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

Yat Sun Or, Guoqiang Wang, Ruichao Shen and Xuechao Xing

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/076,323, filed on November 6, 2014 and U.S. Provisional Application No. 62/107,725, filed on January 26, 2015. The entire teachings of the above applications are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates generally to compounds and pharmaceutical compositions useful as FXR/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 includingthe 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, and WO 2008/025540, WO 2011/020615, and WO 2013/007387.

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

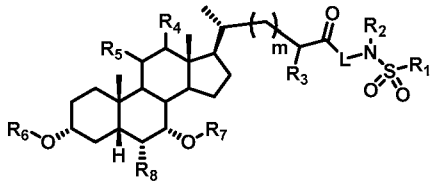
an attractive target for the treatment of disease e.g., obesity, diabetes and metabolic syndrome.

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.

There is a need for the development of FXR and/or TGR5 modulators for the treatment and prevention of disease. The present invention has identified compounds, which contain an acylsulfonamide moiety, which modulate FXR and/or TGR as well as methods of using these compounds to treat diease.

SUMMARY OF THE INVENTION

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



(I)

wherein:

R_1 is selected from the group consisting of:

1) Halogen;
2) Hydroxyl;
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;
6) Substituted or unsubstituted $-C_3$-C_8 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) $-NR_9R_{10}$; wherein, R_9 and R_{10} 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_9 and R_{10} are taken together with the nitrogen they attached form a hetercyclic ring;

R_2 is hydrogen or substituted or unsubstituted $-C_1$-C_8 alkyl;

R_3 is selected from the group consisting of:

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

L is absent or $-NR_{11}CHR_{12}C(O)$-, wherein R_{11} and R_{12} are each independently selected from R_3;

m is selected from 0, 1, 2 or 3;

R_4 is hydrogen, hydroxyl, $-OSO_3H$, $-OSO_3^-$, -OAc, $-OPO_3H_2$ or $-OPO_3^{2-}$;

R_5 is hydrogen, halogen, CN, N_3, hydroxyl, $-OSO_3H$, $-OSO_3^-$, -OAc, $-OPO_3H_2$, $-OPO_3^{2-}$, $-SR_2$ or $-NHR_2$, wherein, R_2 is as defined previously;

or R_4 and R_5 are taken together with the carbon atoms to which they are attached to form –CH=CH- or cycloalkyl ring or heterocycloalkyl ring such as, but not limited to cyclopropyl, or epoxide;

R_6 and R_7 are each independently selected from hydrogen or hydroxyl protecting group such as, but not limited to acetyl, trimethylsilyl, or benzyl;

R_8 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 another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt form, stereoisomer, solvate, hydrate or combination thereof, in combination with a pharmaceutically acceptable carrier or excipient.

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

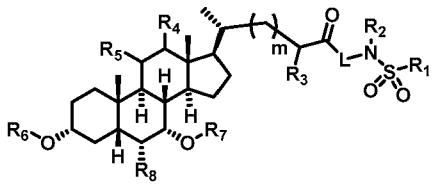
In yet another embodiment, the present invention provides a method for the prevention or treatment of a TGR5 mediated disease or condition. The method comprises administering a therapeutically effective amount of a compound of Formula (I). The present invention also provides the use of a compound of Formula (I) for the preparation of a medicament for the prevention or treatment of 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 I as described above, or a pharmaceutically acceptable salt, hydrate, solvate, ester or prodrug thereof.

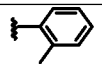
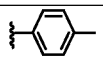
In a preferred embodiment, the compounds of the invention have the stereochemistry depicted in Formula Ia:



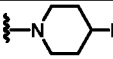
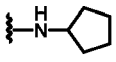
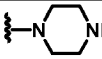
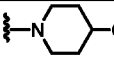
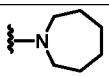
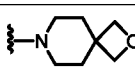
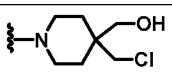
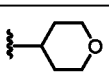
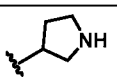
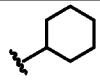
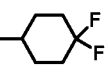
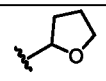
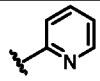
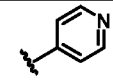
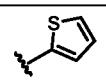
(Ia)

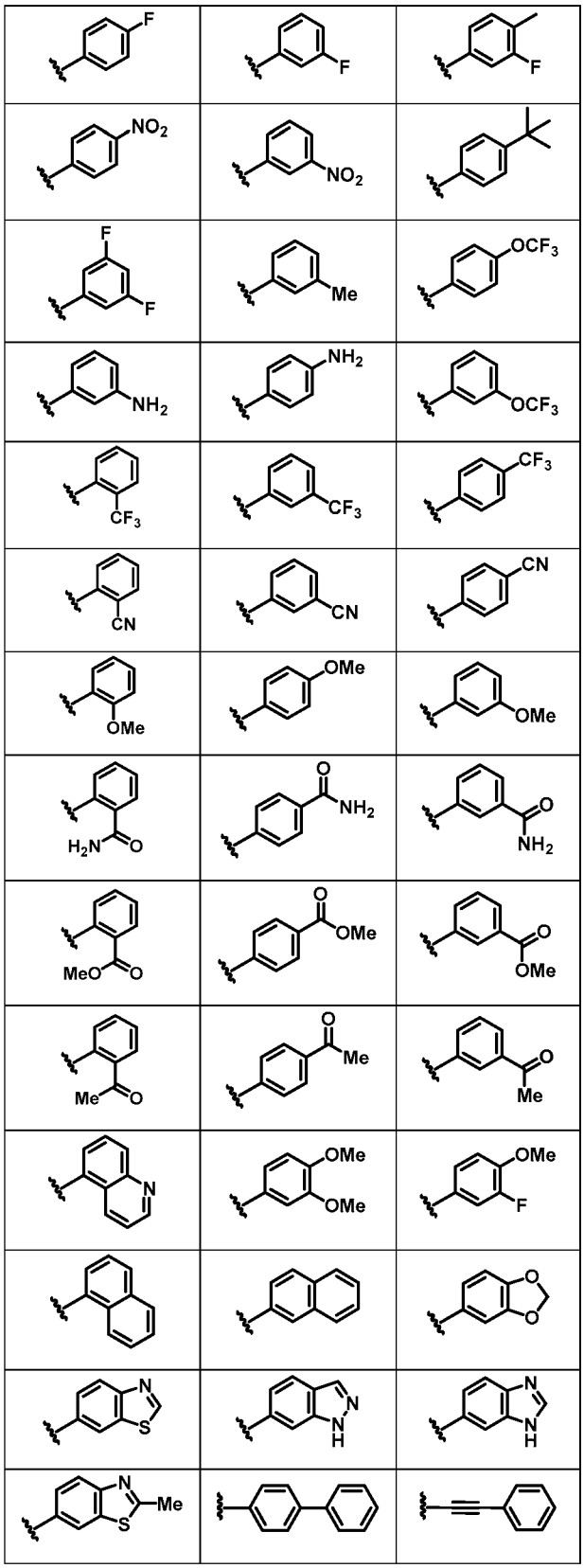
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, L and m have the meanings given for these variables above.

In certain embodiments of the compounds of the invention, R_1 is C_1-C_4 alkyl, phenyl, substituted phenyl, C_2-C_4-alkenyl, trifluoromethyl, amino, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-C_1-C_4-alkyl, halogen or 4 to 6-membered heterocycloalkyl. In certain embodiments of the compounds of Formula I, R_1 is selected from the groups set forth in the table below:

Methyl	Ethyl	Isopropyl		NH_2
Butyl	t-Butyl	Propyl		
Benzyl	Vinyl	Allyl		
CF_3				
			F	

In certain embodiments of the compounds of Formula I, R_1 is selected from the groups set forth in the table below:



In certain embodiments of the compounds of the invention, R_2 is hydrogen.

In certain embodiments of the compounds of the invention, R_3 is hydrogen or methyl.

In certain embodiments of the compounds of the invention, R_4 is hydrogen or hydroxyl.

In certain embodiments of the compounds of the invention, R_5 is hydrogen.

In certain embodiments of the compounds of the invention, R_6 is hydrogen.

In certain embodiments of the compounds of the invention, R_7 is hydrogen.

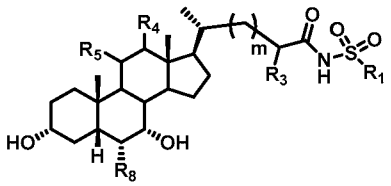
In certain embodiments of the compounds of the invention, R_8 is ethyl.

In certain embodiments of the compounds of the invention, m is 0, 1 or 2.

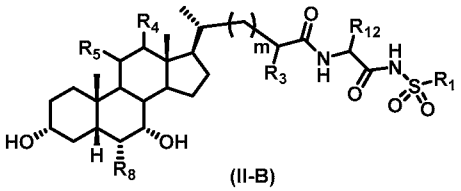
In certain embodiments of the compounds of the invention, R_2 is hydrogen; R_3 is hydrogen or methyl; R_4 is hydroxyl; R_5, R_6 and R_7 are hydrogen; R_8 is ethyl; and m is 0, 1 or 2.

In embodiments of the compounds of the invention wherein R_2 is hydrogen, this position 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+}.

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



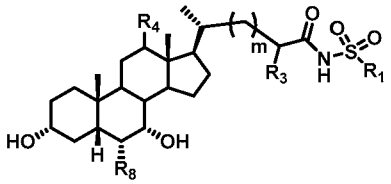
(II-A)



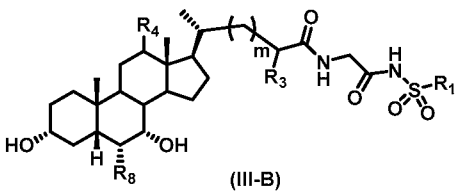
(II-B)

wherein, R_1, R_3, R_4, R_5, R_8, R_{12} 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:



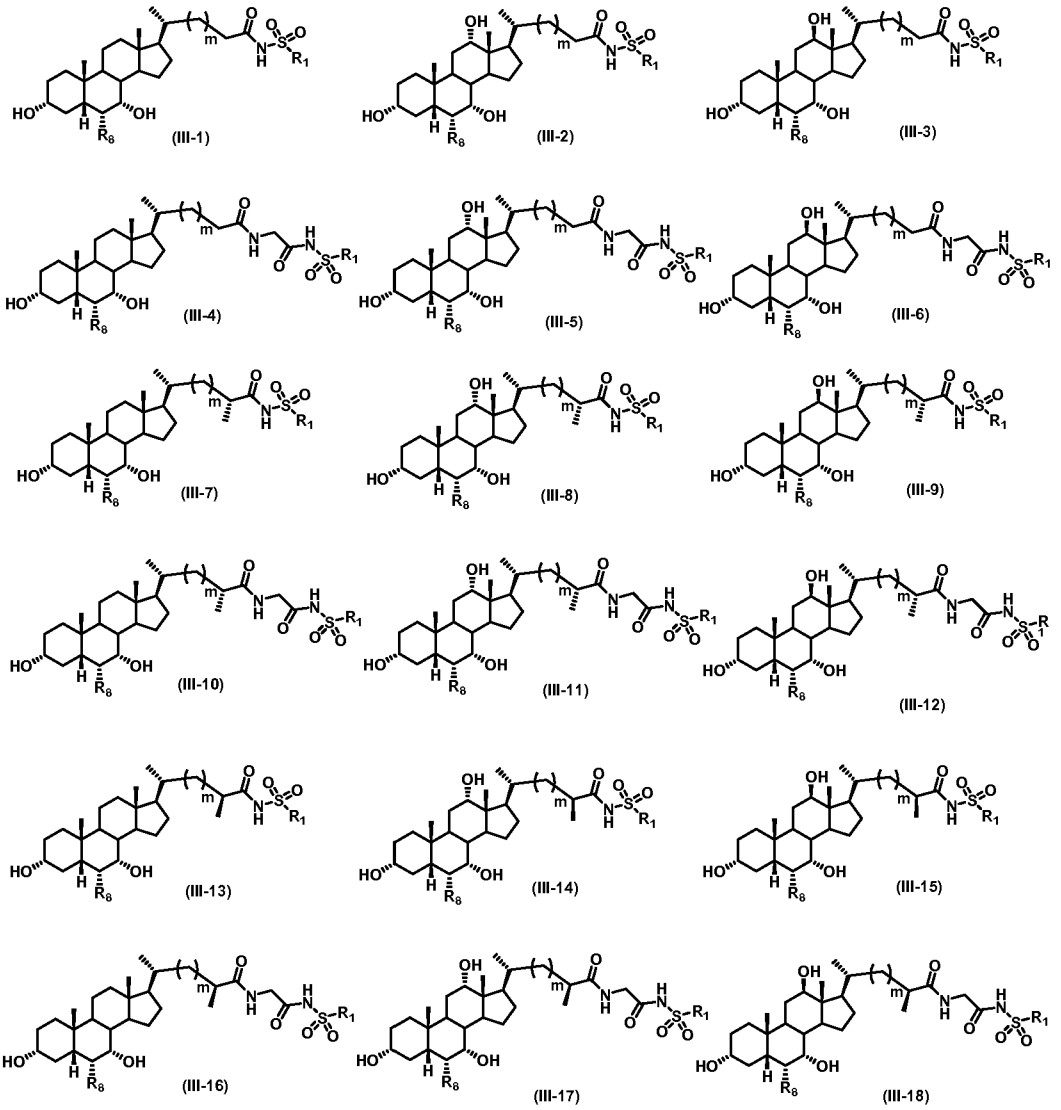
(III-A)



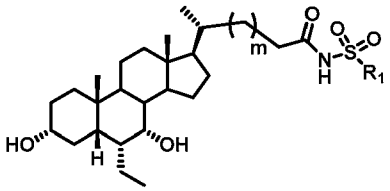
(III-B)

wherein, R_1, R_3, R_4, R_8,and m are as previously defined.

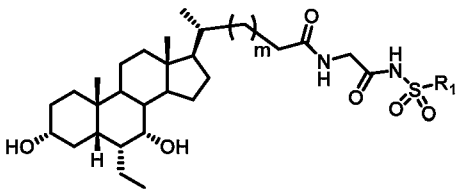
Illustrative structures of formula (III-A) and formula (III-B) can be represented by, but are not limited to, formulas (III-1)-(III-18), where R_1, R_8 and m are as previously defined:



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,



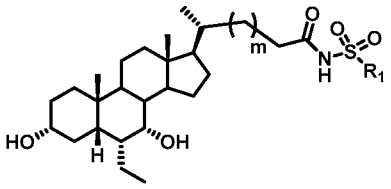
(IV-A)



(IV-B)

wherein R_1 and m are as previously defined.

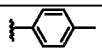
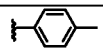
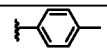
Representative compounds of the invention include, but are not limited to, the following compounds (example 1 to example 75 in Table 1) according to Formula IV-A, wherein, R_1 and m are delineated for each example in Table 1.



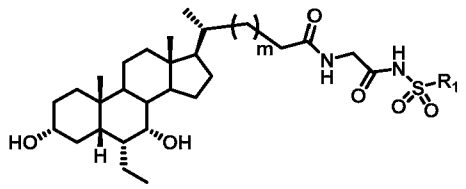
(IV-A)

Table 1

Example	m	R_1	Example	m	R_1	Example	m	R_1
1	0	Methyl	26	1	Methyl	51	2	Methyl
2	0	Ethyl	27	1	Ethyl	52	2	Ethyl
3	0	Isopropyl	28	1	Isopropyl	53	2	Isopropyl
4	0	Butyl	29	1	Butyl	54	2	Butyl
5	0	t-Butyl	30	1	t-Butyl	55	2	t-Butyl
6	0	Propyl	31	1	Propyl	56	2	Propyl
7	0	Benzyl	32	1	Benzyl	57	2	Benzyl
8	0	Vinyl	33	1	Vinyl	58	2	Vinyl
9	0	Allyl	34	1	Allyl	59	2	Allyl
10	0	CF_3	35	1	CF_3	60	2	CF_3
11	0		36	1		61	2	
12	0		37	1		62	2	
13	0		38	1		63	2	
14	0		39	1		64	2	
15	0		40	1		65	2	

16	0		41	1		66	2	
17	0	NH_2	42	1	NH_2	67	2	NH_2
18	0		43	1		68	2	
19	0		44	1		69	2	
20	0		45	1		70	2	
21	0		46	1		71	2	
22	0		47	1		72	2	
23	0		48	1		73	2	
24	0		49	1		74	2	
25	0	F	50	1	F	75	2	F

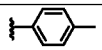
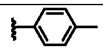
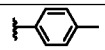
Representative compounds of the invention include, but are not limited to, the following compounds (example 76 to example 150 in Table 2) according to Formula IV-B, wherein R_1 and m are delineated for each example in Table 2.



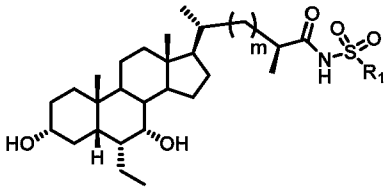
(IV-B)

Table 2

Example	m	R_1	Example	m	R_1	Example	m	R_1
76	0	Methyl	101	1	Methyl	126	2	Methyl
77	0	Ethyl	102	1	Ethyl	127	2	Ethyl
78	0	Isopropyl	103	1	Isopropyl	128	2	Isopropyl
79	0	Butyl	104	1	Butyl	129	2	Butyl
80	0	t-Butyl	105	1	t-Butyl	130	2	t-Butyl
81	0	Propyl	106	1	Propyl	131	2	Propyl
82	0	Benzyl	107	1	Benzyl	132	2	Benzyl
83	0	Vinyl	108	1	Vinyl	133	2	Vinyl

84	0	Allyl	109	1	Allyl	134	2	Allyl
85	0	CF_3	110	1	CF_3	135	2	CF_3
86	0		111	1		136	2	
87	0		112	1		137	2	
88	0		113	1		138	2	
89	0		114	1		139	2	
90	0		115	1		140	2	
91	0		116	1		141	2	
92	0	NH_2	117	1	NH_2	142	2	NH_2
93	0		118	1		143	2	
94	0		119	1		144	2	
95	0		120	1		145	2	
96	0		121	1		146	2	
97	0		122	1		147	2	
98	0		123	1		148	2	
99	0		124	1		149	2	
100	0	F	125	1	F	150	2	F

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:

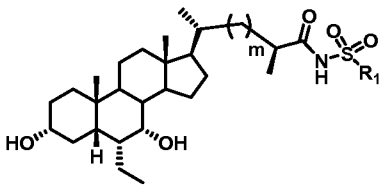


(V-A)

(V-B)

wherein R_1 and m are as previously defined.

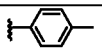
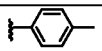
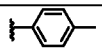
Representative compounds of the invention include, but are not limited to, the following compounds (example 151 to example 225 in Table 3) according to Formula V-A, wherein R_1 and m are delineated for each example in Table 3.



(V-A)

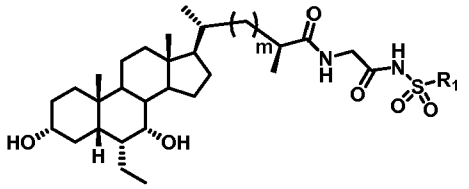
Table 3

Example	m	R_1	Example	m	R_1	Example	m	R_1
151	0	Methyl	176	1	Methyl	201	2	Methyl
152	0	Ethyl	177	1	Ethyl	202	2	Ethyl
153	0	Isopropyl	178	1	Isopropyl	203	2	Isopropyl
154	0	Butyl	179	1	Butyl	204	2	Butyl
155	0	t-Butyl	180	1	t-Butyl	205	2	t-Butyl
156	0	Propyl	181	1	Propyl	206	2	Propyl
157	0	Benzyl	182	1	Benzyl	207	2	Benzyl
158	0	Vinyl	183	1	Vinyl	208	2	Vinyl
159	0	Allyl	184	1	Allyl	209	2	Allyl
160	0	CF_3	185	1	CF_3	210	2	CF_3
161	0		186	1		211	2	
162	0		187	1		212	2	
163	0		188	1		213	2	
164	0		189	1		214	2	
165	0		190	1		215	2	
166	0		191	1		216	2	
167	0	NH_2	192	1	NH_2	217	2	NH_2
168	0		193	1		218	2	
169	0		194	1		219	2	
170	0		195	1		220	2	

171	0		196	1		221	2	
172	0		197	1		222	2	
173	0		198	1		223	2	
174	0		199	1		224	2	
175	0	F	200	1	F	225	2	F

Representative compounds of the invention include, but are not limited to, the following compounds (example 226 to example 300 in Table 4) according to Formula V-B, wherein, $R_1$and m are delineated for each example in Table 4.

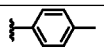
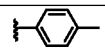
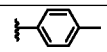
5



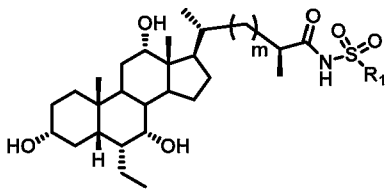
(V-B)

Table 4

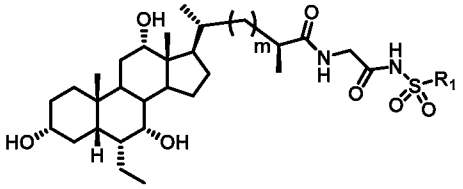
Example	m	R_1	Example	m	R_1	Example	m	R_1
226	0	Methyl	251	1	Methyl	276	2	Methyl
227	0	Ethyl	252	1	Ethyl	277	2	Ethyl
228	0	Isopropyl	253	1	Isopropyl	278	2	Isopropyl
229	0	Butyl	254	1	Butyl	279	2	Butyl
230	0	t-Butyl	255	1	t-Butyl	280	2	t-Butyl
231	0	Propyl	256	1	Propyl	281	2	Propyl
232	0	Benzyl	257	1	Benzyl	282	2	Benzyl
233	0	Vinyl	258	1	Vinyl	283	2	Vinyl
234	0	Allyl	259	1	Allyl	284	2	Allyl
235	0	CF_3	260	1	CF_3	285	2	CF_3
236	0		261	1		286	2	
237	0		262	1		287	2	
238	0		263	1		288	2	
239	0		264	1		289	2	

240	0		265	1		290	2	
241	0		266	1		291	2	
242	0	NH_2	267	1	NH_2	292	2	NH_2
243	0		268	1		293	2	
244	0		269	1		294	2	
245	0		270	1		295	2	
246	0		271	1		296	2	
247	0		272	1		297	2	
248	0		273	1		298	2	
249	0		274	1		299	2	
250	0	F	275	1	F	300	2	F

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:



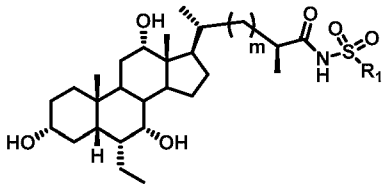
(VI-A)



(VI-B)

wherein R_1 and m are as previously defined.

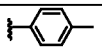
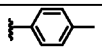
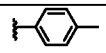
Representative compounds of the invention include, but are not limited to, the following compounds (example 301 to example 375 in Table 5) according to Formula VI-A, wherein, R_1 and m are delineated for each example in Table 5.



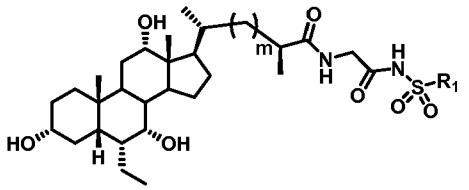
(VI-A)

Table 5

Example	m	R_1	Example	m	R_1	Example	m	R_1
301	0	Methyl	326	1	Methyl	351	2	Methyl
302	0	Ethyl	327	1	Ethyl	352	2	Ethyl
303	0	Isopropyl	328	1	Isopropyl	353	2	Isopropyl
304	0	Butyl	329	1	Butyl	354	2	Butyl
305	0	t-Butyl	330	1	t-Butyl	355	2	t-Butyl
306	0	Propyl	331	1	Propyl	356	2	Propyl
307	0	Benzyl	332	1	Benzyl	357	2	Benzyl
308	0	Vinyl	333	1	Vinyl	358	2	Vinyl
309	0	Allyl	334	1	Allyl	359	2	Allyl
310	0	CF_3	335	1	CF_3	360	2	CF_3
311	0		336	1		361	2	
312	0		337	1		362	2	
313	0		338	1		363	2	
314	0		339	1		364	2	
315	0		340	1		365	2	
316	0		341	1		366	2	
317	0	NH_2	342	1	NH_2	367	2	NH_2
318	0		343	1		368	2	
319	0		344	1		369	2	
320	0		345	1		370	2	
321	0		346	1		371	2	
322	0		347	1		372	2	

323	0		348	1		373	2	
324	0		349	1		374	2	
325	0	F	350	1	F	375	2	F

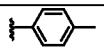
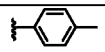
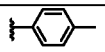
Representative compounds of the invention include, but are not limited to, the following compounds (example 376 to example 450 in Table 6) according to Formula VI-B, wherein R_1 and m are delineated for each example in Table 6.



(VI-B)

Table 6

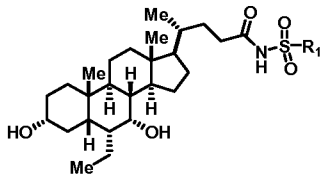
Example	m	R_1	Example	m	R_1	Example	m	R_1
376	0	Methyl	401	1	Methyl	426	2	Methyl
377	0	Ethyl	402	1	Ethyl	427	2	Ethyl
378	0	Isopropyl	403	1	Isopropyl	428	2	Isopropyl
379	0	Butyl	404	1	Butyl	429	2	Butyl
380	0	t-Butyl	405	1	t-Butyl	430	2	t-Butyl
381	0	Propyl	406	1	Propyl	431	2	Propyl
382	0	Benzyl	407	1	Benzyl	432	2	Benzyl
383	0	Vinyl	408	1	Vinyl	433	2	Vinyl
384	0	Allyl	409	1	Allyl	434	2	Allyl
385	0	CF_3	410	1	CF_3	435	2	CF_3
386	0		411	1		436	2	
387	0		412	1		437	2	
388	0		413	1		438	2	
389	0		414	1		439	2	
390	0		415	1		440	2	
391	0		416	1		441	2	

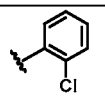
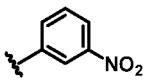
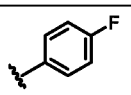
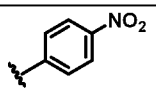
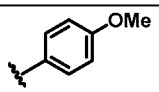
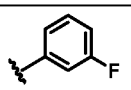
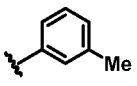
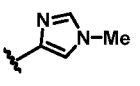
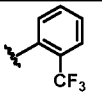
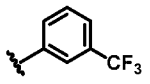
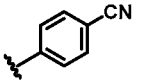
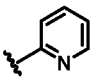
392	0	NH_2	417	1	NH_2	442	2	NH_2
393	0		418	1		443	2	
394	0		419	1		444	2	
395	0		420	1		445	2	
396	0		421	1		446	2	
397	0		422	1		447	2	
398	0		423	1		448	2	
399	0		424	1		449	2	
400	0	F	425	1	F	450	2	F

Representative compounds of the invention include, but are not limited to, the following compounds (example 451 to example 492) delineated in Table 7 and Table 8.

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Table 7: Compounds 451-484



Example	R_1	Example	R_1	Example	R_1
451		452		453	
454		455		456	
457		458		459	
460		461		462	

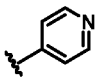
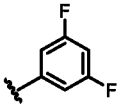
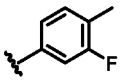
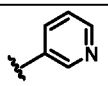
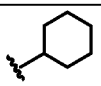
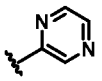
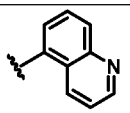
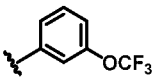
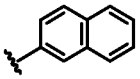
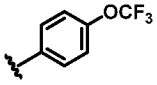
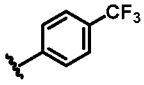
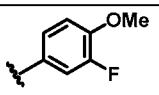
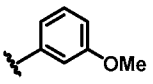
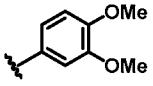
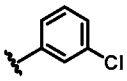
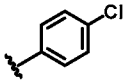
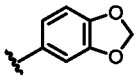
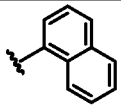
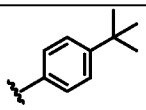
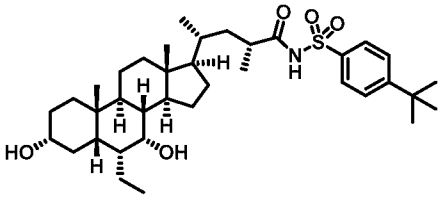
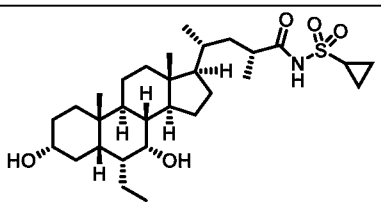
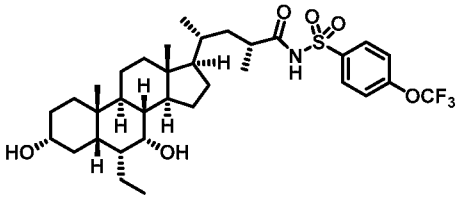
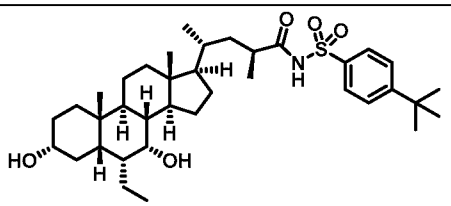
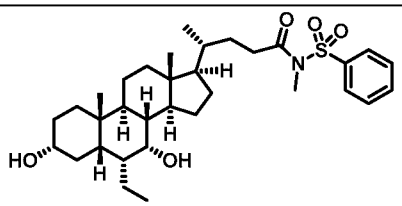
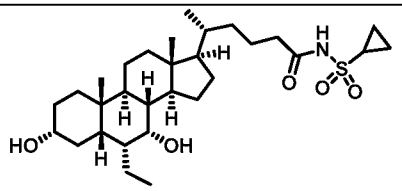
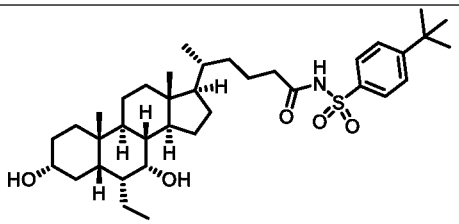
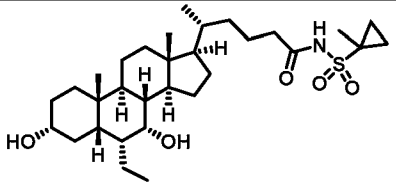
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484					

Table 8: Compounds 485-492

Example	Structure
485	
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In certain embodiments, the present invention provides a method for the prevention or treatment of an FXR mediated disease or condition. The method comprises administering a therapeutically effective amount of a compound of formula (I). The present invention also provides the use of a compound of formula (I) for the preparation of a medicament for the prevention or treatment of an FXR mediated disease or condition.

In certain embodiments, the FXR-mediated disease or condition is cardiovascular disease, atherosclerosis, arteriosclerosis, hypercholesteremia, or hyperlipidemia chronic liver disease, gastrointestinal disease, renal disease, metabolic disease, cancer (i.e., colorectal cancer), or neurological indications such as stroke.

In certain embodiments, the chronic liver disease is primary biliary cirrhosis (PBC), cerebrotendinous xanthomatosis (CTX), primary sclerosing cholangitis (PSC),

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

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

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

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

In 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 invention provides for the use, wherein 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 invention provides for the use, wherein 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 invention provides for the use, wherein 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 invention provides for the use, wherein the disease is kidney disease selected from diabetic nephropathy, chronic renal failure, hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant giomerulopathy, chronic interstitial nephritis, and polysystic kidney disease. The invention includes a method of treating or preventing kidney diease selected from diabetic nephropathy, chronic renal failure, hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, and polysystic kidney disease.

In one aspect, the invention provides for the use, wherein the disease is cancer selected from colorectal cancer, liver cancer, heptacellular carcinoma, cholangio carcinoma, renal cancer, gastric cancer, pancreatic cancer, prostate cancer, and insulanoma. The invention includes a method of treating or preventing cancer selected from colorectal cancer, liver cancer, heptacellular carcinoma, cholangio carcinoma, renal cancer, gastric cancer, pancreatic cancer, prostate cancer, and insulanoma.

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 hydrocarbongroup. Preferred alkyl radicals include C_1-C_6 alkyl and C_1-C_8 alkyl radicals. Examples of C_1-C_6 alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, n-hexyl groups; and examples of C_1-C_8 alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, n-hexyl, heptyl, and octyl groups.

The term "alkenyl", as used herein, denote a monovalent group derived from a hydrocarbon moiety by the removal of a single hydrogen atom wherein the hydrocarbon moiety has at least one carbon-carbon double bond. Preferred alkenyl groups include C_2-C_6 alkenyl and C_2-C_8 alkenyl groups. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

The term "alkynyl", as used herein, denotes a monovalent group derived from a hydrocarbon moiety by the removal of a single hydrogen atom wherein the hydrocarbon moiety has at least one carbon-carbon triple bond. Preferred alkynyl groups include C_2-C_6 alkynyl and C_2-C_8 alkynyl groups. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butynyl, heptynyl, octynyl and the like.

The term "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 C_4-C_6 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 C_3-C_8 cycloalkyl and C_3-C_{12} cycloalkyl groups. Examples of C_3-C_8-cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and

examples of C_3-C_{12}-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, 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 C_3-C_8 cycloalkenyl and C_3-C_{12} cycloalkenyl groups. Examples of C_3-C_8-cycloalkenyl include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C_3-C_{12}-cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like.

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

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

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

The term “heteroarylalkyl,” as used herein, refers to a C_1–C_3 alkyl or C_1–C_6 alkyl residue 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, -NO_2, -CN, -NH_2, N_3, protected amino, alkoxy, thioalkoxy, oxo, -halo- C_1-C_{12}-alkyl, -halo- C_2-C_{12}-alkenyl, -halo- C_2-C_{12}-alkynyl, -halo-C_3-C_{12}-cycloalkyl, -NH -C_1-C_{12}-alkyl, -NH -C_2-C_{12}-alkenyl, -NH -C_2-C_{12}-alkynyl, -NH -C_3-C_{12}-cycloalkyl, -NH -aryl, -NH -

heteroaryl, -NH -heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C_1-C_{12}-alkyl, -O-C_2-C_{12}-alkenyl, -O-C_2-C_{12}-alkynyl, -O-C_3-C_{12}-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)- C_1-C_{12}-alkyl, -C(O)- C_2-C_{12}-alkenyl, -C(O)- C_2-C_{12}-alkynyl, -C(O)-C_3-C_{12}-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -$CONH_2$, -CONH- C_1-C_{12}-alkyl, -CONH- C_2-C_{12}-alkenyl, -CONH-C_2-C_{12}-alkynyl, -CONH-C_3-C_{12}-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO_2- C_1-C_{12}-alkyl, -OCO_2- C_2-C_{12}-alkenyl, -OCO_2- C_2-C_{12}-alkynyl, -OCO_2-C_3-C_{12}-cycloalkyl, -OCO_2-aryl, -OCO_2-heteroaryl, -OCO_2-heterocycloalkyl, -$OCONH_2$, -OCONH- C_1-C_{12}-alkyl, -OCONH- C_2-C_{12}-alkenyl, -OCONH- C_2-C_{12}-alkynyl, -OCONH- C_3-C_{12}-cycloalkyl, -OCONH- aryl, -OCONH-heteroaryl, -OCONH- heterocycloalkyl, -NHC(O)- C_1-C_{12}-alkyl, -NHC(O)-C_2-C_{12}-alkenyl, -NHC(O)-C_2-C_{12}-alkynyl, -NHC(O)-C_3-C_{12}-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -$NHCO_2$- C_1-C_{12}-alkyl, -$NHCO_2$-C_2-C_{12}-alkenyl, -$NHCO_2$- C_2-C_{12}-alkynyl, -$NHCO_2$- C_3-C_{12}-cycloalkyl, -$NHCO_2$-aryl, -$NHCO_2$- heteroaryl, -$NHCO_2$- heterocycloalkyl, -$NHC(O)NH_2$, -NHC(O)NH-C_1-C_{12}-alkyl, -NHC(O)NH-C_2-C_{12}-alkenyl, -NHC(O)NH-C_2-C_{12}-alkynyl, -NHC(O)NH-C_3-C_{12}-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, $NHC(S)NH_2$, -NHC(S)NH- C_1-C_{12}-alkyl, -NHC(S)NH-C_2-C_{12}-alkenyl, -NHC(S)NH-C_2-C_{12}-alkynyl, -NHC(S)NH-C_3-C_{12}-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -$NHC(NH)NH_2$, -NHC(NH)NH- C_1-C_{12}-alkyl, -NHC(NH)NH-C_2-C_{12}-alkenyl, -NHC(NH)NH-C_2-C_{12}-alkynyl, -NHC(NH)NH-C_3-C_{12}-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C_1-C_{12}-alkyl, -NHC(NH)-C_2-C_{12}-alkenyl, -NHC(NH)-C_2-C_{12}-alkynyl, -NHC(NH)-C_3-C_{12}-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C_1-C_{12}-alkyl, -C(NH)NH-C_2-C_{12}-alkenyl, -C(NH)NH-C_2-C_{12}-alkynyl, -C(NH)NH-C_3-C_{12}-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C_1-C_{12}-alkyl, - S(O)-C_2-C_{12}-alkenyl, - S(O)-C_2-C_{12}-alkynyl, - S(O)-C_3-C_{12}-cycloalkyl, - S(O)-aryl, - S(O)-heteroaryl, - S(O)-heterocycloalkyl - SO_2NH_2, -SO_2NH- C_1-C_{12}-alkyl, -SO_2NH- C_2-C_{12}-alkenyl, -SO_2NH- C_2-C_{12}-alkynyl, -SO_2NH- C_3-C_{12}-cycloalkyl, -SO_2NH- aryl, -SO_2NH- heteroaryl, -SO_2NH-heterocycloalkyl, -$NHSO_2$-C_1-C_{12}-alkyl, -$NHSO_2$-C_2-C_{12}-alkenyl, - $NHSO_2$-C_2-C_{12}-alkynyl, -$NHSO_2$-C_3-C_{12}-cycloalkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -$NHSO_2$-heterocycloalkyl, -CH_2NH_2, -$CH_2SO_2CH_3$, -aryl, -arylalkyl, -heteroaryl, -

heteroarylalkyl, -heterocycloalkyl, -C_3-C_{12}-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C_1-C_{12}-alkyl, -S-C_2-C_{12}-alkenyl, -S-C_2-C_{12}-alkynyl, -S-C_3-C_{12}-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, methylthiomethyl, or –L'–R', wherein L' is C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, and R' is aryl, heteroaryl, heterocyclic, C_3-C_{12}cycloalkyl or C_3-C_{12}cycloalkenyl. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted. In some cases, each substituent in a substituted moiety is additionally optionally substituted with one or more groups, each group being independently selected from -F, -Cl, -Br, -I, -OH, -NO_2, -CN, or -NH_2.

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

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

The term "alicyclic," as used herein, denotes a monovalent group derived from a monocyclic or polycyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl. Such alicyclic groups may be further substituted.

The term "heterocycloalkyl" and "heterocyclic" can be used interchangeably and refer to a non-aromatic 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 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.

It will be apparent that in various embodiments of the invention, the substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, arylalkyl, heteroarylalkyl, and heterocycloalkyl are intended to be monovalent or divalent. Thus, alkylene, alkenylene, and alkynylene, cycloaklylene, cycloalkenylene, cycloalkynylene, arylalkylene, hetoerarylalkylene and heterocycloalkylene groups are to be included in the 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*-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 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 as described herein may be selectively removed. Hydroxy protecting groups as known in the are described generally in T.H. Greene and P.G., S. 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-methoxybenzyldiphenylmethyl, 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 -C(O)CH_3), benzoyl (Bz or -C(O)C_6H_5), and trimethylsilyl (TMS or-Si$(CH_3)_3$).

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

The compounds described herein may 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 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 free base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts e.g., salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

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

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

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound, which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to afford any compound delineated by the formulae of the instant invention. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed.), *Methods in Enzymology*, Vol. 4, Academic Press (1985); Krogsgaard-Larsen, *et al.*, (ed.). "Design and Application of Prodrugs, *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991); Bundgaard, *et al.*, *Journal of Drug Deliver Reviews, 8*:1-38(1992);

Bundgaard, J. of *Pharmaceutical Sciences, 77*:285 et seq. (1988); Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, *American Chemical Society* (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

The term "treating", as used herein, means relieving, lessening, reducing, eliminating, modulating, or ameliorating, i.e. causing regression of the disease state or condition. Treating can also include inhibiting, i.e., arresting the development, of 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 compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

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

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

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are

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

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

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

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

purposes of illustration only and variation of the reaction conditions can produce the desired 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

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants

can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

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

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

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils

are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

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

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

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

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar,

calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

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

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

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

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

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

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

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

Abbreviations

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

ACN for acetonitrile;

BME for 2-mercaptoethanol;

BOP for benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate;

BzCl for benzoyl chloride

CDI for carbonyldiimidazole;

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)- aminohexyl-1-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite;

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

DCC for N, N'-dicyclohexylcarbodiimide;

DCM for dichloromethane;

DIAD for diisopropyl azodicarboxylate;

DIBAL-H for diisobutylaluminum hydride;

DIPEA for diisopropyl ethylamine;

DMAP for N,N-dimethylaminopyridine;

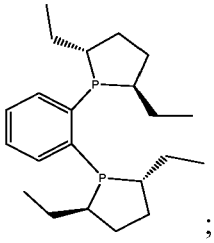
DME for ethylene glycol dimethyl ether;

DMEM for Dulbecco's Modified Eagles Media;

DMF for N,N-dimethyl formamide;

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;

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;

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;

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;

TEA for triethyl amine;

Tf_2O for trifluoromethanesulfonic anhydride;

TFA for trifluoroacetic acid;

THF for tetrahydrofuran;

TLC for thin layer chromatography;

$(TMS)_2NH$ for hexamethyldisilazane;

TMSOTf for trimethylsilyl trifluoromethanesulfonate;

TBS for t-Butyldimethylsilyl;

TMS for trimethylsilyl;

TPAP tetrapropylammonium perruthenate;

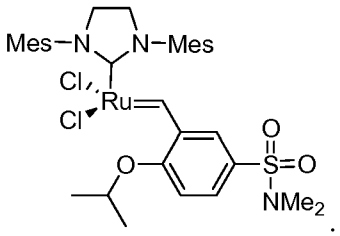
TPP or PPh_3 for triphenylphosphine;

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

Zhan 1 B for 

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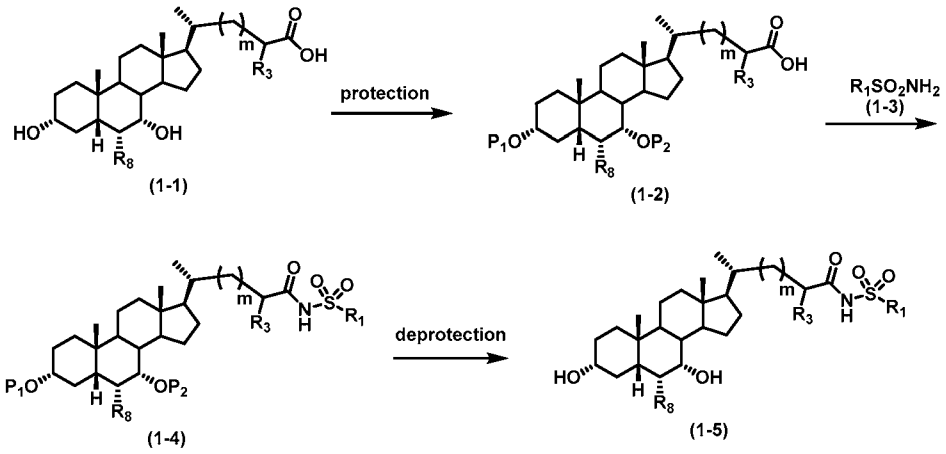
Synthetic Methods

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 (1-5) are prepared from the compound of formula (1-1), wherein R_1, R_3, m and R_8 are defined as previously, P_1 and P_2 are hydroxyl protecting group. Thus, the two

hydroxyl groups of the compound of formula (1-1) are protected with P1 and P2 groups. P1 and P2 can be same or different. P1 and P2 can be any hydroxyl protecting group such as, but not limited to Ac, chloroacetyl, TMS, TBS. 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. Then the hydroxyl protected compound of formula (1-2) is coupled with sulfonamide compound of formula (1-3) using suitable coupling condition to give the compound of formula (1-4). 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 1

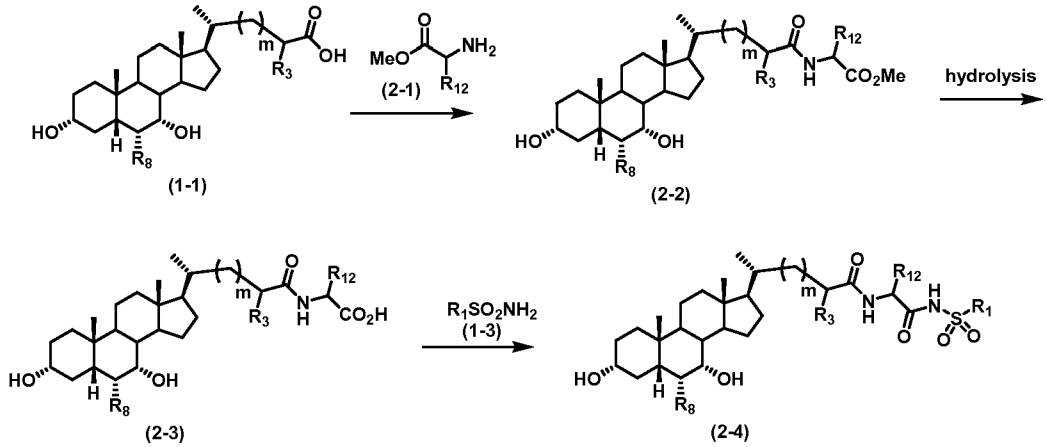


Deprotection of hydroxyl protecting groups of P1 and P2 of compound of formula (1-4) to give the compound of formula (1-5). A more detailed discussion of the procedures, reagents and conditions for deprotection of hydroxyl protecting group is described in literature, for example, by T.W. Greene and P.G.M. Wuts in *"Protective Groups in Organic Synthesis"* 3rd ed., John Wiley & Son, Inc., 1999.

The compound of formula (1-5) can also be prepared by direct coupling compound of formula (1-1) with sulfonamide compound of formula (1-3) without protection of hydroxyl group in suitable coupling condition.

Scheme 2 illustrates the preparation of the compound of formula (2-4) from the compound of formula (1-1), wherein R_1, R_3, m, R_{12} and R_8 are defined as previously. Thus, the compound of formula (1-1) is coupled with a 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, 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. 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 (1-3) affords the compound of formula (2-4).

Scheme 2

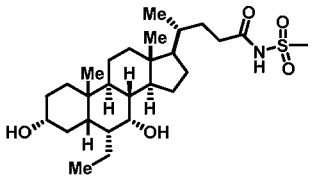


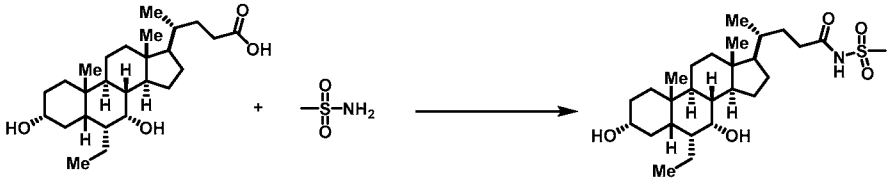
Examples

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

invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Example 1:





6(α)-ethyl-chenodeoxycholic acid (6-ECDCA) (63 mg, 0.15 mmol) was dissolved in DCM (2 mL). To the solution was added methanesulfonamide (3.0 eq, 0.45 mmol), DMAP (2.0 eq, 0.3 mmol, 37 mg) and EDCI (2.0 eq, 0.3 mmol, 58 mg). The mixture was stirred at room temperature for 2 h (Monitoring by TLC and LC/MS indicated the reaction was complete). The mixture was quenched with water and extracted with DCM (2 ×). The combined organic layers were washed with 1M HCl, sat. NaCl, dried over Na_2SO_4, and then concentrated *in vacuo*. Purification of the residue on SiO_2 column (12 g) with 0-50% acetone in hexane provided desired acylsulfonamide product example 1 as a white solid (27 mg).

The examples from example 2 to example 7, example 9 to example 12, example 14, example 16 to example 25, and from example 451 to example 484 were prepared using the same procedure as the one used in example 1 preparation. The MS data and 1H NMR data are delineated in Table 9.

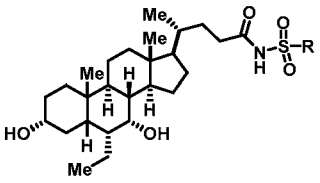
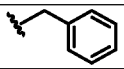
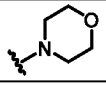
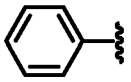
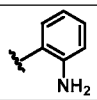
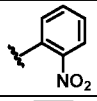
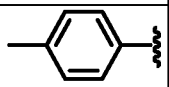
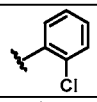
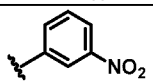
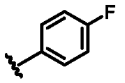
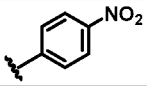
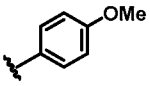
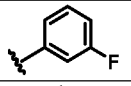
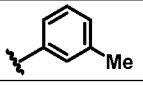
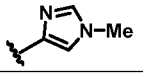
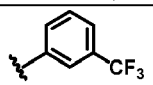
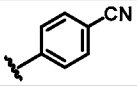
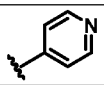
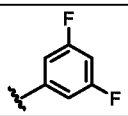
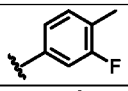
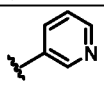
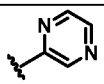
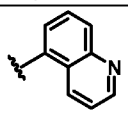
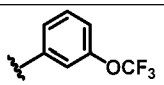
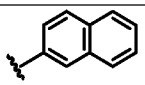
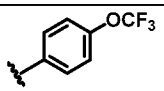
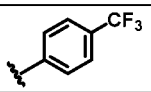
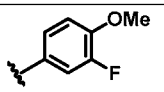
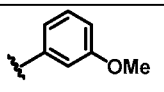
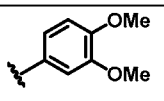
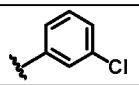
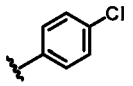
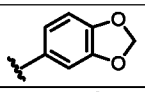
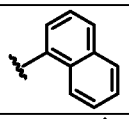
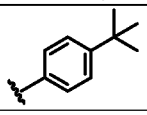


Table 9

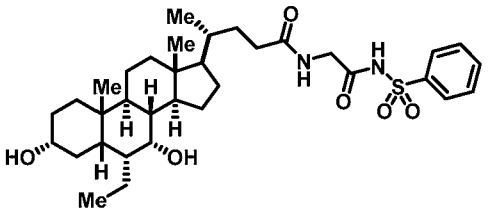
Example	R	yield	MS data (M-1)	^{1}H NMR (500MHz)
1	Me	36%	496.22	($CDCl_3$) 8.11 (1H, br s), 3.70 (1H, s), 3.40 (1H, br s), 3.30 (3H, s), 2.40 (1H, m), 2.25 (1H, m), 0.94 (3H, d, J = 6.5 Hz), 0.89 (3H, s), 0.66 (3H, s).
2	Et	34%	510.23	($CDCl_3$) 7.62 (1H, br s), 3.70 (1H, s), 3.47 (2H, q, J = 7.0 Hz), 3.40 (1H, br s), 2.40 (1H, m), 2.25 (1H, m), 0.94 (3H, d, J = 6.5 Hz), 0.90 (3H, s), 0.66 (3H, s).
3	*i*-Pr	33%	524.24	($CDCl_3$) 7.60 (1H, br s), 3.81 (1H, m), 3.70 (1H, s), 3.41 (1H, br s), 2.40 (1H, m), 2.25 (1H, m), 1.43 (6H, d, J = 6.5 Hz), 0.94 (3H, d, J = 6.5 Hz), 0.89 (3H, s), 0.66 (3H, s).
4			538.29	
5			538.30	
6	*n*-Pr	32%	524.24	($CDCl_3$) 7.85 (1H, br s), 3.70 (1H, s), 3.42 (3H, m), 2.38 (1H, m), 2.22 (1H, m), 1.08 (3H, t, J = 7.0 Hz), 0.94 (3H, d, J = 6.5 Hz), 0.90 (3H, s), 0.66 (3H, s).
7			572.35	
9			522.23	
10	CF_3	75%	550.19	(CD_3OD) 3.65 (1H, s), 2.62 (1H, s), 2.34 (1H, m), 2.18 (1H, m), 0.95 (3H, d, J = 6.0 Hz), 0.91 (3H, s), 0.90 (3H, t, J = 6.0 Hz), 0.69 (3H, s).
11		26%	522.23	($CDCl_3$) 7.63 (1H, br s), 3.70 (1H, s), 3.42 (1H, br s), 2.95 (1H, m), 2.40 (1H, m), 2.25 (1H, m), 0.94 (3H, d, J = 6.5 Hz), 0.89 (3H, s), 0.66 (3H, s).
12			536.27	
14			521.28	
16			567.35	

17			497.24	
18		60%	558.23	($CDCl_3$) 8.07 (2H, d, *J* = 7.0 Hz), 7.95 (1H, br s), 7.65 (1H, t, *J* = 7.0 Hz), 7.55 (2H, d, *J* = 7.0 Hz), 3.69 (1H, s), 3.41 (1H, br s), 2.28 (1H, m), 2.15 (1H, m), 0.88 (3H, s), 0.85 (3H, d, *J* = 6.5 Hz), 0.60 (3H, s).
19			573.30	
20			572.40	
22			576.32	
23			603.24	
24		65%	572.25	
25	F	39%	500.19	(DMSO-d6) 3.48 (1H, s), 3.10 (1H, br s), 2.09 (1H, m), 1.90 (1H, m), 0.84 (3H, d, *J* = 6.0 Hz), 0.81 (3H, s), 0.80 (3H, m), 0.58 (3H, s).
451			592.25	
452			603.32	
453			576.21	
454			603.23	
455			588.26	
456			576.25	
457			572.29	
458			608.26 (M+HCOOH-1)	
459			626.24	
460			626.24	

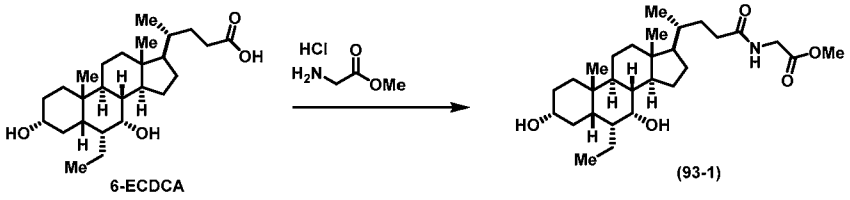
461			583.25	
462			559.25	
463			559.25	
464			594.23	
465			590.26	
466			559.25	
467			564.22	
468			564.31	
469			560.24	
470			609.26	
471			642.24	
472			608.28	
473			642.23	
474			565.21	
475			626.24	
476			606.26	
477			588.26	
478			618.26	

479			592.20	
480			592.21	
481			602.24	
482			550.30	
483			608.28	
484			614.32	

Example 93:

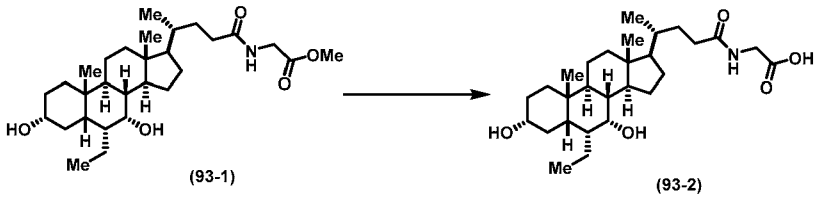


Step 93a:



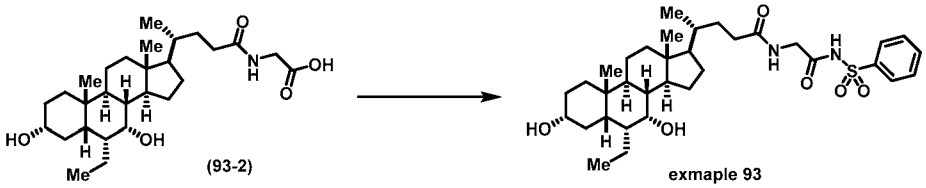
6(α)-ethyl-chenodeoxycholic acid (6-ECDCA) (300 mg, 0.71 mmol) and glycine methyl ester hydrochloride (224 mg, 1.79 mmol) were dissolved in DCM (4 mL) and DMF (1 mL). To the solution was added Et_3N (0.3 mL, 2.13 mmol), DMAP (17 mg, 0.14 mmol) and EDCI (272 mg, 1.42 mmol) sequentially. The resulting mixture was stirred at room temperature for 3 h, quenched with water, and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with 1 M HCl (10 mL), sat. $NaHCO_3$ (10 mL), saturated NaCl, and dried over Na_2SO_4. Concentration *in vacuo* provided amide compound (93-1) (305 mg). ^{1}HNMR (500MHz, $CDCl_3$) 5.96 (1H, br s), 4.05 (2H, s), 3.76 (3H, s), 3.70 (1H, s), 3.40 (1H, br s), 2.31 (1H, m), 2.14 (1H, m), 1.98-1.72 (7H, m), 1.69-1.15 (22H, m), 1.00 (1H, m), 0.94 (3H, d, J = 6.0 Hz), 0.89 (6H, m), 0.65 (3H, s).

Step 10-2:



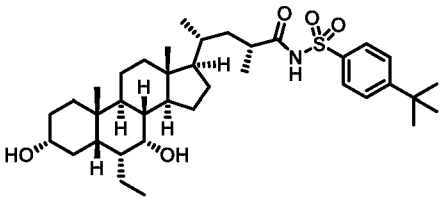
Methyl ester compound (93-1) (305 mg, 0.62 mmol) was dissolved in MeOH (6.2 mL) and aq. NaOH (1 M, 6.2 mL) was added. The mixture was stirred at room temperature for 3 h and MeOH was removed *in vacuo*. The residue wasacidified with aq. HCl (1 M, 10 mL) and extracted with EtOAc (3 x 20 ml). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Compound (93-2) was obtained as a white solid (229 mg). ^{1}HNMR (500MHz, CD_3OD) 3.88 (2H, s), 3.65 (1H, s), 3.30 (1H, s), 2.30 (1H, m), 2.15 (1H, m), 1.95-1.70 (7H, m), 1.62-1.08 (12H, m), 0.98 (3H, d, J = 6.0 Hz), 0.91 (3H, s), 0.90 (3H, m), 0.70 (3H, s). LC/MS observed M-1, 476.25.

Step 93b:

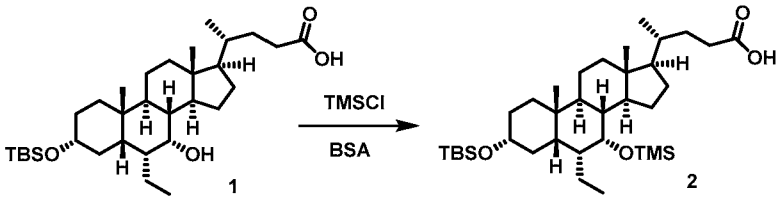


Acid compound (93-2) (101 mg, 0.21 mmol) and benzenesulfonamide (99 mg, 0.63 mmol) were dissolved in THF (2 mL). To the solution was added DMAP (51 mg, 0.42 mmol) and EDCI (81 mg, 0.42 mmol). The mixture was stirred at room temperature for 3 h, quenched with water, and extracted with EtOAc (3 x 20 ml). The combined organic layer was washed with aq. 1M HCl, sat. NaCl, dried over Na_2SO_4, and then concentrated *in vacuo*. Purification of the residue on SiO_2 column with 0-15% MeOH in DCM provided acylsulfonamide product example 93 (13 mg). ^{1}HNMR (500MHz, CD_3OD) 7.95 (2H, d, J = 8.0 Hz), 7.60 (1H, m), 7.51 (2H, m), 3.40 (2H, s), 3.65 (1H, s), 2.26 (1H, m), 2.12 (1H, m), 1.98 (1H, br d), 0.94 (3H, d, J = 6.0 Hz), 0.91 (3H, s), 0.90 (3H, m), 0.67 (3H, s). LC/MS observed M-1, 615.27.

Example 485

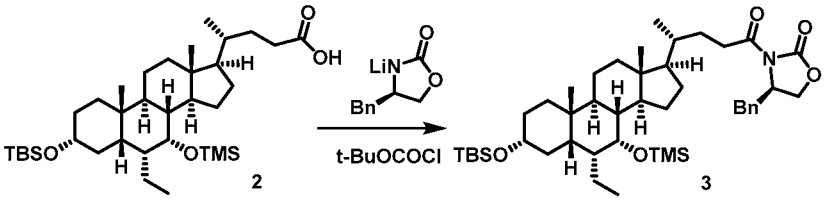


Step 485a:



To a stirred solution of (**1**) (3.2 g, 6.0 mmol) and NMI (1.2 mL, 15.0 mmol) in DCM (80 mL) at 0 °C under N_2 was added BSA (7.3 mL, 30.0 mmol), followed by TMSCl (1.2 mL, 9.0 mmol). The reaction mixture was stirred at 0 °C for 2.5h, then quenched slowly with brine at 0 °C and 5% citric acid, and extracted with EtOAc. The organic layer was washed with brine and concentrated. The residue was purified by chromatography on silica gel using hexane/EtOAc (100/0 to 70/30, 10 min) to give a pure product (**2**) as a white foam (2.3 g, 64% yield) and some impure product.

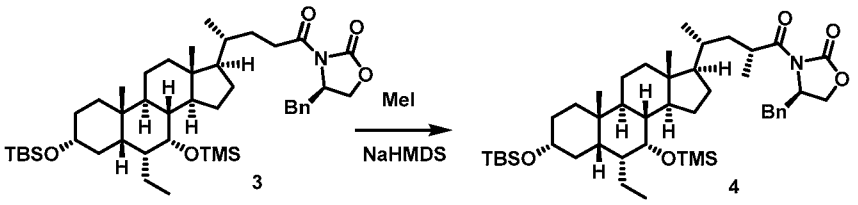
Step 485b:



To a solution of (**2**) (607 mg, 1.0 mmol) and Et_3N (165 µL, 1.2 mmol) in THF (5 mL) at -78 °C under N_2 was added trimethyl acetyl chloride (125 µL, 1.1 mmol). The mixture was stirred at -78 °C for 10 min and then at 0 °C for 30 min, recooled to -78 °C, and a -78 °C solution of lithium oxazolidinone was added. The lithium oxazolidinone was prepared by addition of 2.5 M n-BuLi in hexane (0.4 mL, 1.0 mmol) to a -78 °C solution of (*R*)-4-benzyl-2-oxazolidinone (178 mg, 1.0 mmol) in THF (5 mL). The reaction mixture was allowed to warm up to 0 °C and stirred for another 30 min, then quenched with sat NH_4Cl (30 mL), and concentrated to remove volatiles. The residue was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography on silica gel using hexane/acetone (100/0 to 70/30, 12

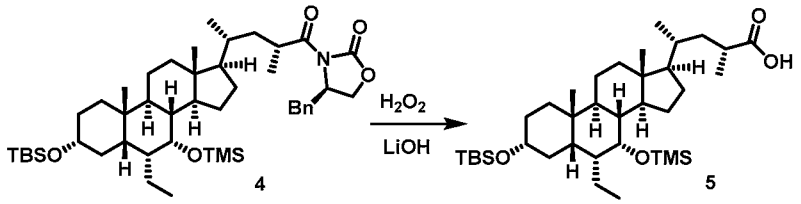
min) to afford a pure product (**3**) as a white foam (544 mg, 71% yield) and some impure product.

Step 485c:



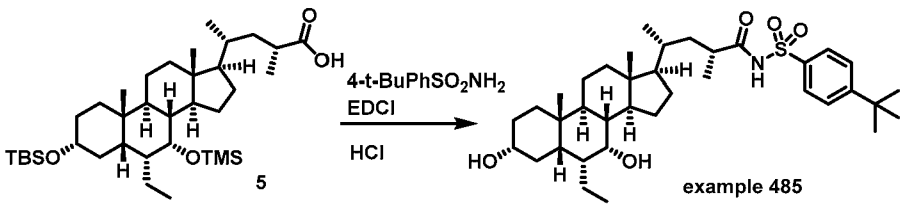
A 0 °C solution of (**3**) (383 mg, 0.5 mmol) in THF (3 mL) was added drop wise to a 1 M solution of NaHMDS in THF (1.25 mL) at -78 °C under N_2. After stirring at -78 °C for 30 min, a -78 °C solution of MeI (156 µL, 2.5 mmol) in THF (1.5 mL) was added. The reaction mixture was stirred at -78 °C for 4h, then quenched with sat NH_4Cl (10 mL), warmed up to RT, and extracted with ethyl acetate. The combined organic layers were washed with 1M sodium bisulfate (10 mL) and brine, and concentrated. The residue was purified by chromatography on silica gel using hexane/EtOAc (100/0 to 75/25, 15 min) to provide a pure product (**4**) as a white foam (220 mg, 56% yield).

Step 485d:



To a stirred solution of (**4**) (202 mg, 0.26 mmol) in THF/H_2O (2/1, 9 mL) at 0 °C was added H_2O_2 (30% in H_2O, 0.16 mL, 1.56 mmol) and LiOH monohydrate (44 mg, 1.04 mmol). The mixture was stirred at 0 °C for 2h, then quenched with 1.0 M Na_2SO_3 solution and 1N 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 70/30, 10 min) to obtain a pure product as a white solid (**5**) (158 mg, 98% yield). ^{1}HNMR (500 MHz, $CDCl_3$): δ 3.60 (1H, s), 3.29 (1H, br s), 2.48 (1H, m), 1.09 (3H, d, J = 6.5 Hz), 0.83 (9H, s), 0.82 (6H, br s), 0.60 (3H, s), 0.04 (9H, s), 0.00 (6H, s).

Step 485e:



DMAP (17 mg, 0.14 mmol), EDCI (27 mg, 0.14 mmol) and 4-tert-butylbenzenesulfonamide (45 mg, 0.21 mmol) were added to a solution of (**5**) in DCM/DMF (4/1, 2.5 mL). The reaction mixture was stirred at RT for 3h, then quenched with 3% citric acid and brine, 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 70/30, 10 min) to give a product as a colorless oil (50 mg, 87% yield), which was then dissolved in THF (3 mL) and treated with HCl (37%, 0.1 mL). The mixture was stirred at RT for 1.5h, quenched with H_2O/brine (1/1), 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 70/30, 10 min) to obtain a pure product as a white solid as example **485** (24 mg, 65% yield). LC-MS observed M-1 = 628.40 (Calcd. 628.41). ^{1}HNMR (500 MHz, $CDCl_3$): δ 8.06 (1H, s), 7.97 (2H, d, J = 9.0 Hz), 7.55 (2H, d, J = 9.0 Hz), 3.69 (1H, s), 3.41 (1H, br s), 2.31(1H, br s), 1.35 (9H, s), 1.05 (3H, d, J = 7.0 Hz), 0.89 (6H, s), 0.82 (3H, d, J = 0.65 Hz), 0.63 (3H, s).

Examples 486 and 487 in Table 10 were prepared using similar procedures as used in the preparation of Example 485.

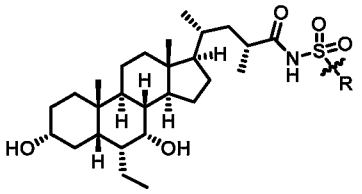
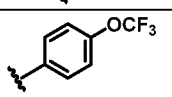
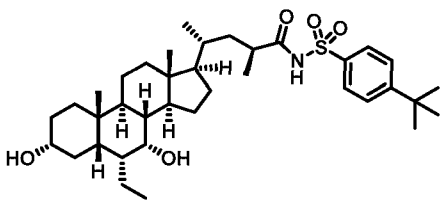


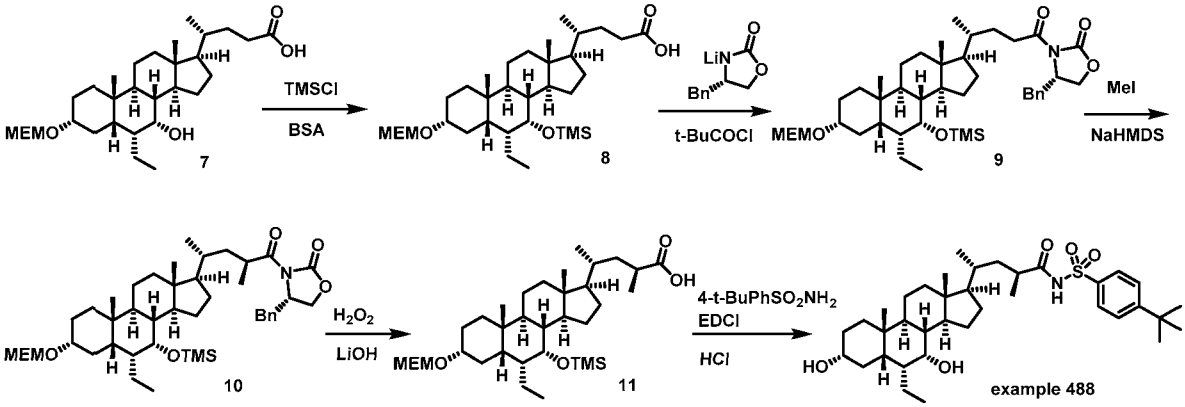
Table 10

Example #	R =	MS data [M-1]$^-$
486		536.34
487		656.32

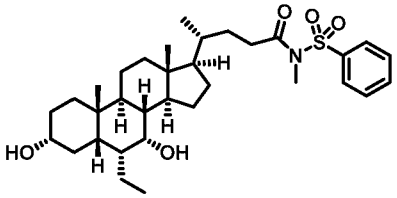
Example 488



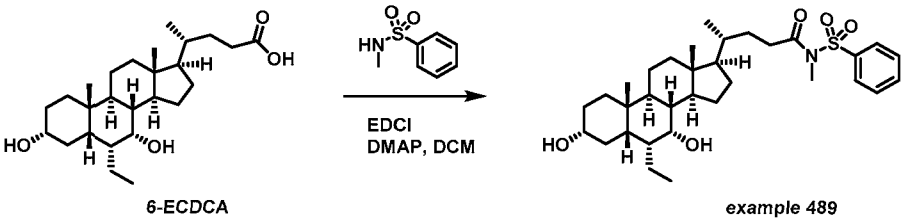
Example **488** was prepared following the same procedure as for the example **485** except using (*S*)-benzyl oxazolidinone as chiral auxiliary and MEM as protecting group of starting materials **7**.



Example 489



The examples **489** were prepared using same procedure as the one used in example 1 preparation. LC-MS of example 489 was observed [M-2H_2O+ 1] = 538.45.



ASSAYS

Human FXR (NR1H4) Assay

Determination of a ligand mediated Gal4 promoter driven transactivation to quantify ligand binding mediated activation of FXR. FXR Reporter Assay kit purchased from Indigo Bioscience (Catalogue number: IB00601) to determine the potency and efficacy of compound developed by Enanta that can induce FXR activation. The principle application of this reporter assay system is to quantify functional activity of human FXR. The assay utilizes non-human mammalian cells, CHO (Chinese hamster ovary) cells engineered to express human NR1H4 protein (referred to as FXR). Reporter cells also incorporate the cDNA encoding beetle luciferase which catalyzes the substrates and yields photon emission. Luminescence intensity of the reaction is quantified using a plate-reading luminometer, Envision. Reporter Cells include the luciferase reporter gene functionally linked to an FXR responsive promoter. Thus, quantifying changes in luciferase expression in the treated reporter cells provides a sensitive surrogate measure of the changes in FXR activity. EC_{50} and efficacy (normalize to CDCA set as 100%) is determined by XLFit. The assay is according to the manufacturer's instructions. In brief, the assay was performed in white, 96 well plates using final volume of 200ul containing cells with different doses of compounds. Retrieve Reporter Cells from -80°C storage. Perform a rapid thaw of the frozen cells by transferring a 10 ml volume of 37°C cell recovery medium into the tube of frozen cells. Recap the tube of Reporter Cells and immediately place it in a 37°C water bath for 5-10 minutes. Retrieve the tube of Reporter Cell Suspension from the water bath. Sanitize the outside surface of the tube with a 70% alcohol swab, and then transfer it into the cell culture hood. Dispense 100 µl of cell suspension into each well of the 96-well Assay Plate. Transfer the plate into 37°C incubator, allowing the cells adherent to the bottom of the well. Dilute compounds in Dilution Plate (DP), and administrate to cells at Assay Plate (AP). DMSO content of the samples was kept at 0.2%. Cells were incubated for additional 22 hours before luciferase activities were measured. Thirty minutes before intending to quantify FXR activity, remove Detection Substrate and Detection Buffer from the refrigerator and place them in a low-light area so that they may equilibrate to room temperature. Remove the plate's lid and discard all media contents by ejecting it into an appropriate waste container. Gently tap the inverted plate onto a clean absorbent paper towel to remove residual droplets. Cells will remain tightly adhered to well

bottoms. Add 100 µl of luciferase detection reagent to each well of the assay plate. Allow the assay plate to rest at room temperature for at least 5 minutes following the addition of LDR. Set the instrument (Envision) to perform a single 5 second "plate shake" prior to reading the first assay well. Read time may be 0.5 second (500mSec) per well. EC_{50} and Efficacy (normalize to CDCA set as 100%) is determined by XLFit.

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 (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 induces the production of 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, 5% CO_2 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 µL Cell Assay Buffer/cAMP Antibody Reagent). For each dilution, the final concentration of solvent should remain constant. Transfer 15 µL diluted compound the assay plate and incubate the plate for 30 minutes at 37°C. Following agonist incubation, add 60 µL 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 µl 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 EC_{50} after logarithm transformation.

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 11. The efficacy was normalized to chenodeoxycholic acid (CDCA) set as 100%. (A: EC50 < 0.1 μM; B: 0.1 μM < EC50 < 1.0 μM; C:1.0 μM < EC50 < 10 μM; D=:EC50 > 10 μM).

Table 11

Example	EC50 (μM)	Efficacy (%)
CDCA	D	100
6-ECDCA	B	223
1	B	254
2	B	258
3	B	289
4	B	376
5	A	218
6	B	295
7	C	178
9	B	248
10	C	244
11	B	315
12	B	331
14	B	316
16	C	219
17	C	349
18	A	329
19	B	176
20	B	348
22	B	259
23	B	280
24	A	271
25	C	347
451	B	274
452	C	292
453	B	240
454	B	353
455	A	417
456	A	415
457	A	382
458	C	339
459	B	310
460	A	291
461	B	283

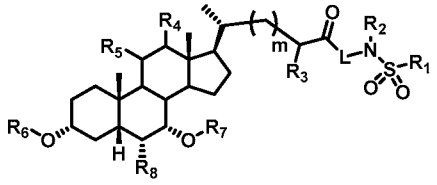
462	B	297
463	C	251
464	B	293
465	A	303
466	C	258
467	B	315
468	A	480
469	C	447
470	B	439
471	A	467
472	A	580
473	A	606
474	C	463
475	A	590
476	A	593
477	A	596
478	B	589
479	A	572
480	A	346
481	A	359
482	A	342
483	A	308
484	A	349
485	B	185
486	B	387
487	A	287
488	B	132
489	C	231
490	B	223
491	A	182
492	B	226

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

CLAIMS

WHAT IS CLAIMED IS:

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



(I)

wherein:

R_1 is selected from the group consisting of:

1) Halogen;
2) Hydroxyl;
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;
6) Substituted or unsubstituted $-C_3$-C_8 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) $-NR_9R_{10}$; wherein, R_9 and R_{10} 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 $-C_3$-C_8 cycloalkyl, or R_9 and R_{10} are taken together with the nitrogen they attached to form a hetercyclic ring;

R_2 is hydrogen or Substituted or unsubstituted $-C_1$-C_8 alkyl;

R_3 is independently 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;

L is absent or $-NR_{11}CHR_{12}C(O)$-, wherein R_{11} and R_{12} are independently selected from R_3;

m is selected from 0, 1, 2 or 3;

R_4 is hydrogen, hydroxyl, $-OSO_3H$, $-OSO_3^-$, -OAc, $-OPO_3H_2$ or $-OPO_3^{2-}$;

R_5 is hydrogen, halogen, CN, N_3, hydroxyl, $-OSO_3H$, $-OSO_3^-$, -OAc, $-OPO_3H_2$, $-OPO_3^{2-}$, $-SR_2$ or $-NHR_2$, wherein, R_2 is as defined previously;

or R_4 and R_5 are taken together with the carbons they attached to form –CH=CH- or cycloalkyl ring or heterocycloalkyl ring such as, but not limited to cyclopropyl, or expoxide;

R_6 and R_7 are independently selected from hydrogen or hydroxyl protecting group such as, but not limited to acetyl, trimethyl silyl, or benzyl;

R_8 is selected from the group consisting of:

1) Hydrogen;

2) Halogen;

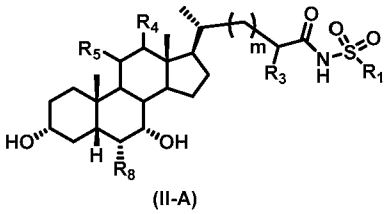
3) Substituted or unsubstituted $-C_1$-C_8 alkyl;

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

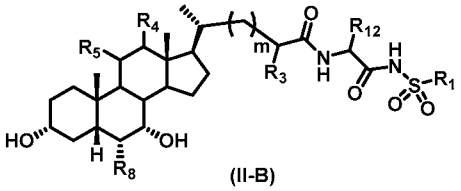
5) Substituted or unsubstituted $-C_2$-C_8 alkynyl; and

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

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:



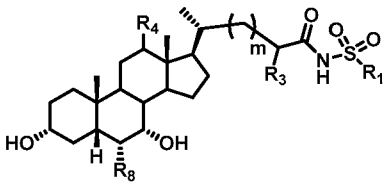
(II-A)

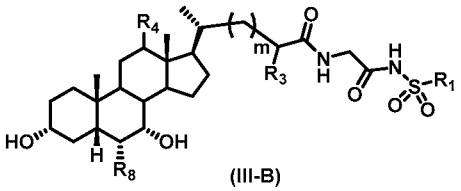


(II-B)

wherein, R_1, R_3, R_4, R_5, R_8, R_{12} and m are as defined in claim 1.

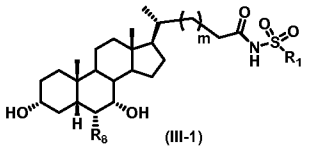
3. A compound of claim 1, represented by Formula III-A or Formula III-B or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, or combination thereof:

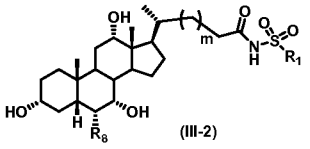

(III-A)

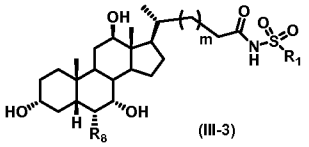

(III-B)

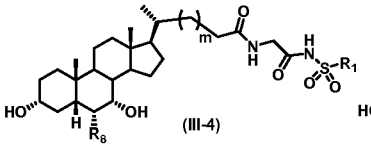
wherein, R_1, R_3, R_4, R_8 and m are as defined in claim 1.

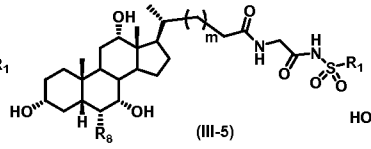
4. The compound of claim 1, represented by one of formulas (III-1) to (III-18), wherein R_1, R_8 and m are as defined in claim 1:

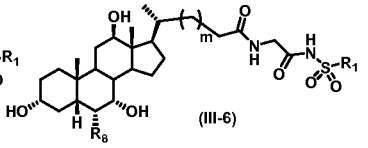

(III-1)

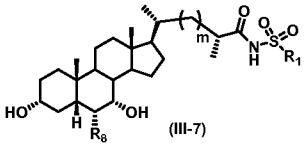

(III-2)

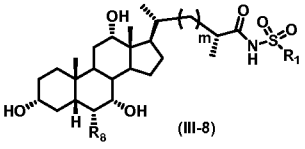

(III-3)

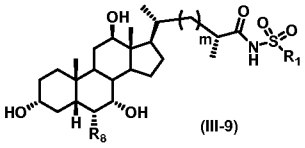

(III-4)

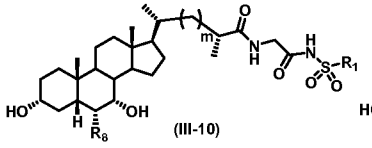

(III-5)

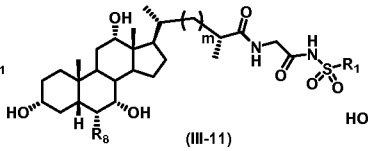

(III-6)

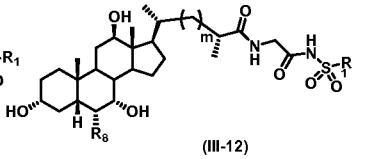

(III-7)

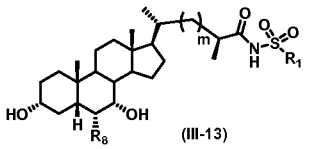

(III-8)

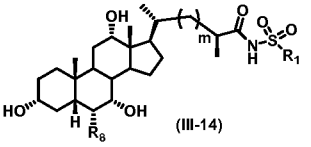

(III-9)

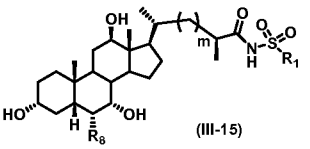

(III-10)

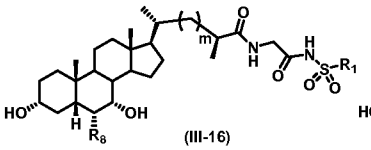

(III-11)

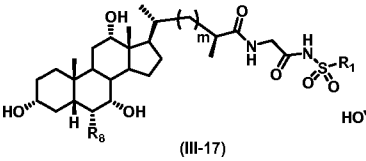

(III-12)

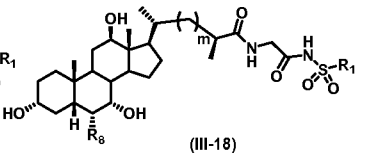

(III-13)


(III-14)


(III-15)

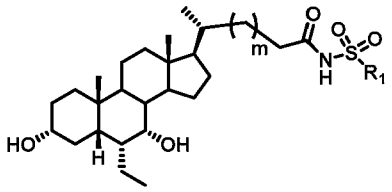

(III-16)


(III-17)

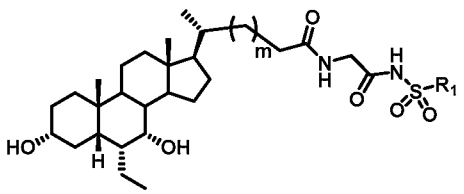

(III-18)

.

5. 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:



(IV-A)

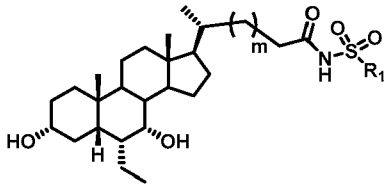


(IV-B)

wherein, R_1 and m are as defined in claim 1.

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

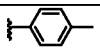
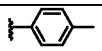
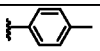
(a) Compounds according to Formula IV-A wherein, R_1 and m are delineated for each example in Table 1:



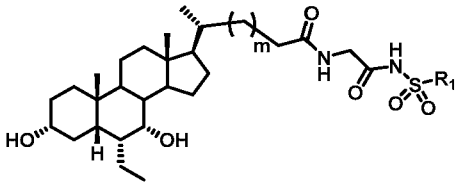
(IV-A)

Table 1

Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
1	0	Methyl	26	1	Methyl	51	2	Methyl
2	0	Ethyl	27	1	Ethyl	52	2	Ethyl
3	0	Isopropyl	28	1	Isopropyl	53	2	Isopropyl
4	0	Butyl	29	1	Butyl	54	2	Butyl
5	0	t-Butyl	30	1	t-Butyl	55	2	t-Butyl
6	0	Propyl	31	1	Propyl	56	2	Propyl
7	0	Benzyl	32	1	Benzyl	57	2	Benzyl
8	0	Vinyl	33	1	Vinyl	58	2	Vinyl
9	0	Allyl	34	1	Allyl	59	2	Allyl
10	0	CF_3	35	1	CF_3	60	2	CF_3
11	0		36	1		61	2	
12	0		37	1		62	2	

13	0		38	1		63	2	
14	0		39	1		64	2	
15	0		40	1		65	2	
16	0		41	1		66	2	
17	0	NH_2	42	1	NH_2	67	2	NH_2
18	0		43	1		68	2	
19	0		44	1		69	2	
20	0		45	1		70	2	
21	0		46	1		71	2	
22	0		47	1		72	2	
23	0		48	1		73	2	
24	0		49	1		74	2	
25	0	F	50	1	F	75	2	F

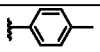
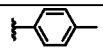
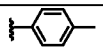
(b) Compounds according to Formula IV-B wherein, R_1 and m are delineated for each example in Table 2:



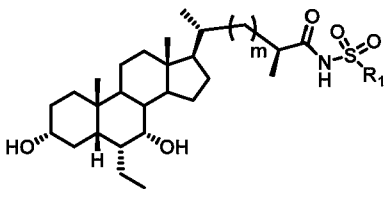
(IV-B)

Table 2

Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
76	0	Methyl	101	1	Methyl	126	2	Methyl
77	0	Ethyl	102	1	Ethyl	127	2	Ethyl
78	0	Isopropyl	103	1	Isopropyl	128	2	Isopropyl
79	0	Butyl	104	1	Butyl	129	2	Butyl
80	0	t-Butyl	105	1	t-Butyl	130	2	t-Butyl
81	0	Propyl	106	1	Propyl	131	2	Propyl

82	0	Benzyl	107	1	Benzyl	132	2	Benzyl
83	0	Vinyl	108	1	Vinyl	133	2	Vinyl
84	0	Allyl	109	1	Allyl	134	2	Allyl
85	0	CF_3	110	1	CF_3	135	2	CF_3
86	0		111	1		136	2	
87	0		112	1		137	2	
88	0		113	1		138	2	
89	0		114	1		139	2	
90	0		115	1		140	2	
91	0		116	1		141	2	
92	0	NH_2	117	1	NH_2	142	2	NH_2
93	0		118	1		143	2	
94	0		119	1		144	2	
95	0		120	1		145	2	
96	0		121	1		146	2	
97	0		122	1		147	2	
98	0		123	1		148	2	
99	0		124	1		149	2	
100	0	F	125	1	F	150	2	F

7. The compound of claim 1, represented by Formula V-A or Formula V-B:



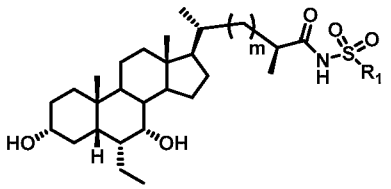
(V-A)

(V-B)

5

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

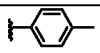
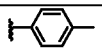
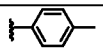
(a) compounds according to Formula V-A wherein, R_1 and m are delineated for each example in Table 3:



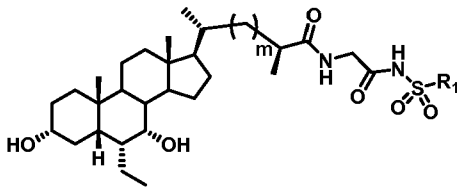
(V-A)

Table 3

Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
151	0	Methyl	176	1	Methyl	201	2	Methyl
152	0	Ethyl	177	1	Ethyl	202	2	Ethyl
153	0	Isopropyl	178	1	Isopropyl	203	2	Isopropyl
154	0	Butyl	179	1	Butyl	204	2	Butyl
155	0	t-Butyl	180	1	t-Butyl	205	2	t-Butyl
156	0	Propyl	181	1	Propyl	206	2	Propyl
157	0	Benzyl	182	1	Benzyl	207	2	Benzyl
158	0	Vinyl	183	1	Vinyl	208	2	Vinyl
159	0	Allyl	184	1	Allyl	209	2	Allyl
160	0	CF_3	185	1	CF_3	210	2	CF_3
161	0		186	1		211	2	
162	0		187	1		212	2	
163	0		188	1		213	2	
164	0		189	1		214	2	
165	0		190	1		215	2	
166	0		191	1		216	2	
167	0	NH_2	192	1	NH_2	217	2	NH_2
168	0		193	1		218	2	
169	0		194	1		219	2	
170	0		195	1		220	2	

171	0		196	1		221	2	
172	0		197	1		222	2	
173	0		198	1		223	2	
174	0		199	1		224	2	
175	0	F	200	1	F	225	2	F

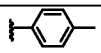
(b) Compounds according to Formula V-B wherein, R_1 and m are delineated for each example in Table 4:



(V-B)

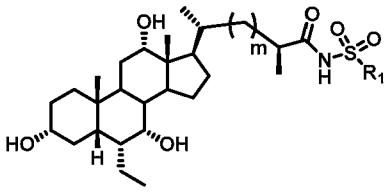
Table 4

Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
226	0	Methyl	251	1	Methyl	276	2	Methyl
227	0	Ethyl	252	1	Ethyl	277	2	Ethyl
228	0	Isopropyl	253	1	Isopropyl	278	2	Isopropyl
229	0	Butyl	254	1	Butyl	279	2	Butyl
230	0	t-Butyl	255	1	t-Butyl	280	2	t-Butyl
231	0	Propyl	256	1	Propyl	281	2	Propyl
232	0	Benzyl	257	1	Benzyl	282	2	Benzyl
233	0	Vinyl	258	1	Vinyl	283	2	Vinyl
234	0	Allyl	259	1	Allyl	284	2	Allyl
235	0	CF_3	260	1	CF_3	285	2	CF_3
236	0		261	1		286	2	
237	0		262	1		287	2	
238	0		263	1		288	2	
239	0		264	1		289	2	
240	0		265	1		290	2	

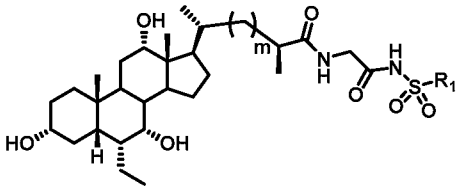
241	0		266	1		291	2	
242	0	NH_2	267	1	NH_2	292	2	NH_2
243	0		268	1		293	2	
244	0		269	1		294	2	
245	0		270	1		295	2	
246	0		271	1		296	2	
247	0		272	1		297	2	
248	0		273	1		298	2	
249	0		274	1		299	2	
250	0	F	275	1	F	300	2	F

.

9. A compound according to claim 1, represented by Formula VI-A or Formula VI-B:



(VI-A)

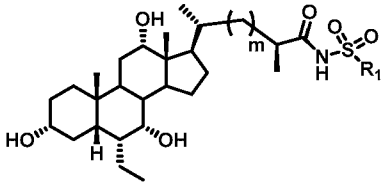


(VI-B)

.

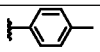
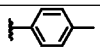
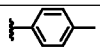
10. A compound according to claim 1, which is selected from:

(a) Compounds according to Formula VI-A wherein, R_1 and m are delineated for each example in Table 5,

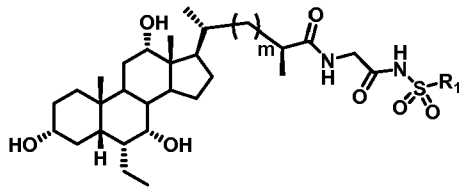


(VI-A)

Table 5

Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
301	0	Methyl	326	1	Methyl	351	2	Methyl
302	0	Ethyl	327	1	Ethyl	352	2	Ethyl
303	0	Isopropyl	328	1	Isopropyl	353	2	Isopropyl
304	0	Butyl	329	1	Butyl	354	2	Butyl
305	0	t-Butyl	330	1	t-Butyl	355	2	t-Butyl
306	0	Propyl	331	1	Propyl	356	2	Propyl
307	0	Benzyl	332	1	Benzyl	357	2	Benzyl
308	0	Vinyl	333	1	Vinyl	358	2	Vinyl
309	0	Allyl	334	1	Allyl	359	2	Allyl
310	0	CF_3	335	1	CF_3	360	2	CF_3
311	0		336	1		361	2	
312	0		337	1		362	2	
313	0		338	1		363	2	
314	0		339	1		364	2	
315	0		340	1		365	2	
316	0		341	1		366	2	
317	0	NH_2	342	1	NH_2	367	2	NH_2
318	0		343	1		368	2	
319	0		344	1		369	2	
320	0		345	1		370	2	
321	0		346	1		371	2	
322	0		347	1		372	2	
323	0		348	1		373	2	
324	0		349	1		374	2	
325	0	F	350	1	F	375	2	F

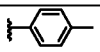
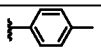
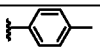
(b) Compounds according to Formula VI-B wherein, R_1 and m are delineated for each example in Table 6,



(VI-B)

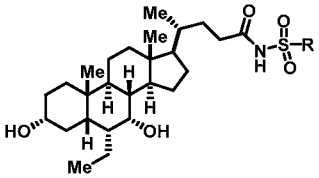
Table 6

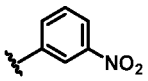
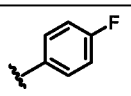
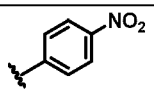
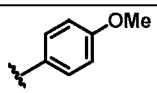
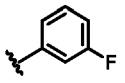
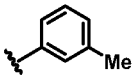
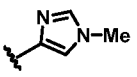
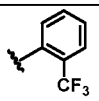
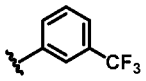
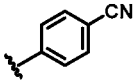
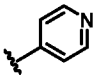
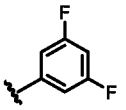
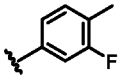
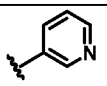
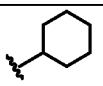
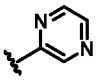
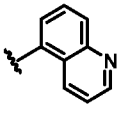
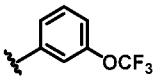
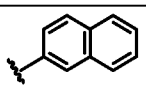
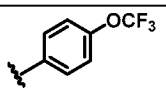
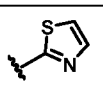
Compound	m	R_1	Compound	m	R_1	Compound	m	R_1
376	0	Methyl	401	1	Methyl	426	2	Methyl
377	0	Ethyl	402	1	Ethyl	427	2	Ethyl
378	0	Isopropyl	403	1	Isopropyl	428	2	Isopropyl
379	0	Butyl	404	1	Butyl	429	2	Butyl
380	0	t-Butyl	405	1	t-Butyl	430	2	t-Butyl
381	0	Propyl	406	1	Propyl	431	2	Propyl
382	0	Benzyl	407	1	Benzyl	432	2	Benzyl
383	0	Vinyl	408	1	Vinyl	433	2	Vinyl
384	0	Allyl	409	1	Allyl	434	2	Allyl
385	0	CF_3	410	1	CF_3	435	2	CF_3
386	0		411	1		436	2	
387	0		412	1		437	2	
388	0		413	1		438	2	
389	0		414	1		439	2	
390	0		415	1		440	2	
391	0		416	1		441	2	
392	0	NH_2	417	1	NH_2	442	2	NH_2
393	0		418	1		443	2	
394	0		419	1		444	2	
395	0		420	1		445	2	
396	0		421	1		446	2	

397	0		422	1		447	2	
398	0		423	1		448	2	
399	0		424	1		449	2	
400	0	F	425	1	F	450	2	F

11. A compound according to claim 1 selected from the group of compounds 451-492 shown below in table 7 and table 8 , or a pharmaceutically acceptable salt thereof:

Table 7 Compounds 451-484



Compound	R	Compound	R	Compound	R
451		452		453	
454		455		456	
457		458		459	
460		461		462	
463		464		465	
466		467		468	
469		470		471	
472		473		474	

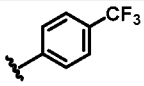
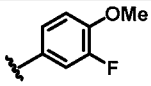
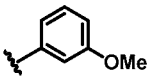
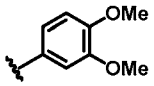
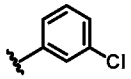
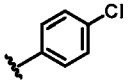
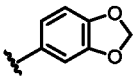
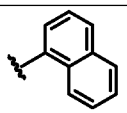
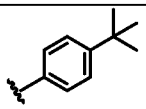
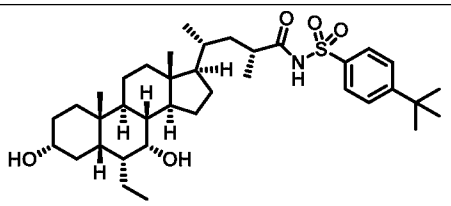
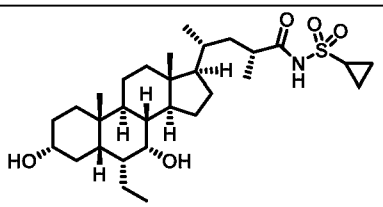
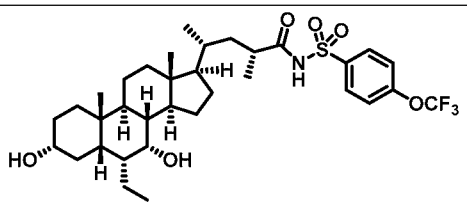
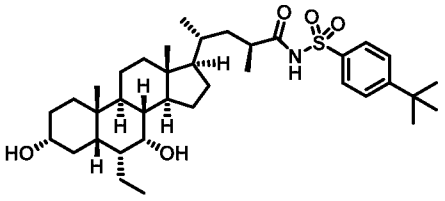
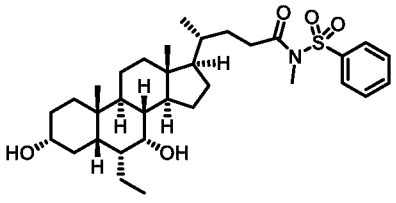
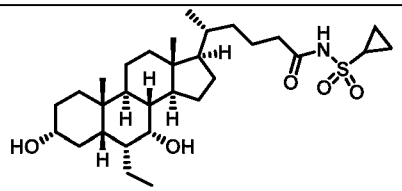
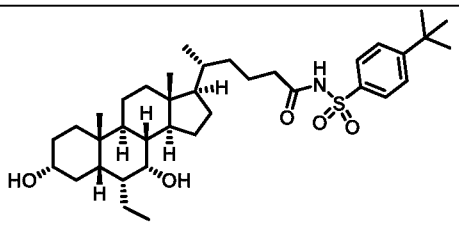
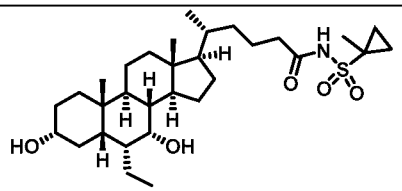
475		476		477	
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Table 8 Compounds 485-492

Compound	**Structure**
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12. A method for the prevention or treatment of an FXR-mediated disease or condition in a mammal comprising administering to the mammal suffering from an FXR-mediated disease or condition a therapeutically effective amount of a compound of formula (I) according to any one of claims 1-11.

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

14. A method according to claim 13, wherein the chronic liver disease is selected from the group consisting of primary biliary cirrhosis (PBC), cerebrotendinous xanthomatosis (CTX), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver transplant associated graft versus host disease, living donor transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic

malignancy, Sjogren's syndrome, Sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, and alpha 1-antitrypsin deficiency.

15. A method according to claim 13, wherein the renal disease is selected from the group consisting of diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), hypertensive nephrosclerosis, chronic glomerulonephritis, chronic transplant glomerulopathy, chronic interstitial nephritis, and polycystic kidney disease.

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

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

18. A 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 of formula (I) according to any one of claims 1-11.

19. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1-11 and a pharmaceutically acceptable carrier.

20. Use of a compound as defined in any one of claims 1-11 for the preparation of a pharmaceutical composition for the prevention or treatment of FXR-mediated or TGR5-mediated diseases or conditions.