₁, R₂, R₃, R₄, R₅, R₉, R₁₀ and m are as previously defined.

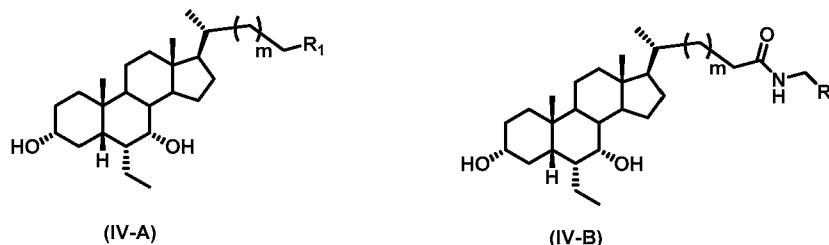
10

3. A compound of claim 1 represented by Formula III-A or Formula III-B or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, or combination thereof:



- 15 wherein, R₁, R₂, R₃, R₇ and m are as previously defined.

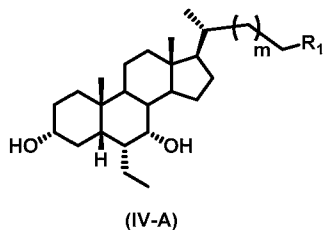
4. A compound of claim 1 represented by Formula IV-A or Formula IV-B or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, or combination thereof:



- 20 wherein R₁ and m are as previously defined.

5. A compound according to claim 1 selected from:

(i) compounds of Formula IV-A,

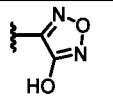
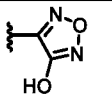
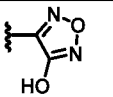
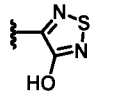
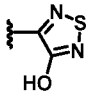
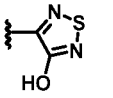
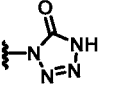
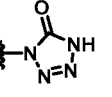
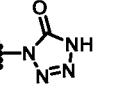
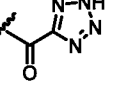
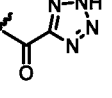
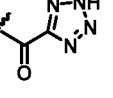
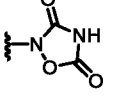
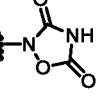
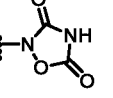
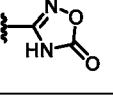
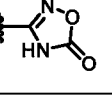
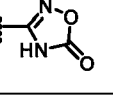
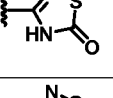
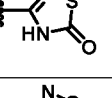
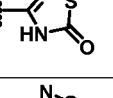
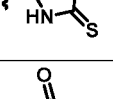
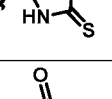
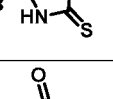
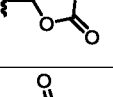
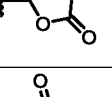
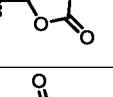
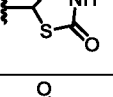
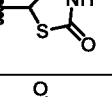
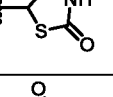
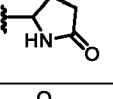
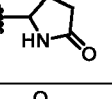
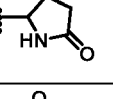
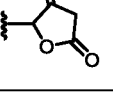
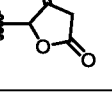
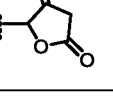
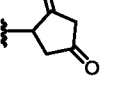
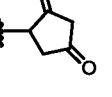
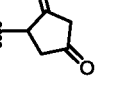
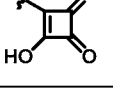
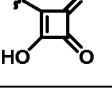
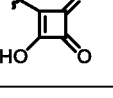


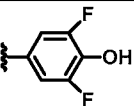
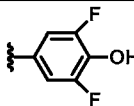
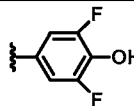
wherein R_1 and m are delineated for each compound in Table 1:

5

Table 1

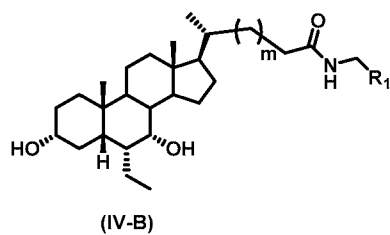
Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
1	0		31	1		61	2	
2	0		32	1		62	2	
3	0		33	1		63	2	
4	0		34	1		64	2	
5	0		35	1		65	2	
6	0		36	1		66	2	
7	0		37	1		67	2	
8	0		38	1		68	2	
9	0		39	1		69	2	
11	0		41	1		71	2	

12	0		42	1		72	2	
13	0		43	1		73	2	
14	0		44	1		74	2	
16	0		46	1		76	2	
17	0		47	1		77	2	
18	0		48	1		78	2	
19	0		49	1		79	2	
20	0		50	1		80	2	
21	0		51	1		81	2	
22	0		52	1		82	2	
23	0		53	1		83	2	
24	0		54	1		84	2	
25	0		55	1		85	2	
26	0		56	1		86	2	

27	0		57	1		87	2	
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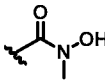
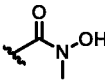
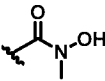
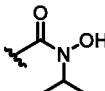
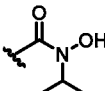
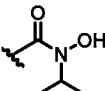
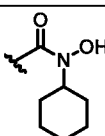
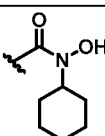
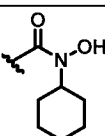
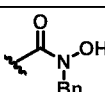
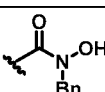
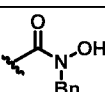
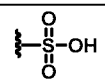
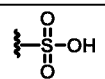
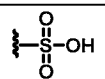
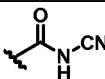
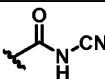
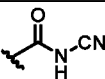
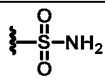
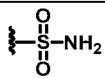
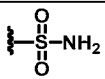
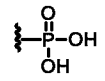
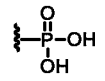
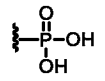
and

(ii) compounds of Formula IV-B,



5 wherein R₁ and m are delineated for each compound in Table 2:

Table 2

Compound	m	R ₁	Compound	m	R ₁	Compound	m	R ₁
91	0		121	1		151	2	
92	0		122	1		152	2	
93	0		123	1		153	2	
94	0		124	1		154	2	
95	0		125	1		155	2	
96	0		126	1		156	2	
97	0		127	1		157	2	
98	0		128	1		158	2	

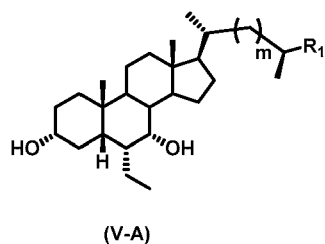
99	0		129	1		159	2	
100	0		130	1		160	2	
101	0		131	1		161	2	
102	0		132	1		162	2	
103	0		133	1		163	2	
104	0		134	1		164	2	
105	0		135	1		165	2	
106	0		136	1		166	2	
107	0		137	1		167	2	
108	0		138	1		168	2	
109	0		139	1		169	2	
110	0		140	1		170	2	
111	0		141	1		171	2	
112	0		142	1		172	2	
113	0		143	1		173	2	

114	0		144	1		174	2	
115	0		145	1		175	2	
116	0		146	1		176	2	
117	0		147	1		177	2	
118	0		148	1		178	2	
119	0		149	1		179	2	
120	0		150	1		180	2	

or a pharmaceutically acceptable salt or prodrug thereof.

6. A compound according to claim 1, which is selected from:

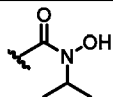
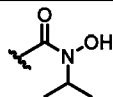
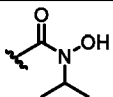
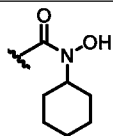
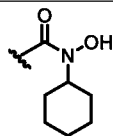
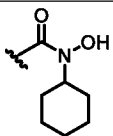
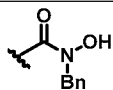
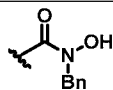
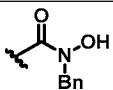
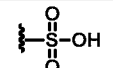
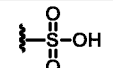
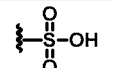
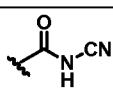
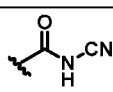
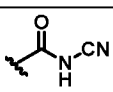
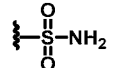
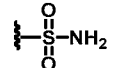
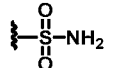
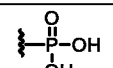
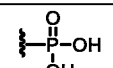
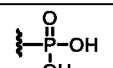
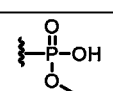
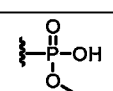
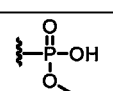
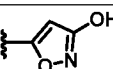
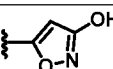
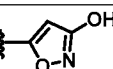
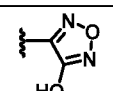
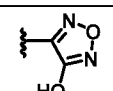
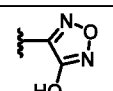
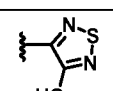
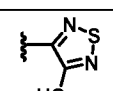
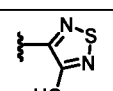
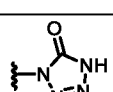
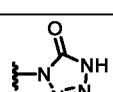
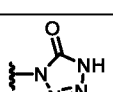
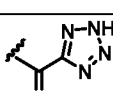
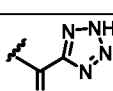
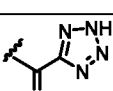
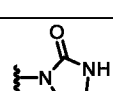
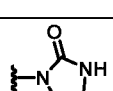
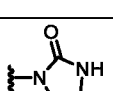
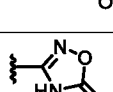
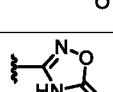
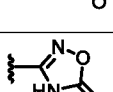
5 (i) compounds of Formula V-A,



wherein R_1 and m are delineated for each compound in Table 3:

Table 3

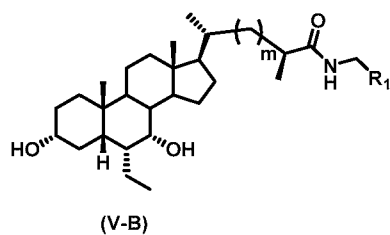
Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
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182	0		212	1		242	2	
183	0		213	1		243	2	
184	0		214	1		244	2	
185	0		215	1		245	2	
186	0		216	1		246	2	
187	0		217	1		247	2	
188	0		218	1		248	2	
189	0		219	1		249	2	
191	0		221	1		251	2	
192	0		222	1		252	2	
193	0		223	1		253	2	
194	0		224	1		254	2	
196	0		226	1		256	2	
197	0		227	1		257	2	
198	0		228	1		258	2	

199	0		229	1		259	2	
200	0		230	1		260	2	
211	0		231	1		261	2	
212	0		232	1		262	2	
213	0		233	1		263	2	
214	0		234	1		264	2	
215	0		235	1		265	2	
216	0		236	1		266	2	
217	0		237	1		267	2	

and

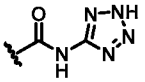
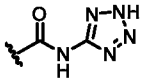
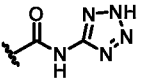
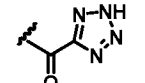
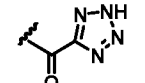
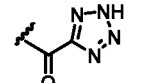
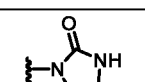
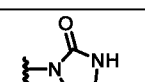
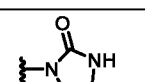
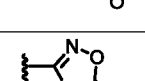
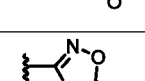
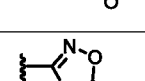
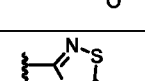
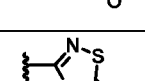
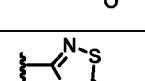
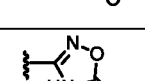
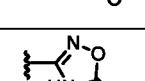
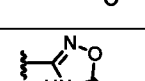
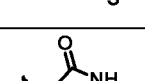
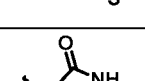
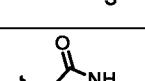
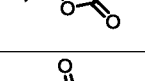
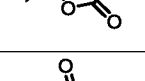
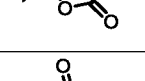
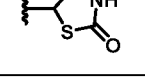
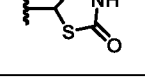
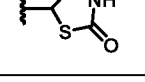
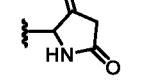
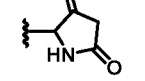
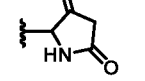
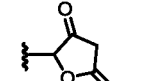
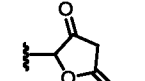
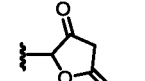
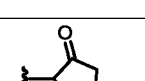
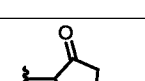
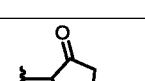
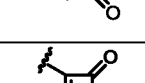
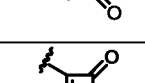
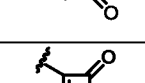
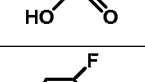
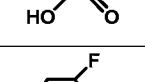
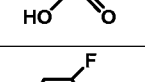
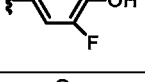
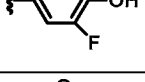
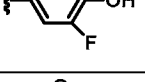
(ii) compounds of Formula V-B,



5 wherein R₁ and m are delineated for each compound in Table 4:

Table 4

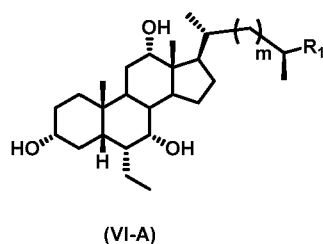
Compound	m	R ₁	Compound	m	R ₁	Compound	m	R ₁
271	0		301	1		331	2	
272	0		302	1		332	2	
273	0		303	1		333	2	
274	0		304	1		334	2	
275	0		305	1		335	2	
276	0		306	1		336	2	
277	0		307	1		337	2	
278	0		308	1		338	2	
279	0		309	1		339	2	
280	0		310	1		340	2	
281	0		311	1		341	2	
282	0		312	1		342	2	
283	0		313	1		343	2	
284	0		314	1		344	2	

285	0		315	1		345	2	
286	0		316	1		346	2	
287	0		317	1		347	2	
288	0		318	1		348	2	
289	0		319	1		349	2	
290	0		320	1		350	2	
291	0		321	1		351	2	
292	0		322	1		352	2	
293	0		323	1		353	2	
294	0		324	1		354	2	
295	0		325	1		355	2	
296	0		326	1		356	2	
297	0		327	1		357	2	
298	0		328	1		358	2	
299	0		329	1		359	2	

300	0		330	1		360	2	

or a pharmaceutically acceptable salt or prodrug thereof.

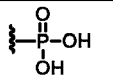
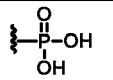
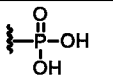
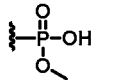
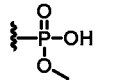
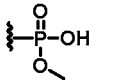
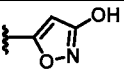
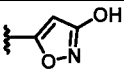
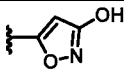
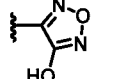
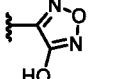
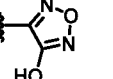
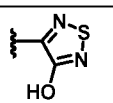
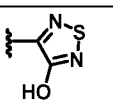
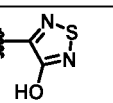
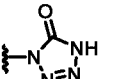
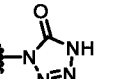
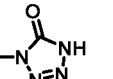
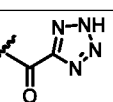
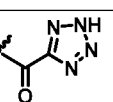
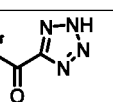
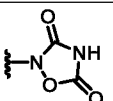
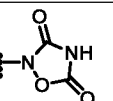
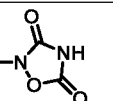
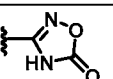
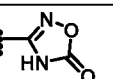
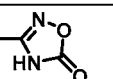
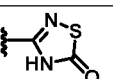
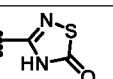
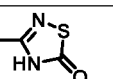
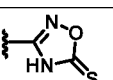
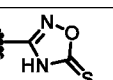
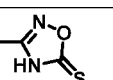
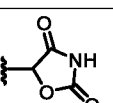
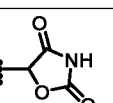
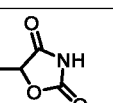
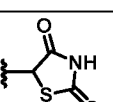
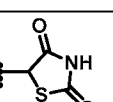
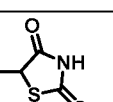
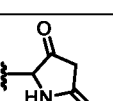
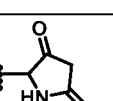
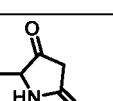
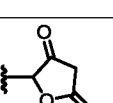
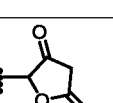
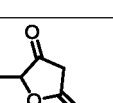
7. A compound according to claim 1 which is selected from
- 5 (i) compounds of Formula VI-A,



wherein R₁ and m are delineated for each compound in Table 5:

Table 5

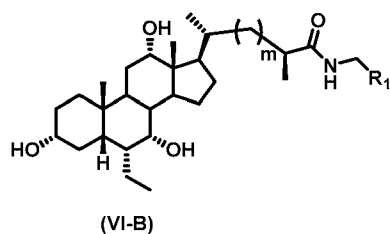
Compound	m	R ₁	Compound	m	R ₁	Compound	m	R ₁
361	0		391	1		421	2	
362	0		392	1		422	2	
363	0		393	1		423	2	
364	0		394	1		424	2	
365	0		395	1		425	2	
366	0		396	1		426	2	
367	0		397	1		427	2	

368	0		398	1		428	2	
369	0		399	1		429	2	
371	0		401	1		431	2	
372	0		402	1		432	2	
373	0		403	1		433	2	
374	0		404	1		434	2	
376	0		406	1		436	2	
377	0		407	1		437	2	
378	0		408	1		438	2	
379	0		409	1		439	2	
380	0		410	1		440	2	
381	0		411	1		441	2	
382	0		412	1		442	2	
383	0		413	1		443	2	
384	0		414	1		444	2	

385	0		415	1		445	2	
386	0		416	1		446	2	
387	0		417	1		447	2	

and

(ii) compounds of Formula VI-B

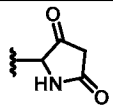
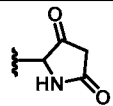
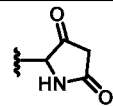
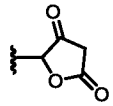
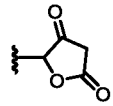
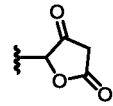
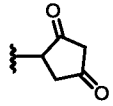
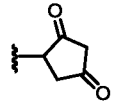
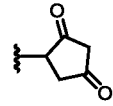
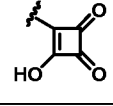
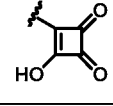
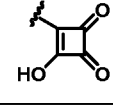
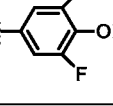
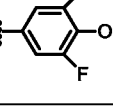
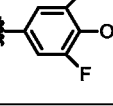
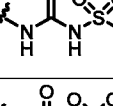
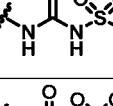
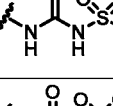
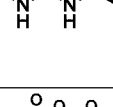
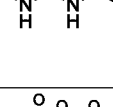
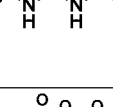
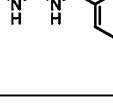
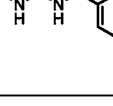
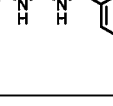


5 wherein R_1 and m are delineated for each compound in Table 6:

Table 6

Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
451	0		481	1		511	2	
452	0		482	1		512	2	
453	0		483	1		513	2	
454	0		484	1		514	2	
455	0		485	1		515	2	
456	0		486	1		516	2	

457	0		487	1		517	2	
458	0		488	1		518	2	
459	0		489	1		519	2	
460	0		490	1		520	2	
461	0		491	1		521	2	
462	0		492	1		522	2	
463	0		493	1		523	2	
464	0		494	1		524	2	
465	0		495	1		525	2	
466	0		496	1		526	2	
467	0		497	1		527	2	
468	0		498	1		528	2	
469	0		499	1		529	2	
470	0		500	1		530	2	
471	0		501	1		531	2	
472	0		502	1		532	2	

473	0		503	1		533	2	
474	0		504	1		534	2	
475	0		505	1		535	2	
476	0		506	1		536	2	
477	0		507	1		537	2	
478	0		508	1		538	2	
479	0		509	1		539	2	
480	0		510	1		540	2	

or a pharmaceutically acceptable salt or prodrug thereof.

8. A method for the prevention or treatment of an FXR-mediated disease or condition
 5 in a mammal comprising administering to the mammal suffering from an FXR-mediated disease or condition a therapeutically effective amount of a compound according to any one of claims 1-7.

9. A method according to claim 8, wherein the FXR-mediated disease or condition is
 10 selected from the group consisting of chronic liver disease, gastrointestinal disease, renal disease, cardiovascular disease, and metabolic disease.

10. A method according to claim 9, 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
- 5 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.
- 10 11. A method according to claim 9, wherein the renal disease is selected from the group consisting of diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, and polycystic kidney disease.
- 15 12. A method according to claim 9, wherein the cardiovascular disease is selected from the group consisting of atherosclerosis, arteriosclerosis, dyslipidemia, hypercholesterolemia, and hypertriglyceridemia.
- 20 13. A method according to claim 9, wherein the metabolic disease is selected from the group consisting of insulin resistance, Type I and Type II diabetes, and obesity.
- 25 14. A method for the prevention or treatment of an TGR5-mediated disease or condition in a mammal comprising administering to the mammal suffering from an TGR5-mediated disease or condition a therapeutically effective amount of a compound according to any one of claims 1-7.
15. A pharmaceutical composition comprising a compound according to any one of claims 1-7 and a pharmaceutically acceptable carrier.
- 30 16. Use of a compound of any one of claims 1-7 for the preparation of pharmaceutical compositions for the prevention or treatment of FXR-mediated or TGR5-mediated diseases or conditions.