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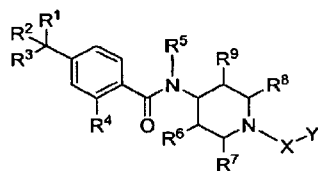
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(54) Title: BENZAMIDE DERIVATIVES AND USES RELATED THERETO



(I)

(57) Abstract: Benzamide derivatives of formula I are described and have therapeutic utility, particularly in the treatment of diabetes, obesity and related conditions and disorders:



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BENZAMIDE DERIVATIVES AND USES RELATED THERETO

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Patent Application No. 60/811,759, which was filed on June 8, 2006.

BACKGROUND OF THE INVENTION

[0002] This invention is generally directed to novel compounds, compositions, and the use of either in methods for modulating hydroxysteroid dehydrogenases, such as 11 β -HSD1, and for treating or preventing diseases associated with the modulation of hydroxysteroid dehydrogenases, such as diabetes and obesity. The methods comprise the administration, to a patient in need thereof, of a therapeutically effective amount of a benzamide derivative. Novel benzamide derivatives or pharmaceutically acceptable salts, solvates, stereoisomers, or prodrugs thereof are presented herein.

[0003] Hydroxysteroid dehydrogenases (HSDs) regulate the occupancy and activation of steroid hormone receptors by converting steroid hormones into their inactive metabolites. For a recent review, see Nobel et al., *Eur. J. Biochem.* 2001, 268:4113-4125.

[0004] There exist numerous classes of HSDs. The 11-beta-hydroxysteroid dehydrogenases (11 β -HSDs) catalyze the interconversion of active glucocorticoids (such as cortisol and corticosterone), and their inert forms (such as cortisone and 11-dehydrocorticosterone). The isoform 11-beta-hydroxysteroid dehydrogenase type 1 (11 β -HSD1) is expressed in liver, adipose tissue, brain, lung and other glucocorticoid tissue and is a potential target for therapy directed at numerous disorders that may be ameliorated by reduction of glucocorticoid action, such as diabetes, obesity and age-related cognitive dysfunction. Seckl, et al., *Endocrinology*, 2001, 142:1371-1376.

[0005] It is well known that glucocorticoids play a central role in the development of diabetes and that glucocorticoids enable the effect of glucagon on the liver. Long et al., *J. Exp. Med.* 1936, 63: 465-490; and Houssay, *Endocrinology* 1942, 30: 884-892. In addition, it has been well substantiated that 11 β -HSD1 plays an important role in the regulation of

local glucocorticoid effect and of glucose production in the liver. Jamieson et al., *J. Endocrinol.* 2000, 165:685-692.

[0006] Furthermore, the hypothesized mechanism of action of HSDs in the treatment of diabetes has been supported by various experiments conducted in mice and rats. These studies showed that the mRNA levels and activities of two key enzymes in hepatic glucose production, phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase (G6Pase) were reduced upon administration of HSD inhibitors. In addition, blood glucose levels and hepatic glucose production were shown to be reduced in 11 β -HSD1 knockout mice. Additional data gathered using this murine knockout model also confirm that inhibition of 11 β -HSD1 will not cause hypoglycemia, since the basal levels of PEPCK and G6Pase are regulated independently of glucocorticoids. Kotelevtsev et al., *Proc. Natl. Acad. Sci. USA* 1997, 94: 14924-14929.

[0007] HSDs also play a role in obesity. Obesity is an important factor in Syndrome X as well as type II (non-insulin dependent) diabetes, and omental fat appears to be of central importance in the development of both of these disease, as abdominal obesity has been linked with glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and other factors of Syndrome X (e.g., raised blood pressure, decreased levels of HDL and increased levels of VLDL). Montague et al., *Diabetes* 2000, 49:883-888, 2000. It has also been reported that inhibition of the 11 β -HSDs in pre-adipocytes (stromal cells) resulted in a decreased rate of differentiation into adipocytes. This is predicted to result in diminished expansion (possibly reduction) of the omental fat depot, which may lead to reduced central obesity. Bujalska et al., *Lancet* 1997, 349:1210-1213.

[0008] Inhibition of 11 β -HSD1 in mature adipocytes is expected to attenuate secretion of the plasminogen activator inhibitor 1 (PAI-1), which is an independent cardiovascular risk factor, as reported in Halleux et al., *J. Clin. Endocrinol. Metab.* 1999, 84:4097-4105. In addition, a correlation has been shown to exist between glucocorticoid activity and certain cardiovascular risk factors. This suggests that a reduction of the glucocorticoid effects would be beneficial in the treatment or prevention of certain cardiovascular diseases. Walker et al., *Hypertension* 1998, 31:891-895; and Fraser et al., *Hypertension* 1999, 33:1364-1368.

[0009] HSDs have also been implicated in the process of appetite control and therefore are believed to play an additional role in weight-related disorders. It is known that adrenalectomy attenuates the effect of fasting to increase both food intake and hypothalamic neuropeptide Y expression. This suggests that glucocorticoids play a role in promoting food intake and that inhibition of 11β -HSD1 in the brain may increase satiety, thus resulting in a decreased food intake. Woods et al., Science 1998, 280:1378-1383.

[0010] Another possible therapeutic effect associated with modulation of HSDs is that which is related to various pancreatic ailments. It is reported that inhibition of 11β -HSD1 in murine pancreatic β -cells results in increased insulin secretion. Davani et al., J. Biol. Chem. 2000, 275:34841-34844. This follows from the discovery that glucocorticoids were previously found to be responsible for reduced pancreatic insulin release *in vivo*, Billaudel et al., Horm. Metab. Res. 1979, 11:555-560. Thus, it is suggested that inhibition of 11β -HSD1 would yield other beneficial effects in the treatment of diabetes other than the predicted effects on the liver and fat reduction.

[0011] 11β -HSD1 also regulates glucocorticoid activity in the brain and thus contributes to neurotoxicity. Rajan et al., Neuroscience 1996, 16:65-70; and Seckl et al., Neuroendocrinol. 2000, 18:49-99. Stress and/or glucocorticoids are known to influence cognitive function (de Quervain et al., Nature 1998, 394:787-790), and unpublished results indicate significant memory improvement in rats treated with a non-specific 11β -HSD inhibitor. These reports, in addition to the known effects of glucocorticoids in the brain, suggest that inhibiting HSDs in the brain may have a positive therapeutic effect against anxiety and related conditions. Tronche et al., Nature Genetics 1999, 23:99-103. 11β -HSD1 reactivates 11-DHC to corticosterone in hippocampal cells and can potentiate kinase neurotoxicity, resulting in age-related learning impairments. Therefore, selective inhibitors of 11β -HSD1 are believed to protect against hippocampal function decline with age. Yau et al., Proc Natl. Acad. Sci. USA 2001, 98:4716-4721. Thus, it has been hypothesized that inhibition of 11β -HSD1 in the human brain would protect against deleterious glucocorticoid-mediated effects on neuronal function, such as cognitive impairment, depression, and increased appetite.

[0012] HSDs are believed to play a role in immunomodulation based on the general perception that glucocorticoids suppress the immune system. There is known to be a dynamic interaction between the immune system and the HPA (hypothalamopituitary-adrenal) axis (Rook, *Baillier's Clin. Endocrinol. Metab.* 2000, 13: 576-581), and glucocorticoids help balance between cell-mediated responses and humoral responses. Increased glucocorticoid activity, which may be induced by stress, is associated with a humoral response and as such, the inhibition of 11β -HSD1 may result in shifting the response towards a cell-based reaction. In certain disease states, such as tuberculosis, leprosy, and psoriasis, the immune reaction is typically biased towards a humoral response when a cell-based response might be more appropriate. Inhibition of 11β -HSD1 is being studied for use to direct a cell-based response in these instances. Mason, *Immunology Today* 1991, 12:57-60. It follows then, that an alternative utility of 11β -HSD1 inhibition would be to bolster a temporal immune response in association with immunization to ensure that a cell based response would be obtained.

[0013] Recent reports suggest that the levels of glucocorticoid target receptors and of HSDs are connected with the risks of developing glaucoma. Stokes et al., *Invest. Ophthalmol.* 2000, 41:1629-1638. Further, a connection between inhibition of 11β -HSD1 and a lowering of the intraocular pressure was reported. Walker et al., poster P3-698 at the Endocrine society meeting June 12-15, 1999, San Diego. It was shown that administration of the nonspecific 11β -HSD1 inhibitor, carbenoxolone, resulted in the reduction of the intraocular pressure by 20% in normal patients. In the eye, 11β -HSD1 is expressed exclusively in the basal cells of the corneal epithelium, the non-pigmented epithelium of the cornea (the site of aqueous production), ciliary muscle, and the sphincter and dilator muscles of the iris. In contrast, the distant isoenzyme 11β -hydroxysteroid dehydrogenase type 2 (" 11β -HSD2") is highly expressed in the non-pigmented ciliary epithelium and corneal endothelium. No HSDs have been found at the trabecular meshwork, which is the site of drainage. Therefore, 11β -HSD1 is suggested to have a role in aqueous production.

[0014] Glucocorticoids also play an essential role in skeletal development and function but are detrimental to such development and function when present in excess. Glucocorticoid-induced bone loss is partially derived from suppression of osteoblast proliferation and collagen synthesis, as reported in Kim et al., *J. Endocrinol.* 1999, 162:371

379. It has been reported that the detrimental effects of glucocorticoids on bone nodule formation can be lessened by administration of carbenoxolone, which is a non-specific 11β -HSD1 inhibitor. Bellows et al., *Bone* 1998, 23:119-125. Additional reports suggest that 11β -HSD1 may be responsible for providing increased levels of active glucocorticoid in osteoclasts, and thus in augmenting bone resorption. Cooper et al., *Bone* 2000, 27:375-381. This data suggests that inhibition of 11β -HSD1 may have beneficial effects against osteoporosis via one or more mechanisms which may act in parallel.

[0015] It is known that bile acids inhibit 11β -HSD2 and that such inhibition results in a shift in the cortisol/cortisone equilibrium in the favor of cortisol. Quattropani et al., *J. Clin. Invest.* Nov. 2001, 108:1299-305. A reduction in the hepatic activity of 11β -HSD2 is therefore predicted to reverse the cortisol/cortisone equilibrium to favor cortisone, which could provide therapeutic benefit in diseases such as hypertension.

[0016] The various isozymes of the 17-beta-hydroxysteroid dehydrogenases (17β -HSDs) bind to androgen receptors or estrogen receptors and catalyze the interconversion of various sex hormones including estradiol/estrone and testosterone/androstenedione. To date, six isozymes have been identified in humans and are expressed in various human tissues including endometrial tissue, breast tissue, colon tissue, and in the testes. 17-beta-Hydroxysteroid dehydrogenase type 2 (17β -HSD2) is expressed in human endometrium and its activity has been reported to be linked to cervical cancer. Kitawaki et al., *J. Clin. Endocrin. Metab.*, 2000, 85:1371-3292-3296. 17-beta-Hydroxysteroid dehydrogenase type 3 (17β -HSD3) is expressed in the testes and its modulation may be useful for the treatment of androgen-related disorders.

[0017] Androgens and estrogens are active in their 17β -hydroxy configurations, whereas their 17-keto derivatives do not bind to androgen and estrogen receptors and are thus inactive. The conversion between the active and inactive forms (estradiol/estrone and testosterone/androstenedione) of sex hormones is catalyzed by members of the 17β -HSD family. 17β -HSD1 catalyzes the formation of estradiol in breast tissue, which is important for the growth of malignant breast tumors. Labrie et al., *Mol. Cell. Endocrinol.* 1991, 78:C113-C118. A similar role has been suggested for 17β -HSD4 in colon cancer. English et al., *J. Clin. Endocrinol. Metab.* 1999, 84:2080-2085. 17β -HSD3 is almost exclusively expressed in

the testes and converts androstenedione into testosterone. Deficiency of this enzyme during fetal development leads to male pseudohermaphroditism. Geissler et al., Nat. Genet. 1994, 7:34-39. Both 17 β -HSD3 and various 3 α -HSD isozymes are involved in complex metabolic pathways which lead to androgen shuffles between inactive and active forms. Penning et al., Biochem. J. 2000, 351:67-77. Thus, modulation of certain HSDs can have potentially beneficial effects in the treatment of androgen- and estrogen-related disorders.

[0018] The 20-alpha-hydroxysteroid dehydrogenases (20 α -HSDs) catalyze the interconversion of progestins (such as between progesterone and 20 α -hydroxy progesterone). Other substrates for 20 α -HSDs include 17 α -hydroxypregnenolone or 17 α -hydroxyprogesterone, leading to 20 α -OH steroids. Several 20 α -HSD isoforms have been identified and 20 α -HSDs are expressed in various tissues, including the placenta, ovaries, testes and adrenals. Peltoketo, et al., J. Mol. Endocrinol. 1999, 23:1-11.

[0019] The 3-alpha-hydroxysteroid dehydrogenases (3 α -HSDs) catalyze the interconversion of the androgens dihydrotestosterone (DHT) and 5 α -androstane-3 α ,17 β -diol and the interconversion of the androgens DHEA and androstenedione and therefore play an important role in androgen metabolism. Ge et al., Biology of Reproduction 1999, 60:855-860.

[0020] International Publications Nos. WO 2004/089896 and WO 2004/065351 disclose benzamide derivatives and their use as 11 β -HSD1 modulators.

[0021] Despite the previous research done in the field of HSD inhibition, there remains a need for novel compounds that are potent inhibitors of the various families of HSDs and efficacious for the treatment of HSD-mediated conditions such as diabetes, obesity, glaucoma, osteoporosis, cognitive disorders, immune disorders, depression, hypertension, and others.

SUMMARY OF THE INVENTION

[0022] In brief, the present invention relates to novel compounds, compositions thereof and methods for modulating the activity of hydroxysteroid dehydrogenases (HSDs), such as 11 β -hydroxysteroid dehydrogenases, 17 β -hydroxysteroid dehydrogenases, 20 α -hydroxysteroid dehydrogenases, and 3 α -hydroxysteroid dehydrogenases, including all

isoforms thereof, including but not limited to 11 β -hydroxysteroid dehydrogenase type 1 (hereinafter "11 β -HSD1"), 11 β -hydroxysteroid dehydrogenase type 2 (hereinafter "11 β -HSD2"), and 17 β -hydroxysteroid dehydrogenase type 3 (hereinafter "17 β -HSD3"). In one embodiment, the compounds of the invention inhibit HSD activity.

[0023] The present invention also relates to methods for treating or preventing diseases or disorders associated with the action of hydroxysteroid dehydrogenases, comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof. The invention encompasses both selective and non-selective inhibitors of hydroxysteroid dehydrogenases.

[0024] It should be understood that selective and non-selective inhibitors of hydroxysteroid dehydrogenases each have benefits in the treatment or prevention of diseases associated with, for example, abnormal glucose levels or hypothalamic function. The invention also encompasses selective inhibitors of HSDs. Two types of selectivity are contemplated, that with respect to selectivity for HSDs as a class over other types of receptors or gene targets related to glucose metabolism, or those which are selective for various HSDs or specific isoforms thereof compared to other HSDs or specific isoforms thereof.

[0025] In one embodiment, the benzamide derivatives can act as selective or non-selective 11 β -HSD inhibitors. The compounds may inhibit the interconversion of inactive 11-keto steroids with their active hydroxy equivalents. The present invention provides methods by which the conversion of the inactive to the active form may be controlled, and to useful therapeutic effects which may be obtained as a result of such control. More specifically, but not exclusively, the invention is concerned with interconversion between cortisone and cortisol in humans.

[0026] In another embodiment, the benzamide derivatives of the present invention may be orally active.

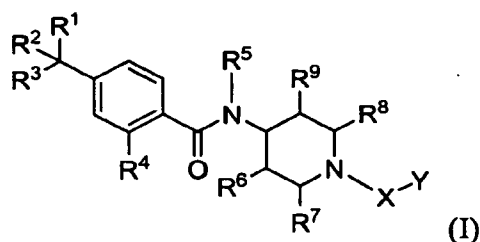
[0027] The benzamide derivatives are also useful for modulation of numerous metabolic functions including, but not limited to, one or more of: (i) regulation of carbohydrate metabolism, (ii) regulation of protein metabolism, (iii) regulation of lipid

metabolism, (iv) regulation of normal growth and/or development, (v) influence on cognitive function, (vi) resistance to stress and mineralocorticoid activity.

[0028] The benzamide derivatives may also be useful for inhibiting hepatic gluconeogenesis, and may also be effective to relieve the effects of endogenous glucocorticoids in diabetes mellitus, obesity (including entripetal obesity), neuronal loss and/or the cognitive impairment of old age. Thus, in a further embodiment, the invention provides the use of an inhibitor of HSDs in methods directed to producing one or more therapeutic effects in a patient to whom the benzamide derivative is administered, said therapeutic effects selected from the group consisting of inhibition of hepatic gluconeogenesis, an increase in insulin sensitivity in adipose tissue and muscle, and the prevention of or reduction in neuronal loss/cognitive impairment due to glucocorticoid-potentiated neurotoxicity or neural dysfunction or damage.

[0029] The invention further provides methods for treating a condition selected from the group consisting of: hepatic insulin resistance, adipose tissue insulin resistance, muscle insulin resistance, neuronal loss or dysfunction due to glucocorticoid potentiated neurotoxicity, and any combination of the aforementioned conditions, the methods comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative.

[0030] The benzamide derivatives of the invention are compounds having Formula (I)



or pharmaceutically acceptable salts, solvates, stereoisomers or prodrugs thereof.

[0031] R^1 is a member selected from the group consisting of -OH, halogen and (C₁-C₈)haloalkyl.

[0032] R^2 and R^3 are members independently selected from the group consisting of halogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₁-C₈)haloalkyl, (C₂-

C₈)hydroxyalkyl and (C₃-C₈)cycloalkyl, wherein no more than two of R¹, R² and R³ are halogen.

[0033] R⁴ is a member selected from the group consisting of hydrogen, halogen, (C₁-C₈)alkyl and (C₃-C₈)cycloalkyl.

[0034] R⁵ is selected from the group consisting of (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, (C₂-C₈)hydroxyalkyl, (C₃-C₈)cycloalkyl, and (C₃-C₈)heterocycloalkyl.

[0035] For R⁵, any cycloalkyl or heterocycloalkyl portion can be substituted with from one to two members selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₂-C₄)hydroxyalkyl, and (C₁-C₄)alkoxy.

[0036] X is selected from the group consisting of a bond, (C₁-C₈)alkylene, (C₀-C₈)alkylene-SO₂, and (C₀-C₈)alkylene-C(O).

[0037] Y is selected from the group consisting of H, -CN, -N(R')₂, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)haloalkyl, (C₂-C₈)hydroxyalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, heteroaryl, and aryl.

[0038] For Y, any cycloalkyl portion, heterocycloalkyl portion, aryl portion or heteroaryl portion is optionally substituted with from one to four members selected from the group consisting of halogen, -CN, -NO₂, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₁-C₈)haloalkyl, (C₂-C₈)hydroxyalkyl, aryl, heteroaryl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, (C₃-C₈)heterocycloalkyl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl or aryl(C₁-C₆)alkyl, -C(O)R', -C(O)OR', -NR'C(O)OR', -OR', -SR', -OC(O)R', -C(O)N(R')₂, -S(O)R', -SO₂R', -SO₂N(R')₂, -N(R')₂, -NR'C(O)R', -NR'SO₂R', -Z-C(O)R', -Z-CN, -Z-C(O)OR', -Z-NR'C(O)OR', -Z-OR', -Z-OC(O)R', -Z-C(O)N(R')₂, -Z-S(O)R', -Z-SO₂R', -Z-SO₂N(R')₂, -Z-N(R')₂ and -Z-NR'C(O)R'.

[0039] R⁶ to R⁹ are members independently selected from hydrogen and (C₁-C₈)alkyl.

[0040] Z is a branched or straight chain (C₁-C₈)alkylene group.

[0041] Each occurrence of R' is independently H or an unsubstituted member selected from the group consisting of (C₁-C₈)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₈)haloalkyl, (C₂-C₈)hydroxyalkyl, or two R' groups, when attached to the same nitrogen

atom, can be combined with the nitrogen atom to which they are attached to form a heterocycle or heteroaryl group.

[0042] In one embodiment, the invention provides pharmaceutical compositions comprising a benzamide derivatives and a pharmaceutically acceptable vehicle, carrier, excipient or diluent.

[0043] In another embodiment, the invention provides methods for treating insulin-dependent diabetes mellitus comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0044] In another embodiment, the invention provides methods for treating non-insulin-dependent diabetes mellitus comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0045] In another embodiment, the invention provides methods for treating insulin resistance comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0046] In another embodiment, the invention provides methods for treating obesity comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0047] In another embodiment, the invention provides methods for modulating cortisol production comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0048] In another embodiment, the invention provides methods for modulating hepatic glucose production comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0049] In another embodiment, the invention provides methods for modulating hypothalamic function comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0050] In one embodiment, the invention provides methods for treating a hydroxysteroid dehydrogenase-mediated condition or disorder comprising administering to a

patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0051] In a further embodiment, the invention provides methods for modulating a hydroxysteroid dehydrogenase, comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0052] In still another embodiment, the invention provides methods for treating an 11 β -HSD1-mediated condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0053] In yet another embodiment, the invention provides method for modulating the function of 11 β -HSD1 in a cell comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0054] In a further embodiment, the invention provides methods for modulating 11 β -HSD1, comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0055] In one embodiment, the invention provides methods for treating an 11 β -HSD2-mediated condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0056] In another embodiment, the invention provides method for modulating the function of 11 β -HSD2 in a cell comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0057] In a further embodiment, the invention provides methods for modulating 11 β -HSD2, comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0058] In one embodiment, the invention provides methods for treating an 17 β -HSD3-mediated condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0059] In another embodiment, the invention provides method for modulating the function of 17 β -HSD3 in a cell comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0060] In a further embodiment, the invention provides methods for modulating 17 β -HSD3, comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0061] These and other embodiments of this invention will be evident upon reference to the following detailed description. To that end, certain patent and other documents are cited herein to more specifically set forth various embodiments of this invention. Each of these documents are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

[0062] As used herein, the terms have the following meanings:

[0063] The term "alkyl" as used herein refers to a straight or branched chain, saturated hydrocarbon having the indicated number of carbon atoms. For example, (C₁-C₆)alkyl is meant to include, but is not limited to methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, and neohexyl. An alkyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0064] The term "alkenyl" as used herein refers to a straight or branched chain unsaturated hydrocarbon having the indicated number of carbon atoms and at least one double bond. Examples of a (C₂-C₈)alkenyl group include, but are not limited to, ethylene, propylene, 1-butylene, 2-butylene, isobutylene, *sec*-butylene, 1-pentene, 2-pentene, isopentene, 1-hexene, 2-hexene, 3-hexene, isohexene, 1-heptene, 2-heptene, 3-heptene, isoheptene, 1-octene, 2-octene, 3-octene, 4-octene, and isooctene. An alkenyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0065] The term "alkynyl" as used herein refers to a straight or branched chain unsaturated hydrocarbon having the indicated number of carbon atoms and at least one triple bond. Examples of a (C₂-C₈)alkynyl group include, but are not limited to, acetylene, propyne, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 1-heptyne, 2-heptyne, 3-heptyne, 1-octyne, 2-octyne, 3-octyne and 4-octyne. An alkynyl group can be

unsubstituted or optionally substituted with one or more substituents as described herein below.

[0066] The term “alkylene” refers to a divalent alkyl group (e.g., an alkyl group attached to two other moieties, typically as a linking group). Examples of a (C₁-C₇)alkylene include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂CH₂CH₂-, and -CH₂CH₂CH₂CH₂CH₂CH₂CH₂-, as well as branched versions thereof. An alkylene group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0067] The term “alkoxy” as used herein refers to an -O-alkyl group having the indicated number of carbon atoms. For example, a (C₁-C₆)alkoxy group includes -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -O-butyl, -O-*sec*-butyl, -O-*tert*-butyl, -O-pentyl, -O-isopentyl, -O-neopentyl, -O-hexyl, -O-isohexyl, and -O-neohexyl.

[0068] The term “aminoalkyl,” as used herein, refers to an alkyl group (typically one to six carbon atoms) wherein from one or more of the C₁-C₆ alkyl group's hydrogen atoms is replaced with an amine of formula -N(R^a)₂, wherein each occurrence of R^a is independently -H or (C₁-C₆)alkyl. Examples of aminoalkyl groups include, but are not limited to, -CH₂NH₂, -CH₂CH₂NH₂-, -CH₂CH₂CH₂NH₂-, -CH₂CH₂CH₂CH₂NH₂-, -CH₂CH₂CH₂CH₂CH₂NH₂-, -CH₂CH₂CH₂CH₂CH₂CH₂NH₂-, -CH₂CH₂CH₂N(CH₃)₂, *t*-butylaminomethyl, isopropylaminomethyl and the like.

[0069] The term “aryl” as used herein refers to a 6- to 14-membered monocyclic, bicyclic or tricyclic aromatic hydrocarbon ring system. Examples of an aryl group include phenyl and naphthyl. An aryl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0070] The term “cycloalkyl” as used herein refers to a 3- to 14-membered saturated or unsaturated non-aromatic monocyclic, bicyclic or tricyclic hydrocarbon ring system. The bicyclic or tricyclic hydrocarbon ring systems may be spiro-fused. Included in this class are cycloalkyl groups which are fused to a benzene ring. Representative cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, 1,3-cyclohexadienyl, cycloheptyl, cycloheptenyl, 1,3-cycloheptadienyl, 1,4-cycloheptadienyl, -1,3,5-

cycloheptatrienyl, cyclooctyl, cyclooctenyl, 1,3-cyclooctadienyl, 1,4-cyclooctadienyl, -1,3,5-cyclooctatrienyl, spiro[5,4]decane, decahydronaphthalene, octahydronaphthalene, hexahydronaphthalene, octahydroindene, hexahydroindene, tetrahydroinden, decahydrobenzocycloheptene, octahydrobenzocycloheptene, hexahydrobenzocycloheptene, tetrahydrobenzocycloheptene, dodecahydroheptalene, decahydroheptalene, octahydroheptalene, hexahydroheptalene, and tetrahydroheptalene. A cycloalkyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0071] The term “halo” as used herein refers to -F, -Cl, -Br or -I.

[0072] The term “haloalkyl,” as used herein, refers to a C₁-C₆ alkyl group wherein from one or more of the C₁-C₆ alkyl group's hydrogen atom is replaced with a halogen atom, which can be the same or different. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, pentachloroethyl, and 1,1,1-trifluoro-2-bromo-2-chloroethyl.

[0073] The term “heteroaryl” as used herein refers to an aromatic heterocycle ring of 5 to 14 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including monocyclic, bicyclic, and tricyclic ring systems. Representative heteroaryls are triazolyl, tetrazolyl, oxadiazolyl, pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, quinazolinyl, pyrimidyl, azepinyl, oxepinyl, quinoxalinyl. A heteroaryl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0074] As used herein, the term “heteroatom” is meant to include oxygen (O), nitrogen (N), and sulfur (S).

[0075] As used herein, the term “heterocycle” or “heterocycloalkyl” as used herein refers to 5- to 14-membered ring systems which are either saturated, unsaturated, or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and

the nitrogen heteroatom may be optionally quaternized, including monocyclic, bicyclic, and tricyclic ring systems. The bicyclic or tricyclic ring systems may be spiro-fused. The bicyclic and tricyclic ring systems may encompass a heterocycle or heteroaryl fused to a benzene ring. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Representative examples of heterocycles include, but are not limited to, aziridinyl, oxiranyl, thiiranyl, triazolyl, tetrazolyl, azirinyl, diaziridinyl, diazirinyl, oxaziridinyl, azetidiny, azetidiny, oxetanyl, thietanyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, oxazinyl, thiazinyl, diazinyl, dioxanyl, triazinyl, tetrazinyl, imidazolyl, tetrazolyl, pyrrolidinyl, isoxazolyl, furanyl, furazanyl, pyridinyl, oxazolyl, benzoxazolyl, benzisoxazolyl, thiazolyl, benzthiazolyl, thiophenyl, pyrazolyl, triazolyl, pyrimidinyl, benzimidazolyl, isoindolyl, indazolyl, benzodiazolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, purinyl, indolyl, isoquinolinyl, quinolinyl and quinazolinyl. A heterocycle group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0076] The term "hydroxyalkyl," as used herein, refers to an alkyl group having the indicated number of carbon atoms wherein one or more of the alkyl group's hydrogen atoms is replaced with an -OH group. Examples of hydroxyalkyl groups include, but are not limited to, -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -CH₂CH₂CH₂CH₂OH, -CH₂CH₂CH₂CH₂CH₂OH, -CH₂CH₂CH₂CH₂CH₂CH₂OH, and branched versions thereof.

[0077] Substituents for the groups referred to as alkyl, heteroalkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl and heterocycloalkenyl can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halo, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)NR'R'', -NR''SO₂NR'R'', -NR''CO₂R', -NHC(NH₂)=NH, -NR'C(NH₂)=NH, -NHC(NH₂)=NR', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R', -CN and -NO₂, in a number ranging from zero to three, with those groups having zero, one or two substituents being exemplary. R', R'' and R''' each independently refer to hydrogen, unsubstituted (C₁-C₈)alkyl, unsubstituted hetero(C₁-C₈)alkyl, unsubstituted aryl and aryl substituted with one to three substituents selected from -halo, unsubstituted alkyl, unsubstituted alkoxy, unsubstituted thioalkoxy and unsubstituted aryl(C₁-C₄)alkyl. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. For example, -

NR'R'' is meant to include 1-pyrrolidinyl and 4-morpholinyl. An alkyl or heteroalkyl group will have from zero to three substituents, with those groups having two or fewer substituents being exemplary in the present invention. In some embodiments, an alkyl or heteroalkyl radical will be unsubstituted or monosubstituted. An alkyl or heteroalkyl radical can be unsubstituted. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as trihaloalkyl (*e.g.*, -CF₃ and -CH₂CF₃).

[0078] Exemplary substituents for the alkyl and heteroalkyl radicals are selected from: -OR', =O, -NR'R'', -SR', -halo, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -C(O)NR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''CO₂R', -NR'''SO₂NR'R'', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R', -CN and -NO₂, where R', R'' and R''' are as defined above. Typical substituents are selected from: -OR', =O, -NR'R'', -halo, -OC(O)R', -CO₂R', -C(O)NR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''CO₂R', -NR'''SO₂NR'R'', -SO₂R', -SO₂NR'R'', -NR''SO₂R', -CN and -NO₂.

[0079] Similarly, substituents for the aryl and heteroaryl groups are varied and selected from: -halo, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -C(O)NR'R'', -C(O)R', -OC(O)NR'R'', -NR''C(O)R', -NR''CO₂R', -NR'''C(O)NR'R'', -NR'''SO₂NR'R'', -NHC(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R', -N₃, -CH(Ph)₂, perfluoroalkoxy and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'' and R''' are independently selected from hydrogen, unsubstituted (C₁-C₈)alkyl, unsubstituted hetero(C₁-C₈)alkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted aryl(C₁-C₄)alkyl and unsubstituted aryloxy(C₁-C₄)alkyl. Typically, an aryl or heteroaryl group will have from zero to three substituents, with those groups having two or fewer substituents being exemplary in the present invention. In one embodiment of the invention, an aryl or heteroaryl group will be unsubstituted or monosubstituted. In another embodiment, an aryl or heteroaryl group will be unsubstituted.

[0080] Exemplary substituents for aryl and heteroaryl groups are selected from: -halo, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR''C(O)R', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R', -N₃, -CH(Ph)₂,

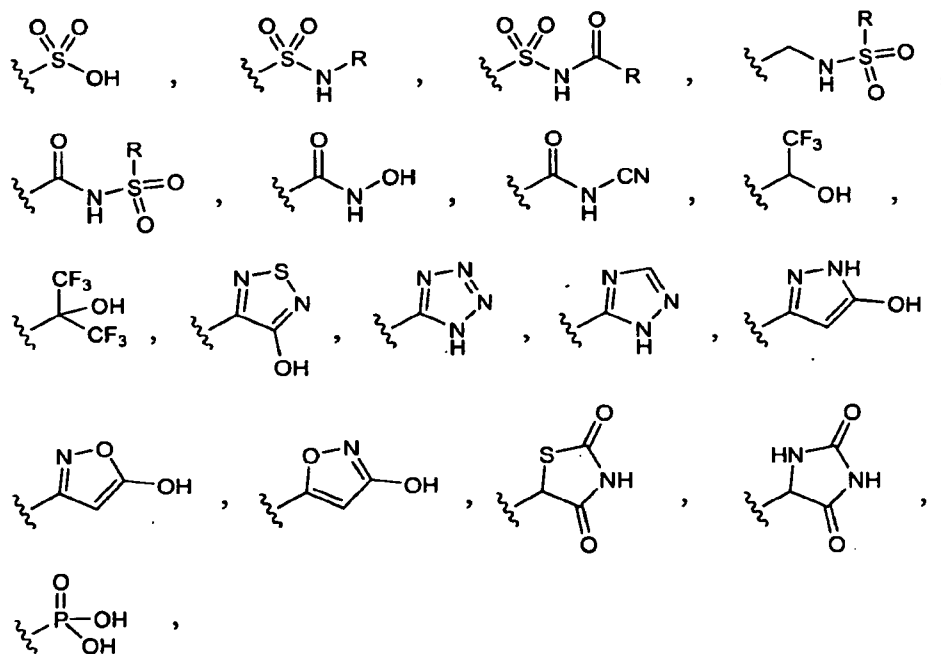
perfluoroalkoxy and perfluoro(C₁-C₄)alkyl, where R' and R'' are as defined above.

Typically, substituents are selected from: -halo, -OR', -OC(O)R', -NR'R'', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -NR''C(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R', perfluoroalkoxy and perfluoro(C₁-C₄)alkyl.

[0081] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂- or a single bond, and q is an integer of from 0 to 2.

Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CH₂)_s-X-(CH₂)_t-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituent R' in -NR'- and -S(O)₂NR'- is selected from hydrogen or unsubstituted (C₁-C₆)alkyl.

[0082] It is to be understood that the substituent -CO₂H, as used herein, may be optionally replaced with bioisosteric replacements such as:



and the like. See, e.g., *The Practice of Medicinal Chemistry*; Wermuth, C.G., Ed.; Academic Press: New York, 1996; p. 203.

[0083] The benzamide derivative can also exist in various isomeric forms, including configurational, geometric and conformational isomers, as well as existing in various tautomeric forms, particularly those that differ in the point of attachment of a hydrogen atom. As used herein, the term “isomer” is intended to encompass all isomeric forms of a benzamide derivative, including tautomeric forms of the compound.

[0084] Certain benzamide derivatives may have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. A benzamide derivative can be in the form of an optical isomer or a diastereomer. Accordingly, the invention encompasses benzamide derivatives and their uses as described herein in the form of their optical isomers, diastereomers and mixtures thereof, including a racemic mixture. Optical isomers of the benzamide derivatives can be obtained by known techniques such as asymmetric synthesis, chiral chromatography, simulated moving bed technology or via chemical separation of stereoisomers through the employment of optically active resolving agents.

[0085] As used herein and unless otherwise indicated, the term “stereoisomer” or means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, for example, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, or greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound.

[0086] It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure controls. In addition, if the

stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

[0087] A benzamide derivative can be in the form of a pharmaceutically acceptable salt. Depending on its structure, the phrase “pharmaceutically acceptable salt,” as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a benzamide derivative. Representative pharmaceutically acceptable salts include, *e.g.*, alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2, 2'-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulinate, dihydrochloride, edetate, edisylate, estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts. Furthermore, a pharmaceutically acceptable salt can have more than one charged atom in its structure. In this instance the pharmaceutically acceptable salt can have multiple counterions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counterions.

[0088] As used herein, the term “isolated and purified form” means that when isolated (*e.g.*, from other components of a synthetic organic chemical reaction mixture), the isolate contains at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% of a benzamide derivative by weight of the isolate. In one embodiment, the isolate contains at least 95% of a benzamide derivative by weight of the isolate.

[0089] As used herein, the term “prodrug” means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide an active compound, particularly a benzamide derivative. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a benzamide derivative that include biohydrolyzable groups such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues (*e.g.*, monophosphate, diphosphate or triphosphate). Prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by *Burger’s Medicinal Chemistry and Drug Discovery* 6th ed. (Donald J. Abraham *ed.*, 2001, Wiley) and *Design and Application of Prodrugs* (H. Bundgaard *ed.*, 1985, Harwood Academic Publishers Gmhf).

[0090] As used herein, the terms “treat”, “treating” and “treatment” refer to the eradication or amelioration of a disease or symptoms associated with a disease. In certain embodiments, such terms refer to minimizing the spread or worsening of the disease resulting from the administration of one or more prophylactic or therapeutic agents to a patient with such a disease.

[0091] As used herein, the terms “prevent”, “preventing” and “prevention” refer to the prevention of the onset, recurrence or spread of the disease in a patient resulting from the administration of a prophylactic or therapeutic agent.

[0092] The term “effective amount” as used herein refers to an amount of a benzamide derivative or other active ingredient sufficient to provide a therapeutic or prophylactic benefit in the treatment or prevention of a disease or to delay or minimize symptoms associated with a disease. Further, a therapeutically effective amount with respect to a benzamide derivative means that amount of therapeutic agent alone, or in combination with other therapies, that provides a therapeutic benefit in the treatment or prevention of a disease. Used in connection with a benzamide derivative, the term can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease, or enhances the therapeutic efficacy of or synergies with another therapeutic agent.

[0093] As used herein, “syndrome X” refers to a collection of abnormalities including hyperinsulinemia, obesity, elevated levels of triglycerides, uric acid, fibrinogen, small dense LDL particles and plasminogen activator inhibitor 1 (PAI-1), and decreased levels of HDL cholesterol. Syndrome X is further meant to include metabolic syndrome.

[0094] The terms “modulate”, “modulation” and the like refer to the ability of a compound to increase or decrease the function, or activity of, for example, 11 β -HSD1. “Modulation”, as used herein in its various forms, is intended to encompass inhibition, antagonism, partial antagonism, activation, agonism and/or partial agonism of the activity associated with 11 β -HSD1. 11 β -HSD1 inhibitors are compounds that, *e.g.*, bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate signal transduction. 11 β -HSD1 activators are compounds that, *e.g.*, bind to, stimulate, increase, open, activate, facilitate, enhance activation, sensitize or up regulate signal transduction. The ability of a compound to modulate 11 β -HSD1 can be demonstrated in an enzymatic assay or a cell-based assay. For example, the inhibition of 11 β -HSD1 may decrease cortisol levels in a patient and/or increase cortisone levels in a patient by blocking the conversion of cortisone to cortisol. Alternatively, the inhibition of 11 β -HSD2 can increase cortisol levels in a patient and/or decrease cortisone levels in a patient by blocking the conversion of cortisol to cortisone.

[0095] A “patient” includes an animal (*e.g.*, cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig), in one embodiment a mammal such as a non-primate and a primate (*e.g.*, monkey and human), and in another embodiment a human. In one embodiment, a patient is a human. In specific embodiments, the patient is a human infant, child, adolescent or adult.

[0096] The term “HSD” as used herein, refers to hydroxysteroid dehydrogenase enzymes in general, including, but not limited to, 11-beta-hydroxysteroid dehydrogenases (11 β -HSDs), 17-beta-hydroxysteroid dehydrogenases (17 β -HSDs), 20-alpha-hydroxysteroid dehydrogenases (20 α -HSDs), 3-alpha-hydroxysteroid dehydrogenases (3 α -HSDs), and all isoforms thereof.

[0097] The term “11 β -HSD1” as used herein, refers to the 11-beta-hydroxysteroid dehydrogenase type 1 enzyme, variant, or isoform thereof. 11 β -HSD1 variants include

proteins substantially homologous to native 11 β -HSD1, *i.e.*, proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (*e.g.*, 11 β -HSD1 derivatives, homologs and fragments). The amino acid sequence of a 11 β -HSD1 variant can be at least about 80% identical to a native 11 β -HSD1, or at least about 90% identical, or at least about 95% identical.

[0098] The term “11 β -HSD2” as used herein, refers to the 11-beta-hydroxysteroid dehydrogenase type 2 enzyme, variant, or isoform thereof. 11 β -HSD2 variants include proteins substantially homologous to native 11 β -HSD2, *i.e.*, proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (*e.g.*, 11 β -HSD2 derivatives, homologs and fragments). The amino acid sequence of a 11 β -HSD2 variant can be at least about 80% identical to a native 11 β -HSD2, or at least about 90% identical, or at least about 95% identical. (see Bart et al., *J. Med. Chem.*, 2002, 45:3813-3815).

[0099] The term “17 β -HSD3” as used herein, refers to the 17-beta-hydroxysteroid dehydrogenase type 3 enzyme, variant, or isoform thereof. 17 β -HSD3 variants include proteins substantially homologous to native 17 β -HSD3, *i.e.*, proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (*e.g.*, 17 β -HSD3 derivatives, homologs and fragments). The amino acid sequence of a 17 β -HSD3 variant can be at least about 80% identical to a native 17 β -HSD3, or at least about 90% identical, or at least about 95% identical.

[0100] As used herein, the term “HSD-responsive condition or disorder” and related terms and phrases refer to a condition or disorder that responds favorably to modulation of a hydroxysteroid dehydrogenase enzyme (HSD). Favorable responses to HSD modulation include alleviation or abrogation of the disease and/or its attendant symptoms, inhibition of the disease, *i.e.*, arrest or reduction of the development of the disease, or its clinical symptoms, and regression of the disease or its clinical symptoms. An HSD-responsive condition or disease may be completely or partially responsive to HSD modulation. An HSD-responsive condition or disorder may be associated with inappropriate, *e.g.*, less than or greater than normal, HSD activity and at least partially responsive to or affected by HSD modulation (*e.g.*, an HSD inhibitor results in some improvement in patient well-being in at

least some patients). Inappropriate HSD functional activity might arise as the result of HSD expression in cells which normally do not express HSD, decreased HSD expression or increased HSD expression. An HSD-responsive condition or disorder may include condition or disorder mediated by any HSD or isoform thereof.

[0101] As used herein, the term “11 β -HSD1-responsive condition or disorder” and related terms and phrases refer to a condition or disorder that responds favorably to modulation of 11 β -HSD1 activity. Favorable responses to 11 β -HSD1 modulation include alleviation or abrogation of the disease and/or its attendant symptoms, inhibition of the disease, *i.e.*, arrest or reduction of the development of the disease, or its clinical symptoms, and regression of the disease or its clinical symptoms. An 11 β -HSD1-responsive condition or disease may be completely or partially responsive to 11 β -HSD1 modulation. An 11 β -HSD1-responsive condition or disorder may be associated with inappropriate, *e.g.*, less than or greater than normal, 11 β -HSD1 activity and at least partially responsive to or affected by 11 β -HSD1 modulation (*e.g.*, a 11 β -HSD1 inhibitor results in some improvement in patient well-being in at least some patients). Inappropriate 11 β -HSD1 functional activity might arise as the result of 11 β -HSD1 expression in cells which normally do not express 11 β -HSD1, decreased 11 β -HSD1 expression or increased 11 β -HSD1 expression. A 11 β -HSD1-responsive condition or disorder may include a 11 β -HSD1-mediated condition or disorder.

[0102] As used herein, the term “11 β -HSD2-responsive condition or disorder” and related terms and phrases refer to a condition or disorder that responds favorably to modulation of 11 β -HSD2 activity. Favorable responses to 11 β -HSD2 modulation include alleviation or abrogation of the disease and/or its attendant symptoms, inhibition of the disease, *i.e.*, arrest or reduction of the development of the disease, or its clinical symptoms, and regression of the disease or its clinical symptoms. An 11 β -HSD2-responsive condition or disease may be completely or partially responsive to 11 β -HSD2 modulation. An 11 β -HSD2-responsive condition or disorder may be associated with inappropriate, *e.g.*, less than or greater than normal, 11 β -HSD2 activity and at least partially responsive to or affected by 11 β -HSD2 modulation (*e.g.*, a 11 β -HSD2 inhibitor results in some improvement in patient well-being in at least some patients).

[0103] As used herein, the term “17 β -HSD3-responsive condition or disorder” and related terms and phrases refer to a condition or disorder that responds favorably to modulation of 17 β -HSD3 activity. Favorable responses to 17 β -HSD3 modulation include alleviation or abrogation of the disease and/or its attendant symptoms, inhibition of the disease, *i.e.*, arrest or reduction of the development of the disease, or its clinical symptoms, and regression of the disease or its clinical symptoms. An 17 β -HSD3-responsive condition or disease may be completely or partially responsive to 17 β -HSD3 modulation. An 17 β -HSD3-responsive condition or disorder may be associated with inappropriate, *e.g.*, less than or greater than normal, 17 β -HSD3 activity and at least partially responsive to or affected by 17 β -HSD3 modulation (*e.g.*, a 17 β -HSD3 inhibitor results in some improvement in patient well-being in at least some patients). Inappropriate 17 β -HSD3 functional activity might arise as the result of 17 β -HSD3 expression in cells which normally do not express 17 β -HSD3, decreased 17 β -HSD3 expression or increased 17 β -HSD3 expression. A 17 β -HSD3-responsive condition or disorder may include a 17 β -HSD3-mediated condition or disorder.

[0104] As used herein, the term “HSD-mediated condition or disorder” and related terms and phrases refer to a condition or disorder characterized by inappropriate, *e.g.*, less than or greater than normal, activity of a hydroxysteroid dehydrogenase (HSD). An HSD-mediated condition or disorder may be completely or partially characterized by inappropriate HSD activity. However, an HSD-mediated condition or disorder is one in which modulation of an HSD results in some effect on the underlying condition or disease (*e.g.*, an HSD inhibitor results in some improvement in patient well-being in at least some patients).

[0105] As used herein, the term “11 β -HSD1-mediated condition or disorder” and related terms and phrases refer to a condition or disorder characterized by inappropriate, *e.g.*, less than or greater than normal, 11 β -HSD1 activity. A 11 β -HSD1-mediated condition or disorder may be completely or partially characterized by inappropriate 11 β -HSD1 activity. However, a 11 β -HSD1-mediated condition or disorder is one in which modulation of 11 β -HSD1 results in some effect on the underlying condition or disease (*e.g.*, a 11 β -HSD1 inhibitor results in some improvement in patient well-being in at least some patients).

[0106] As used herein, the term “11 β -HSD2-mediated condition or disorder” and related terms and phrases refer to a condition or disorder characterized by inappropriate, *e.g.*,

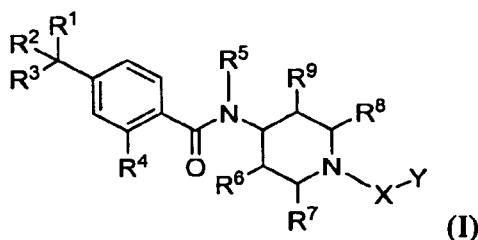
less than or greater than normal, 11β -HSD2 activity. A 11β -HSD2-mediated condition or disorder may be completely or partially characterized by inappropriate 11β -HSD2 activity. However, a 11β -HSD2-mediated condition or disorder is one in which modulation of 11β -HSD2 results in some effect on the underlying condition or disease (*e.g.*, a 11β -HSD2 inhibitor results in some improvement in patient well-being in at least some patients).

[0107] As used herein, the term " 17β -HSD3-mediated condition or disorder" and related terms and phrases refer to a condition or disorder characterized by inappropriate, *e.g.*, less than or greater than normal, 17β -HSD3 activity. A 17β -HSD3-mediated condition or disorder may be completely or partially characterized by inappropriate 17β -HSD3 activity. However, a 17β -HSD3-mediated condition or disorder is one in which modulation of 17β -HSD3 results in some effect on the underlying condition or disease (*e.g.*, a 17β -HSD3 inhibitor results in some improvement in patient well-being in at least some patients).

[0108] The following abbreviations are used herein and have the indicated definitions: DMEM is Dulbecco's Modified Eagle Medium; Et_3N is triethylamine; EtOAc is ethyl acetate; MeOH is methanol; MS is mass spectrometry; NMR is nuclear magnetic resonance; PBS is phosphate-buffered saline; SPA is scintillation proximity assay; THF is tetrahydrofuran; and TMS is trimethylsilyl.

Compounds of the Invention

[0109] The present invention provides compounds of Formula (I) as well as their pharmaceutically acceptable salts, solvates, stereoisomers, or prodrugs thereof, or mixtures thereof, collectively referred to as the "the benzamide derivatives."



where the variables are as defined above.

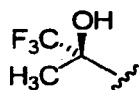
[0110] In one embodiment, R^1 is $-\text{OH}$, R^2 is $(\text{C}_1\text{-C}_3)\text{alkyl}$, R^3 is $(\text{C}_1\text{-C}_3)\text{haloalkyl}$ and R^5 is $(\text{C}_1\text{-C}_8)\text{alkyl}$, in particular, $(\text{C}_1\text{-C}_3)\text{alkyl}$; $(\text{C}_1\text{-C}_8)\text{haloalkyl}$, in particular, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$; or $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, in particular cyclopropyl.

[0111] In another embodiment, R⁵ is cyclopropyl and R⁶, R⁷, R⁸, and R⁹ are hydrogen.

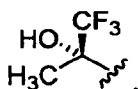
[0112] In still another embodiment, R⁵ is cyclopropyl, X is a bond, and Y is cyclohexyl, which can be substituted with one to four substituents.

[0113] In one embodiment, R¹ is -OH, R² is methyl, and R³ is trifluoromethyl.

[0114] In one embodiment, the R¹-R³ moiety is:



[0115] In another embodiment, the R¹-R³ moiety is:



[0116] In one embodiment, alone or in combination with another embodiment described herein, R¹ can be -OH.

[0117] In another embodiment, alone or in combination with another embodiment described herein, R² can be (C₁-C₈)alkyl or (C₁-C₃)alkyl.

[0118] In another embodiment, alone or in combination with another embodiment described herein, R² can be methyl.

[0119] In yet another embodiment, alone or in combination with another embodiment described herein, R³ can be (C₁-C₈)haloalkyl or (C₁-C₃)haloalkyl.

[0120] In one embodiment, alone or in combination with another embodiment described herein, R³ can be trifluoromethyl.

[0121] In one embodiment, alone or in combination with another embodiment described herein, R⁴ can be hydrogen.

[0122] In one embodiment, alone or in combination with another embodiment described herein, R⁵ can be (C₃-C₆)cycloalkyl.

[0123] In another embodiment, alone or in combination with another embodiment described herein, R⁵ can be cyclopropyl.

[0124] In still another embodiment, alone or in combination with another embodiment described herein, X is a bond and Y is (C₃-C₈)cycloalkyl.

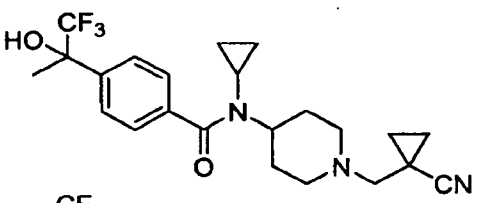
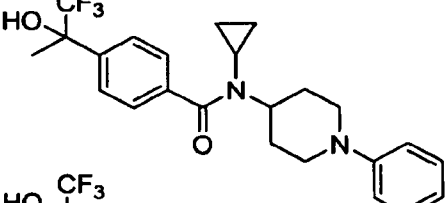
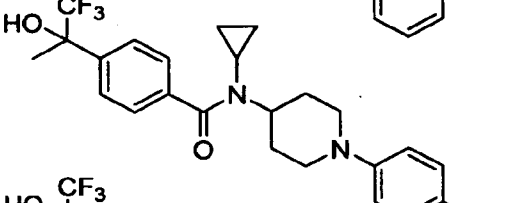
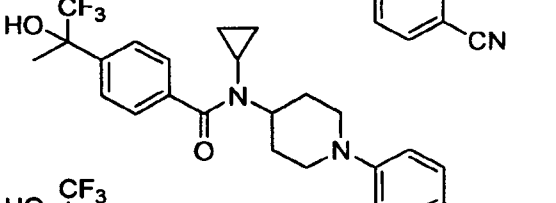
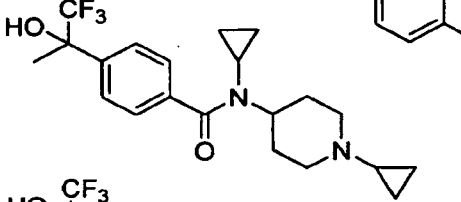
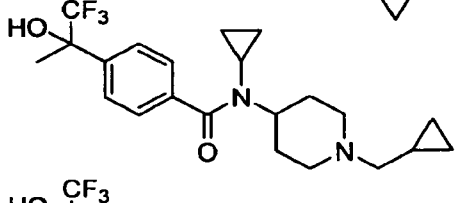
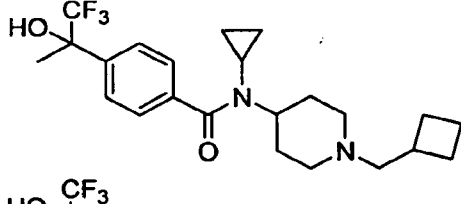
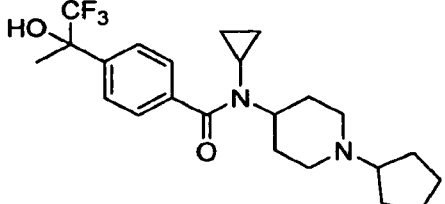
[0125] In yet another embodiment, alone or in combination with another embodiment described herein, X is a (C₁-C₈)alkylene.

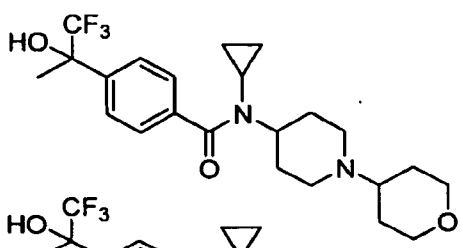
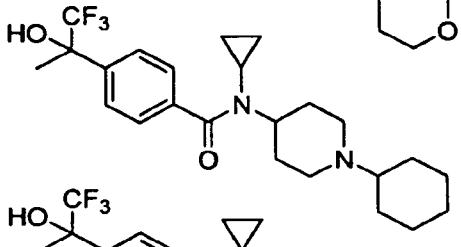
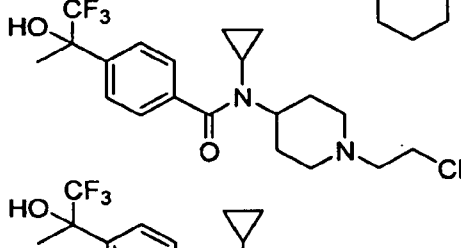
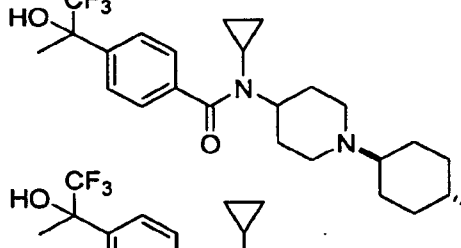
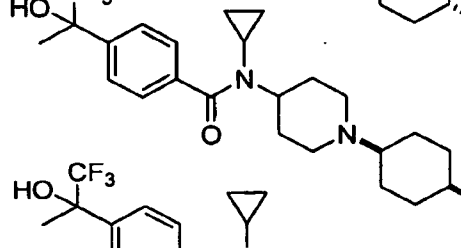
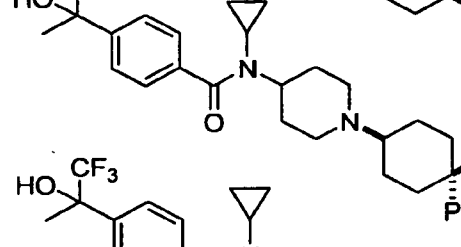
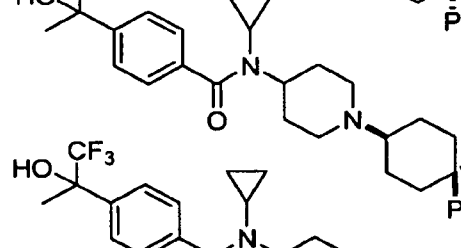
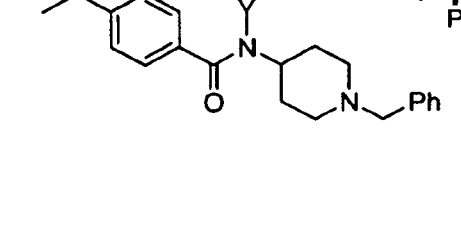
[0126] In still another embodiment, alone or in combination with another embodiment described herein, Y is (C₃-C₈)cycloalkyl.

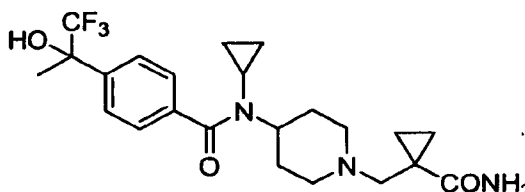
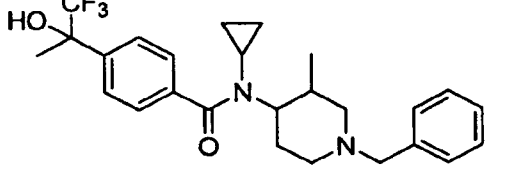
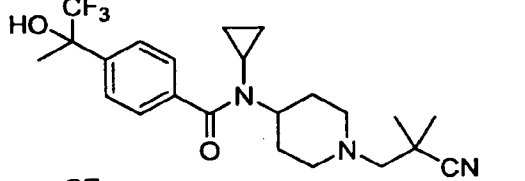
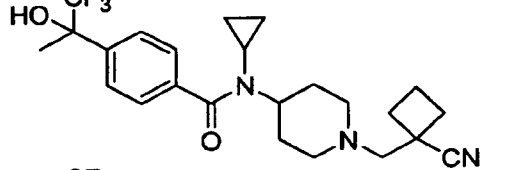
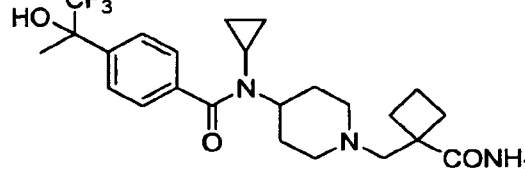
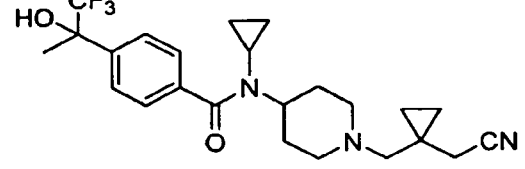
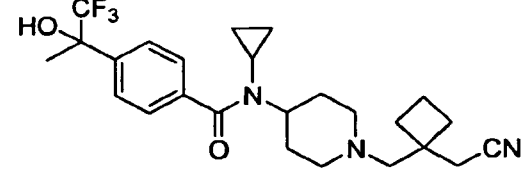
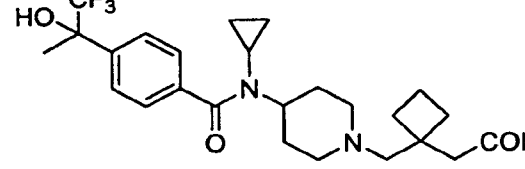
[0127] The benzamide derivatives can have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the benzamide derivatives, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them.

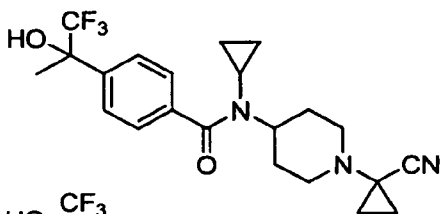
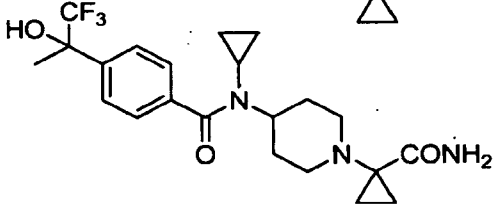
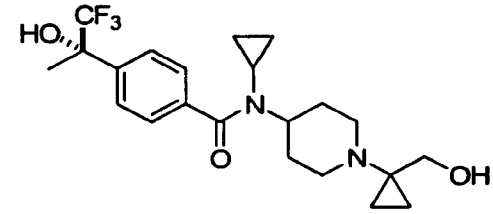
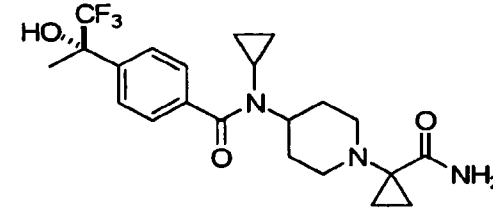
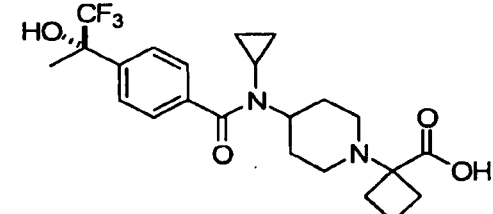
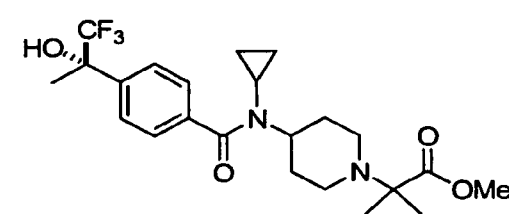
[0128] It should be noted that racemates, racemic mixtures, and stereoisomers, particularly diastereomeric mixtures or diastereomerically pure compounds and enantiomers or enantiomerically pure compounds of the above are all encompassed.

[0129] Specific examples of the compounds of Formula (I) are provided below:

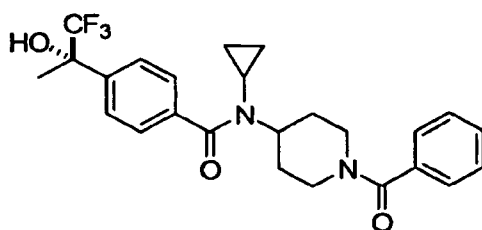
Compound ID	Structure	FW
1		435.5
2		432.5
3		457.5
4		475.5
5		396.5
6		410.5
7		424.5
8		424.5

Compound ID	Structure	FW
9		440.5
10		438.5
11		409.4
12		514.6
13		514.6
14		539.6
15		539.6
16		446.5

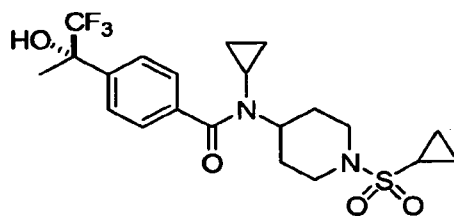
Compound ID	Structure	FW
17		453.5
18		460.5
19		437.5
20		449.5
21		467.5
22		449.5
23		463.5
24		481.6

Compound ID	Structure	FW
25		421.5
26		439.5
27		
28		
29		
30		

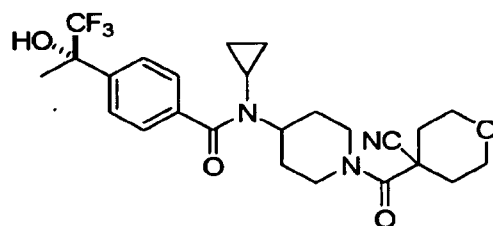
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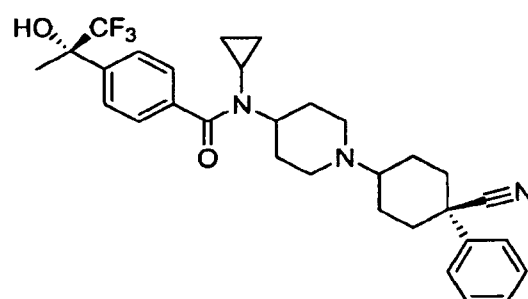
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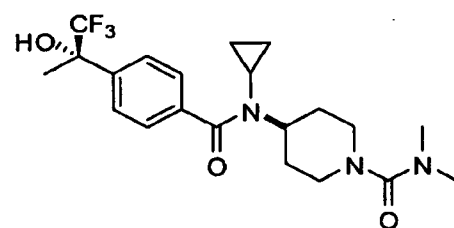
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[0130] The present invention also provides compositions comprising a therapeutically effective amount of a benzamide derivative of Formula (I) and a pharmaceutically acceptable vehicle, carrier, diluent or excipient.

[0131] The invention further provides benzamide derivatives of Formula (I) that are in isolated and purified form.

[0132] The invention provides methods for treating diabetes comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0133] The invention also provides methods for treating obesity comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0134] The invention further provides methods for treating an HSD-mediated condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0135] The invention further provides methods for treating an 11 β -HSD1-mediated condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0136] The invention further provides methods for treating an 11 β -HSD2-mediated condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0137] The invention further provides methods for treating an 17 β -HSD3-mediated condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0138] The invention further provides methods for treating an HSD-responsive condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

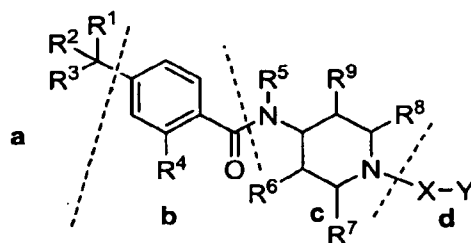
[0139] The invention further provides methods for treating an 11 β -HSD1-responsive condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

[0140] The invention further provides methods for treating an 11 β -HSD2-responsive condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

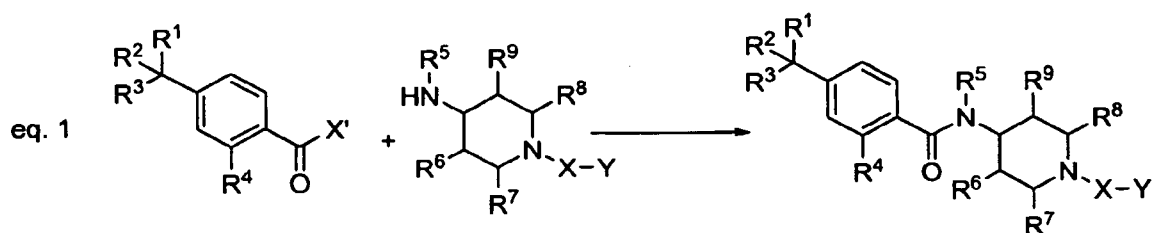
[0141] The invention further provides methods for treating an 17 β -HSD3-responsive condition or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a benzamide derivative of Formula (I).

Preparation of the Benzamide Derivatives of Formula I

[0142] Those skilled in the art will recognize that there are a variety of methods available to synthesize molecules represented in the claims. In general, useful methods for synthesizing compounds represented in the claims consist of three parts, which may be done in any order: Formation of an amide bond, installation of a $-\text{CR}^1\text{R}^2\text{R}^3$ group, and installation or modification of functional groups appended to the piperidine group and the $-\text{R}^4$ containing aryl ring. Retrosynthetic disconnection of the compounds of the invention into fragments **a-d** useful for construction of the compounds, is shown below:

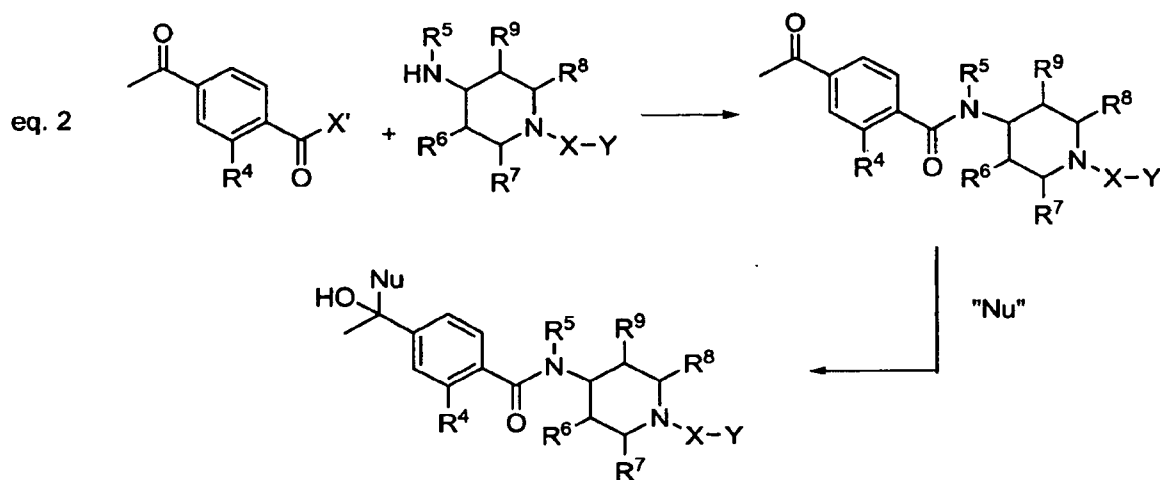


[0143] Several methods for the preparation of claimed compounds are illustrated (eq. 1-3). Equation one demonstrates one method of forming the amide linkage. In the case of eq. 1 X' is chosen from an appropriate group such as OH, Cl, and F, or additionally from any group capable of activating a carbonyl group for displacement by an amine (i.e. OSu, imidazole, etc.).

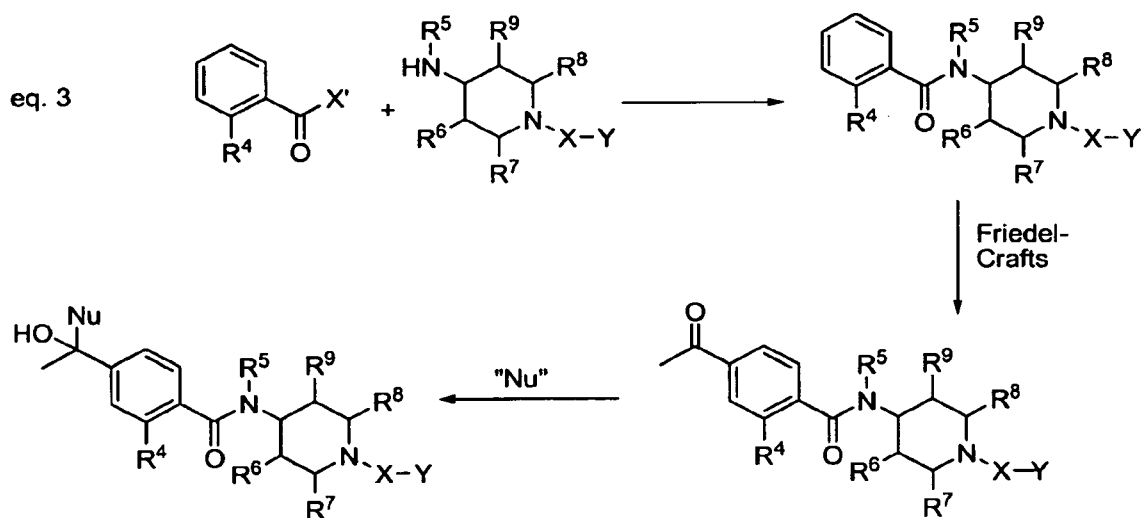


[0144] The coupling referred to in eq. 1 may be assisted by the use of organic or inorganic bases, activating agents such as HBTU, etc., and also by catalysts, in particular by those catalysts known in the art which assist in the formation of amide bonds such as DMAP, HOBT, etc. Example coupling partners include carboxylic acid and amine, acyl chloride and amine, acyl fluoride and amine, COOSu and amine and so forth. Those skilled in the art will recognize there are other possible combinations which will also result in the desired product.

[0145] Installation of the $-\text{CR}^1\text{R}^2\text{R}^3$ group may occur before or after the central coupling reaction, and may be further modified at various times during the preparation of the claimed molecules. Equation 2 demonstrates one method in which the $-\text{CR}^1\text{R}^2\text{R}^3$ group is installed in the form of a ketone before the central coupling reaction, followed by further modification to reach compounds in the claims. Following the central coupling, addition of a nucleophile such as CF_3^- or CH_3^- via addition of CF_3TMS , MeLi , MeMgBr or similar reagent completes the installation of the $-\text{CR}^1\text{R}^2\text{R}^3$ group. This may be followed by further modification of substituents to complete the preparation.

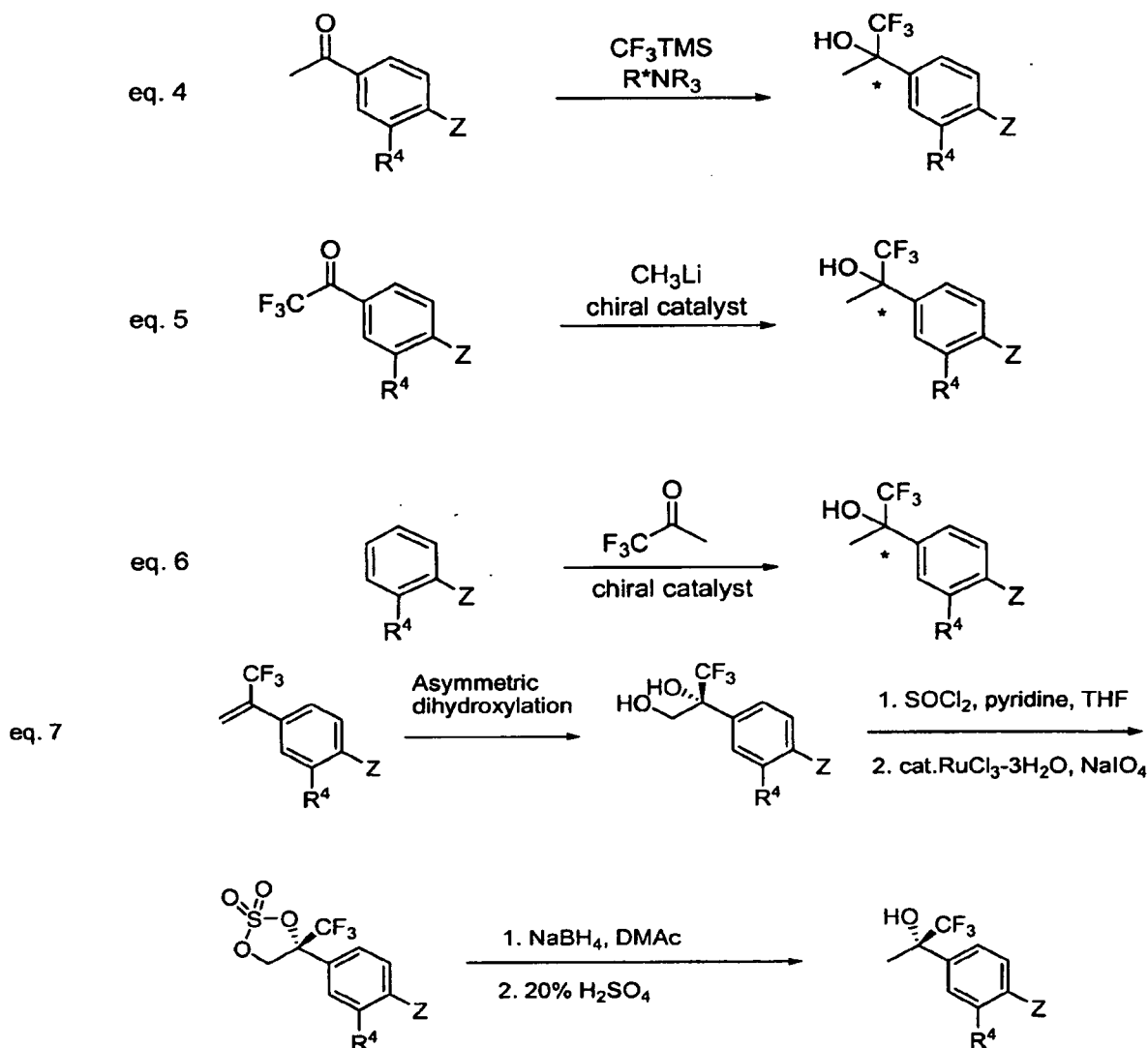


[0146] Alternatively the $-\text{CR}^1\text{R}^2\text{R}^3$ group may be installed following the central coupling via Friedel-Crafts acylation as in eq. 3. Those skilled in the art will understand that this may or may not be advantageous depending on the substituent pattern. Further modification as in eqs. 1 and 2 then provides the compounds of the claims.



[0147] Introduction of the trifluoromethyl carbinol moiety may be achieved via a variety of methods, some of which are exemplified in eq. 4-6. One may introduce the CF_3 group by addition to a ketone via use of CF_3TMS and TBAF, or one may substitute the

quaternary ammonium base of TBAF with a chiral quaternary base such as in eq. 4 to preferentially produce one enantiomer in excess (for an example see Caron et al, *Synthesis*, 2003, 1693-1698).



[0148] Another useful method is the chiral addition of a nucleophile such as MeLi or MeMgBr mediated via an amine or aminoalcohol additive (eq. 5) to a trifluoromethylketone (for an example see Thompson et al, *Tetrahedron lett.*, 1995, 49, 8937-8940. Yet another useful method is Friedel-Crafts alkylation (eq. 6), which may be done in a fashion to give optically active products via the use of chiral catalysts such as binaphthol derived titanium catalysts (Ishii et al, *J. Org. Chem.*, 2000, 65, 1597-1599), and chiral copper

catalysts (Zhuang et al, *J. Org. Chem*, **2001**, *66*, 1009-1013. Asymmetric dihydroxylation of trifluoromethyl styrene can be a highly selective method to synthesize this type of chiral carbinol. Sharpless dihydroxylation is well established and usually highly enantioselective. As shown the diol is transferred to the corresponding cyclic sulfate. The sulfate can then be reduced, subsequent hydrolysis gives the desired carbinol (eq. 7). One skilled in the art will see there are a multitude of methods available for this transformation. For the most efficient preparation of any particular compound in the claims, one skilled in the art will recognize that the timing of the introduction of the $-CR^1R^2R^3$ group can vary, and may be the first, last, or intermediate transformation in the preparation of a given compound.

[0149] A variety of the methods described above have been used to prepare compounds of the invention, some of which are exemplified in the examples.

Pharmaceutical Compositions

[0150] Pharmaceutical compositions and single unit dosage forms comprising a benzamide derivative, or a pharmaceutically acceptable stereoisomer, prodrug, salt, solvate, hydrate, or clathrate thereof, are also encompassed by the invention. Individual dosage forms of the invention may be suitable for oral, mucosal (including sublingual, buccal, rectal, nasal, or vaginal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), transdermal, or topical administration.

[0151] Single unit dosage forms of the invention are suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

[0152] The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of inflammation or a related disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, *e.g.*, Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

[0153] Typical pharmaceutical compositions and dosage forms comprise one or more carriers, excipients or diluents. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form.

[0154] This invention further encompasses anhydrous (*e.g.*, <1% water) pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, *e.g.*, Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[0155] Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine can be anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[0156] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

[0157] The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as “stabilizers,” include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[0158] The benzamide derivatives can be administered to a mammal (human, mouse, rat, rabbit, dog, cat, bovine, pig, monkey *etc.*) as an 11 β -HSD1 modulator, a prophylactic or therapeutic drug of diabetes, a prophylactic or therapeutic drug of diabetic complication (retinopathy, nephropathy, neuropathy, cardiac infarction and cerebral infarction based on arteriosclerosis *etc.*), a prophylactic or therapeutic drug of hyperlipemia, a prophylactic or therapeutic drug of obesity, neurodegenerative disease and the like, or a prophylactic or therapeutic drug of diseases mediated by 11 β -HSD1.

[0159] The benzamide derivatives can be administered to a mammal concurrently with an additional therapeutic agent for the treatment of a disease, such as diabetes or obesity, with the aim of the prophylaxis or treatment of a disease. As such, the benzamide derivatives of the present invention can be administered in combination with other therapeutic agents for the treatment or prevention of numerous diseases, including, but not limited to, diabetes and obesity.

[0160] Depending on the disease to be treated and the patient's condition, the compounds of the invention may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (*e.g.*, transdermal, local) routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. The invention also contemplates administration of the compounds of the invention in a depot formulation, in which the active ingredient is released over a defined time period.

[0161] In the case of a combined administration, the benzamide derivatives may be administered simultaneously with other another therapeutic agent that is useful for the treatment or prevention of diabetes, obesity or other disease or may be administered at a time prior to or subsequent to another therapeutic agent. In the case of combined administration, a pharmaceutical composition containing the benzamide derivative and an additional therapeutic agent can be administered. Alternatively, a pharmaceutical composition containing the benzamide derivative and a pharmaceutical composition containing an additional therapeutic agent may be administered separately. The administration routes of respective pharmaceutical compositions may be the same or different.

[0162] In the case of a combined administration, the benzamide derivatives may be administered at a dose of 50 mg to 800 mg per administration, which is given once to several times a day is contemplated (*e.g.*, once-weekly). In addition, the compound may be administered at a smaller dose. The combined pharmaceutical agent can be administered at a dose generally employed for the prophylaxis or treatment of diabetes or obesity or at a smaller dose than that.

[0163] Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise a benzamide derivative, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, polymorph or prodrug thereof. In the treatment or prevention of diabetes, obesity, glaucoma, osteoporosis, cognitive disorders, immune disorders, depression or other

conditions or disorders associated with the modulation of an hydroxysteroid dehydrogenase, an appropriate dosage level will generally be from about 0.001 to about 100 mg per kg patient body weight per day which can be administered in single or multiple doses. An exemplary dosage level will be from about 0.01 to about 25 mg/kg per day or about 0.05 to about 10 mg/kg per day. In other embodiments, a suitable dosage level may be from about 0.01 to about 25 mg/kg per day, about 0.05 to about 10 mg/kg per day, or about 0.1 to about 5 mg/kg per day. Within this range the dosage may be from about 0.005 to about 0.05, about 0.05 to about 0.5 or about 0.5 to about 5.0 mg/kg per day lie within the range of from about 0.1 mg to about 2000 mg per day, given as a single once-a-day dose in the morning but typically as divided doses throughout the day taken with food. In one embodiment, the daily dose is administered twice daily in equally divided doses. A daily dose range can be from about 5 mg to about 500 mg per day, or between about 10 mg and about 300 mg per day. In managing the patient, the therapy can be initiated at a lower dose, perhaps from about 1 mg to about 25 mg, and increased if necessary up to from about 200 mg to about 2000 mg per day as either a single dose or divided doses, depending on the patient's global response.

[0164] For multidrug therapy, the weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the invention is combined with an NSAID, the weight ratio of the compound of the invention to the NSAID will generally range from about 1000:1 to about 1:1000, or about 200:1 to about 1:200. Combinations of a compound of the invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[0165] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Oral dosage forms

[0166] Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990).

[0167] Typical oral dosage forms of the invention are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[0168] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[0169] For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0170] Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants.

Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[0171] Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[0172] Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

[0173] Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

[0174] Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algin, other celluloses, gums, and mixtures thereof.

[0175] Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

[0176] For oral administration, the compositions can be provided in the form of tablets containing about 1 to about 1000 milligrams of the active ingredient. In other embodiments, the compositions are provided in provided in the form of tablets containing about 1.0, about 5.0, about 10.0, about 15.0, about 20.0, about 25.0, about 50.0, about 75.0, about 100.0, about 150.0, about 200.0, about 250.0, about 300.0, about 400.0, about 500.0, about 600.0, about 750.0, about 800.0, about 900.0, or about 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, such as, for example, once or twice per day.

Delayed release dosage forms

[0177] Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770;

3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

[0178] Controlled-release pharmaceutical products can improve drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[0179] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

Parenteral dosage forms

[0180] Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intra-arterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms can be sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions. For example, lyophilized sterile compositions suitable for reconstitution into particulate-free dosage forms suitable for administration to humans.

[0181] Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[0182] Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

[0183] Parenteral dosage forms are exemplary for the methods of preventing, treating or managing disease in a cancer patient.

Transdermal and topical dosage forms

[0184] Transdermal and topical dosage forms of the invention include, but are not limited to, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. See, *e.g.*, Remington's Pharmaceutical Sciences, 18th eds., Mack Publishing, Easton PA (1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Transdermal dosage forms include "reservoir type"

or “matrix type” patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

[0185] Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal and topical dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels or ointments, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants also can be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, *e.g.*, Remington’s Pharmaceutical Sciences, 18th eds., Mack Publishing, Easton PA (1990).

[0186] Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

[0187] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing

agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Mucosal dosage forms and lung delivery

[0188] Mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, sprays and aerosols, or other forms known to one of skill in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th eds., Mack Publishing, Easton PA (1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels. In one embodiment, the aerosol comprises a carrier. In another embodiment, the aerosol is carrier free.

[0189] A compound of the invention can also be administered directly to the lung by inhalation (see e.g., Tong et al., International Publication No. WO 97/39745; Clark et al, International Publication No. WO 99/47196, which are herein incorporated by reference). For administration by inhalation, a benzamide derivative can be conveniently delivered to the lung by a number of different devices. For example, a Metered Dose Inhaler ("MDI") which utilizes canisters that contain a suitable low boiling propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas can be used to deliver a benzamide derivative directly to the lung. MDI devices are available from a number of suppliers such as 3M Corporation, Aventis, Boehringer Ingelheim, Forest Laboratories, Glaxo-Wellcome, Schering Plough and Vectura.

[0190] Alternatively, a Dry Powder Inhaler (DPI) device can be used to administer a benzamide derivative to the lung (See, e.g., Raleigh et al., Proc. Amer. Assoc. Cancer Research Annual Meeting, 1999, 40, 397, which is herein incorporated by reference). DPI devices typically use a mechanism such as a burst of gas to create a cloud of dry powder inside a container, which can then be inhaled by the patient. DPI devices are also well known in the art and can be purchased from a number of vendors which include, for example, Fisons, Glaxo-Wellcome, Inhale Therapeutic Systems, ML Laboratories, Qdose and Vectura. A popular variation is the multiple dose DPI ("MDDPI") system, which allows for the delivery of more than one therapeutic dose. MDDPI devices are available from companies such as AstraZeneca, GlaxoWellcome, IVAX, Schering Plough, SkyePharma and Vectura.

For example, capsules and cartridges of gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch for these systems.

[0191] Another type of device that can be used to deliver a benzamide derivative to the lung is a liquid spray device supplied, for example, by Aradigm Corporation. Liquid spray systems use extremely small nozzle holes to aerosolize liquid drug formulations that can then be directly inhaled into the lung.

[0192] In one embodiment, a nebulizer device is used to deliver a benzamide derivative to the lung. Nebulizers create aerosols from liquid drug formulations by using, for example, ultrasonic energy to form fine particles that can be readily inhaled (See *e.g.*, Verschoye et al., British J Cancer, 1999, 80, Suppl 2, 96, which is herein incorporated by reference). Examples of nebulizers include devices supplied by Sheffield/Systemic Pulmonary Delivery Ltd. (See, Armer et al., U.S. Pat. No. 5,954,047; van der Linden et al., U.S. Pat. No. 5,950,619; van der Linden et al., U.S. Pat. No. 5,970,974, which are herein incorporated by reference), Aventis and Batelle Pulmonary Therapeutics. Inhaled compounds, delivered by nebulizer devices, are currently under investigation as treatments for aerodigestive cancer (Engelke et al., Poster 342 at American Association of Cancer Research, San Francisco, Calif., Apr. 1-5, 2000) and lung cancer (Dahl et al., Poster 524 at American Association of Cancer Research, San Francisco, Calif., April 1-5, 2000).

[0193] In another embodiment, an electrohydrodynamic ("EHD") aerosol device is used to deliver a benzamide derivative to the lung. EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions (see *e.g.*, Noakes et al., U.S. Pat. No. 4,765,539; Coffee, U.S. Pat. No., 4,962,885; Coffee, International Publication No. WO 94/12285; Coffee, International Publication No. WO 94/14543; Coffee, International Publication No. WO 95/26234, Coffee, International Publication No. WO 95/26235, Coffee, International Publication No. WO 95/32807, which are herein incorporated by reference). The electrochemical properties of the compound of the invention formulation may be important parameters to optimize when delivering this drug to the lung with an EHD aerosol device and such optimization is routinely performed by one of skill in the art. EHD aerosol devices may more efficiently delivery drugs to the lung than existing pulmonary delivery

technologies. Other methods of intra-pulmonary delivery of a benzamide derivative will be known to the skilled artisan and are within the scope of the invention.

[0194] Liquid drug formulations suitable for use with nebulizers and liquid spray devices and EHD aerosol devices will typically include a benzamide derivative with a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutically acceptable carrier is a liquid such as alcohol, water, polyethylene glycol or a perfluorocarbon. Optionally, another material may be added to alter the aerosol properties of the solution or suspension of a benzamide derivative. This material is liquid such as an alcohol, glycol, polyglycol or a fatty acid. Other methods of formulating liquid drug solutions or suspension suitable for use in aerosol devices are known to those of skill in the art (See, *e.g.*, Biesalski, U.S. Pat. Nos. 5,112,598; Biesalski, 5,556,611, which are herein incorporated by reference). A compound of the invention can also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[0195] In addition to the formulations described previously, a benzamide derivative can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Other delivery systems

[0196] Alternatively, other pharmaceutical delivery systems can be employed. Liposomes and emulsions are well known examples of delivery vehicles that can be used to deliver a benzamide derivative. Certain organic solvents such as dimethylsulfoxide can also be employed, although usually at the cost of greater toxicity. A compound of the invention can also be delivered in a controlled release system. In one embodiment, a pump can be used (Sefton, CRC Crit. Ref Biomed Eng., 1987, 14, 201; Buchwald et al., Surgery, 1980, 88, 507; Saudek et al., N. Engl. J Med, 1989, 321, 574). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and

Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J Macromol. Sci. Rev. Macromol. Chem., 1983, 23, 61; see also Levy et al., Science 1985, 228, 190; During et al., Ann. Neurol., 1989, 25, 351; Howard et al., 1989, J. Neurosurg. 71, 105). In yet another embodiment, a controlled-release system can be placed in proximity of the target of the compounds of the invention, e.g., the lung, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115 (1984)). Other controlled-release system can be used (see e.g., Langer, Science, 1990, 249, 1527).

[0197] Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular site or method which a given pharmaceutical composition or dosage form will be administered. With that fact in mind, typical excipients include, but are not limited to, water, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof, which are non-toxic and pharmaceutically acceptable. Examples of such additional ingredients are well known in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th eds., Mack Publishing, Easton PA (1990).

[0198] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, can also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Therapeutic Uses Of The Benzamide Derivatives

[0199] In one embodiment, the invention provides methods of treating or preventing a condition or disorder associated with the modulation of hydroxysteroid dehydrogenases by

administering to a patient having such a condition or disorder a therapeutically effective amount of a compound or composition of the invention. In one group of embodiments, conditions and disorders, including chronic diseases of humans or other species, can be treated with modulators, stimulators, or inhibitors of hydroxysteroid dehydrogenases, such as 11 β -HSD1.

Treatment or prevention of diabetes

[0200] Diabetes and diabetic conditions can be treated or prevented by administration of a therapeutically effective amount of a benzamide derivative.

[0201] Types of diabetes that can be treated or prevented by administering a therapeutically effective amount of a benzamide derivative include type I diabetes mellitus (juvenile onset diabetes, insulin dependent-diabetes mellitus or IDDM), type II diabetes mellitus (non-insulin-dependent diabetes mellitus or NIDDM), insulinopathies, diabetes associated with pancreatic disorders, diabetes associated with other disorders (such as Cushing's Syndrome, acromegaly, pheochromocytoma, glucagonoma, primary aldosteronism, and somatostatinoma), type A and type B insulin resistance syndromes, lipatrophic diabetes, and diabetes induced by β -cell toxins.

[0202] In some embodiments, the type of diabetes being treated is type II diabetes.

Treatment or prevention of obesity

[0203] Obesity can be treated or prevented by administration of a therapeutically effective amount of a benzamide derivative.

[0204] Obesity may have genetic, environmental (*e.g.*, expending less energy than is consumed) and regulatory determinants. Obesity includes exogenous, hyperinsular, hyperplasmic, hypothyroid, hypothalamic, symptomatic, infantile, upper body, alimentary, hypogonadal, simple and central obesity, hypophyseal adiposity and hyperphagia. Metabolic disorders, such as hyperlidemia and diabetes, and cardiovascular disorders, such as hypertension and coronary artery disease, are commonly associated with obesity.

[0205] Complications due to obesity may also be treated or prevented by administering a therapeutically effective amount of a benzamide derivative. Such complications include, but are not limited to, sleep apnea, Pickwickian syndrome, orthopedic

disturbances of weight-bearing and non-weight-bearing joints, and skin disorders resulting from increased sweat or skin secretions.

Treatment or prevention of other conditions

[0206] Other conditions that can be treated or prevented by administering a therapeutically effective amount of a benzamide derivative include, but are not limited to any condition which is responsive to the modulation, such as inhibition, of hydroxysteroid dehydrogenases or specific isoforms thereof, and thereby benefit from administration of such a modulator. Representative conditions in this regard include, but are not limited to, metabolic disorders and related cardiovascular risk factors such as syndrome X, polycystic ovarian disease, eating disorders (e.g., anorexia and bulimia), craniopharyngioma, Prader-Willi syndrome, Frohlich's syndrome, hyperlipidemia, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, low HDL levels, high HDL levels, hyperglycemia, insulin resistance, hyperinsulinemia and Cushing's syndrome; diseases associated therewith such as hypertension, atherosclerosis, vascular restenosis, retinopathy and nephropathy; neurologic disorders such as neurodegenerative disease, neuropathy and muscle wasting; cognitive disorders, such as age-related learning disorders, dementia, neurodegeneration, as well as for improvement of cognitive function in subjects ranging from the severely impaired (e.g., Parkinson's or Alzheimer's associated dementia) to mildly impaired (e.g., age-associated memory impairment, drug-induced cognitive impairment) to unimpaired subjects (e.g., cognitive enhancers for the general population) (see, Sandeep, et al., PNAS, electronically available at www.pnas.org/cgi/doi/10.1073/pnas.0306996101); androgen and/or estrogen-related disorders such as prostate cancer, colon cancer, breast cancer, benign prostatic hyperplasia, ovarian cancer, uterine cancer, and male pseudohermaphrodisim; endometriosis, dementia, depression, psoriasis, glaucoma, osteoporosis, viral infections, inflammatory disorders, and immune disorders.

Additional therapeutic agents

[0207] In one embodiment, the present methods for treating or preventing further comprise the administration of a therapeutically effective amount of another therapeutic agent useful for treating or preventing the diseases or disorders disclosed herein. In this

embodiment, the time in which the therapeutic effect of the other therapeutic agent is exerted overlaps with the time in which the therapeutic effect of the benzamide derivative is exerted.

[0208] The compounds of the invention can be combined or used in combination with other agents useful in the treatment, prevention, suppression or amelioration of the conditions or disorders for which compounds of the invention are useful, including diabetes, obesity, glaucoma, osteoporosis, cognitive disorders, immune disorders, depression and those pathologies noted above.

[0209] Such other agents, or drugs, may be administered, by a route and in an amount commonly used therefor, simultaneously or sequentially with a benzamide derivative. In one embodiment, a pharmaceutical composition contains such other drugs in addition to the compound of the invention when a benzamide derivative is used contemporaneously with one or more other drugs. Accordingly, the pharmaceutical compositions of the invention include those that also contain one or more other active ingredients or therapeutic agents, in addition to a benzamide derivative.

[0210] In one embodiment, for the treatment or prevention of diabetes, a benzamide derivative can be administered with another therapeutic agent, including, but not limited to, anti-diabetic agents such as insulin, inhaled insulin (*Exubera*®), insulin mimetics, insulin secretogues, sulfonylureas (*e.g.*, glyburide, meglitinide, glimepiride, glipizide, glipizide, gliquidone, chlorpropresponsivemide, tolbutamide, acetoexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolclamide and tolazamide), biguanides (*e.g.*, metformin (*Glucophage*®)), α -glucosidase inhibitors (*e.g.*, acarbose, voglibose and miglitol), thiazolidinone compounds (*e.g.*, rosiglitazone (*Avandia*®), troglitazone (*Rezulin*®), ciglitazone, pioglitazone (*Actos*®) and englitazone), prandial glucose regulators (*e.g.*, repaglinide and nateglinide) and glucagon receptor antagonists.

[0211] In another embodiment, for the treatment or prevention of obesity, a benzamide derivative can be administered with another therapeutic agent, including, but not limited to, β 3 adrenergic receptor agonists, leptin or derivatives thereof, neuropeptide Y (*e.g.*, NPY5) antagonists, and mazindol.

[0212] Examples of other therapeutic agents that may be combined with a benzamide derivative, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (i) cholesterol lowering agents such as HMG-CoA reductase inhibitors (*e.g.*, lovastatin, simvastatin (*Zocor*®), pravastatin, fluvastatin, atorvastatin (*Lipitor*®) and other statins), bile acid sequestrants (*e.g.*, cholestyramine and colestipol), vitamin B₃ (also known as nicotinic acid, or niacin), vitamin B₆ (pyridoxine), vitamin B₁₂ (cyanocobalamin), fibric acid derivatives (*e.g.*, gemfibrozil, clofibrate, fenofibrate and benzaifibrate), probucol, nitroglycerin, and inhibitors of cholesterol absorption (*e.g.*, beta-sitosterol and acylCoA-cholesterol acyltransferase (ACAT) inhibitors such as melinamide), HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and squalene synthetase inhibitors; (ii) antithrombotic agents, such as thrombolytic agents (*e.g.*, streptokinase, alteplase, anistreplase and reteplase), heparin, hirudin and warfarin derivatives, β -blockers (*e.g.*, atenolol), β adrenergic agonists (*e.g.*, isoproterenol), angiotensin II antagonists, ACE inhibitors and vasodilators (*e.g.*, sodium nitroprusside, nicardipine hydrochloride, nitroglycerin and enalaprilat); (iii) PPAR agonists, *e.g.*, PPAR γ and PPAR δ agonists; (iv) DP antagonists; (v) lubricants or emollients such as petrolatum and lanolin, keratolytic agents, vitamin D₃ derivatives (*e.g.*, calcipotriene and calcipotriol (*Dovonex*®)), PUVA, anthralin (*Drithrocreme*®), etretinate (*Tegison*®) and isotretinoin; (vi) glaucoma therapies such as cholinergic agonists (*e.g.*, pilocarpine and carbachol), cholinesterase inhibitors (*e.g.*, physostigmine, neostigmine, demecarium, echothiophate iodide and isofluorophate), carbonic anhydrase inhibitors (*e.g.*, acetazolamide, dichlorphenamide, methazolamide, ethoxzolamide and dorzolamide), non-selective adrenergic agonists (*e.g.*, epinephrine and dipivefrin), α_2 -selective adrenergic agonists (*e.g.*, apraclonidine and brimonidine), β -blockers (*e.g.*, timolol, betazolol, levobunolol, carteolol and metipranolol), prostaglandin analogs (*e.g.*, latanoprost) and osmotic diuretics (*e.g.*, glycerin, mannitol and isosorbide); corticosteroids, such as beclomethasone, methylprednisolone, betamethasone, prednisone, prednisolone, dexamethasone, fluticasone and hydrocortisone, and corticosteroid analogs such as budesonide; (vii) immunosuppressants such as cyclosporine (cyclosporine A, *Sandimmune*®, *Neoral*®), tacrolimus (FK-506, *Prograf*®), rapamycin (sirolimus, *Rapamune*®) and other FK-506 type immunosuppressants, and mycophenolate, *e.g.*, mycophenolate mofetil (*CellCept*®); (viii) non-steroidal antiinflammatory agents (NSAIDs)

such as propionic acid derivatives (*e.g.*, alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid and tioxaprofen), acetic acid derivatives (*e.g.*, indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin and zomepirac), fenamic acid derivatives (*e.g.*, flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (*e.g.*, diflunisal and flufenisal), oxicams (*e.g.*, isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (*e.g.*, acetylsalicylic acid and sulfasalazine) and the pyrazolones (*e.g.*, apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone and phenylbutazone); (ix) cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (*Celebrex*[®]) and rofecoxib (*Vioxx*[®]); (xi) inhibitors of phosphodiesterase type IV (PDE-IV); (xii) opioid analgesics such as codeine, fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, propoxyphene, buprenorphine, butorphanol, dezocine, nalbuphine and pentazocine; (xiii) a hepatoprotective agent; and (xiv) other compounds such as 5-aminosalicylic acid and prodrugs thereof.

[0213] The weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a benzamide derivative is combined with an NSAID, the weight ratio of the compound of the invention to the NSAID will generally range from about 1000:1 to about 1:1000, such as about 200:1 to about 1:200. Combinations of a benzamide derivative and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

Kits

[0214] The invention encompasses kits that can simplify the administration of the benzamide derivatives or composition of the invention to a patient.

[0215] A typical kit of the invention comprises a unit dosage of a benzamide derivative. In one embodiment, the unit dosage form is in a container, which can be sterile, containing a therapeutically effective amount of a benzamide derivative and a

pharmaceutically acceptable vehicle. In another embodiment, the unit dosage form is in a container containing a therapeutically effective amount of a benzamide derivative as a lyophilate or pharmaceutically acceptable salt. In this instance, the kit can further comprise another container that contains a solution useful for the reconstitution of the lyophilate or dissolution of the salt. The kit can also comprise a label or printed instructions for use of the benzamide derivatives.

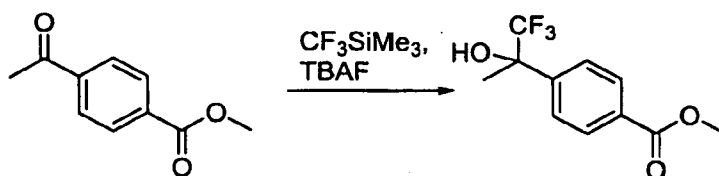
[0216] In a further embodiment, the kit comprises a unit dosage form of a composition of the invention.

[0217] Kits of the invention can further comprise one or more devices that are useful for administering the unit dosage forms of the benzamide derivatives or a composition of the invention. Examples of such devices include, but are not limited to, a syringe, a drip bag, a patch or an enema, which optionally contain the unit dosage forms.

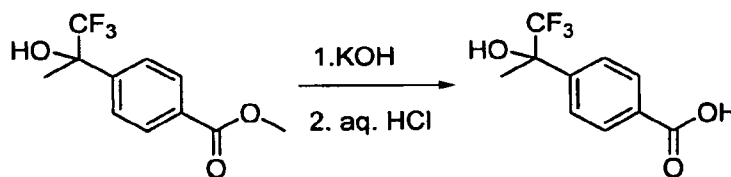
[0218] The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few embodiments of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims. To this end, it should be noted that one or more hydrogen atoms or methyl groups may be omitted from the drawn structures consistent with accepted shorthand notation of such organic compounds, and that one skilled in the art of organic chemistry would readily appreciate their presence.

EXAMPLES

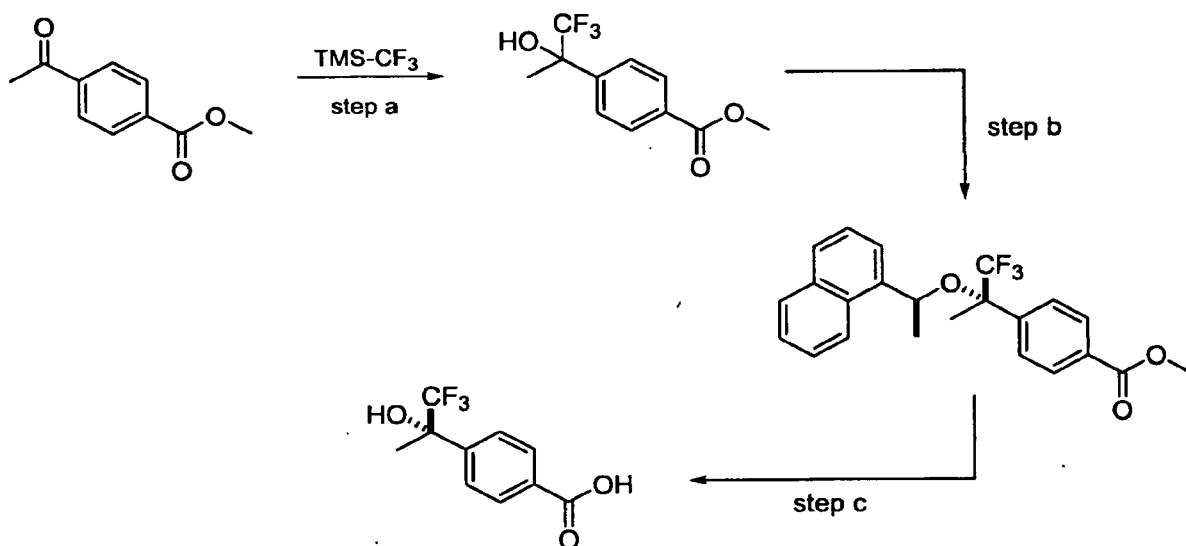
[0219] The benzamide derivatives represented by the formulas of the present invention and the methods of making thereof are explained in detail in the following Examples, which are not to be construed as limiting the invention.



[0220] To a mixture of methyl 4-acetylbenzoate (5.0g, 28.1 mmol) and CF_3SiMe_3 (12.5mL, 84.2 mmol) in THF (150 mL) TBAF (1.0 M, 78.6 mL, 78.6 mmol) was added dropwise at 0 °C. The mixture was then stirred for 2.5 h at room temperature, diluted with Et_2O (100 mL). The solution was washed with saturated aqueous NaHCO_3 , and brine, dried, and concentrated. Flash chromatography of the residue, using 2:8 EtOAc-hexane, gave methyl 4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoate: ^1H NMR (CDCl_3) δ 8.07(d, J = 8.5 Hz, 2 H), δ 7.67(d, J = 8.5 Hz, 2 H), 3.93(s, 3 H), 2.70(br, 1H), 1.80(s, 3H); ms 249.1 ($\text{M}+\text{H}^+$).



[0221] A mixture of methyl 4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoate (6.0g, 24.2 mmol) and KOH (2.72g, 48.4 mmol) in 1,4-dioxane (100mL) and H_2O (50 mL) was refluxed for 2 h. The reaction mixture was cooled to room temperature, evaporation of the solvent 1,4-dioxane *in vacuo*. The aqueous residue was acidified with 2N HCl and extracted with CH_2Cl_2 . The extracts were washed with brine and dried. Flash chromatography of the residue, using 3:7 EtOAc-hexane, gave 4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid: ^1H NMR (CDCl_3) δ 11.0(br, 1H), 7.95(d, J = 6.8 Hz, 2 H), 7.71(d, J = 6.8 Hz, 2 H), 6.73 (s, 1 H), 1.71(s, 3H); ms 235.0 ($\text{M}+\text{H}^+$).



[0222] Synthesis of optically active carboxylic acid: a). Methyl 4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoate: To a 3 L flask containing methyl 4-acetylbenzoate (60 g, 0.34 mol, 1.0 equiv) in 1.0 L THF was charged with 96.6g TMS-CF₃ (0.68 mol, 2.0 equiv) at 0 °C. The solution was allowed to stir for 30 min. 680 mL tetrabutylammonium fluoride (1.0M in THF, 0.68 mol, 2.0 equiv) was added dropwise via addition funnel over a period of 3h. After addition, the solution was allowed to stir for an additional 30min and warm to room temperature. The solution was concentrated down under reduced pressure. Then the mixture was diluted with Sat. NaHCO₃, extracted (4 x 10% MeOH/CH₂Cl₂). The organics were combined, dried (MgSO₄) and concentrated under reduced pressure. Purification by flash chromatography (SiO₂, 15 % EtOAc /Hexanes) gave the product as an orange oil.

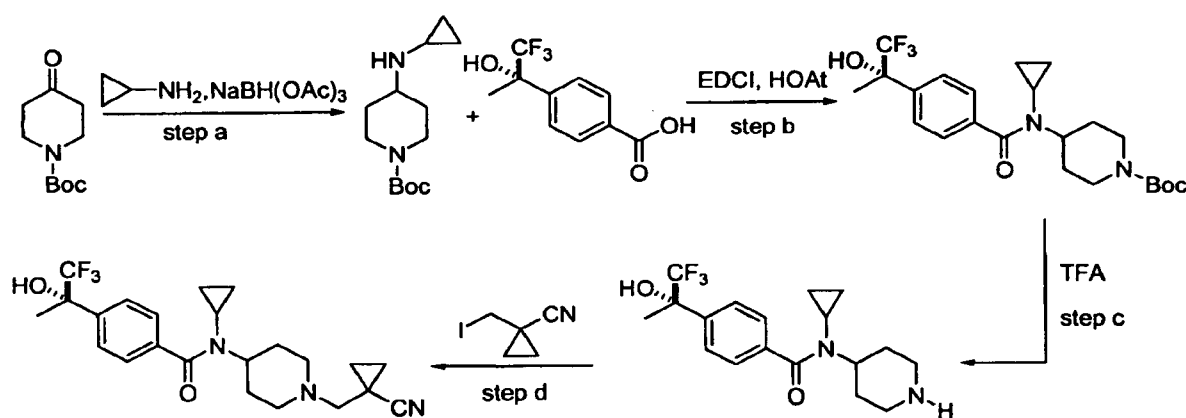
[0223] b). Methyl 4-(((S)-1,1,1-trifluoro-2-(((S)-1-(naphthalen-1-yl)ethyl)carbamoyloxy)-propan-2-yl)benzoate: To a 500 mL flask containing a portion of product obtained above (25 g, 0.1 mol, 1.0 equiv) in 150 mL CH₂Cl₂ was charged with 19.7 g DMAP (0.16 mol, 1.6 equiv) at 0 °C. 28.5 g 4-nitrophenyl chloroformate (0.14 mol, 1.4 equiv) was added in portions. The resulting mixture was allowed to stir for 15 min at 0 °C and 3.0 h at room temperature. The mixture was cooled to 0 °C. 34.2g (S)-1-(1-naphthalenyl)ethanamine (0.2 mol, 2.0 equiv) was added in portions. After addition, the solution was allowed to stir at room temperature for 1h. The mixture was diluted with EtOAc,

washed with 6 x 1 M NaOH, 1 N HCl and brine. The organics was dried and concentrated under reduced pressure. The two diastereomers were purified and separated by flash chromatography (SiO₂, 15 % Methyl-*t*-butyl ether /Hexanes). The first portion of the two close spots was collected and concentrated under reduced pressure to give the pure diastereomer as colorless oil.

[0224] c). (*S*)-4-(1,1,1-Trifluoro-2-hydroxypropan-2-yl)benzoic acid: To a 250 mL flask containing product obtained above (13.5g, 30 mmol, 1.0 equiv) was charged with 70 mL THF, 30 mL H₂O, 30 mL MeOH and 0.73 g LiOH (0.3 mol, 10.0 equiv). The resulting mixture was stirred at 45 °C for overnight. The mixture was extracted with CH₂Cl₂. The aqueous layer was then acidified with 2 N HCl to pH ~ 4 and extracted (5 x 10% MeOH/CH₂Cl₂). The organics were dried (MgSO₄), concentrated under reduced pressure to yield the product as white solid.

Example 1

Preparation of (*S*)-*N*-{1-[(1-cyanocyclopropyl)methyl]piperidin-4-yl}-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0225] a). A solution of 1-Boc-4-piperidone (3.00 g, 15.1 mmol, 1.0 equiv.), cyclopropylamine (1.25 mL, 18.1 mmol, 1.2 equiv.) and AcOH (1.03 mL, 18.1 mmol, 1.2 equiv.) in 1,2-dichloroethane (50 mL) was treated at 0 °C with NaBH(OAc)₃ (4.77 g, 22.5 mmol, 1.5 equiv.). After being stirred for 16 h at 25 °C, the reaction was then diluted (EtOAc) and washed (1 x 1 N aqueous NaOH and 1 x brine). The organic layer was dried

(Na₂SO₄) and concentrated under reduced pressure to provide the product as a pale pink liquid.

[0226] b). A solution of *tert*-butyl-4-(cyclopropylamino)piperidine-1-carboxylate prepared above in step a (1.50 g, 6.24 mmol, 1.1 equiv.) and (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid (1.33 g, 5.67 mmol, 1.0 equiv.) in DMF (28 mL) was treated at 0 °C with EDCI (1.30 g, 6.80 mmol, 1.2 equiv.), HOAt (927 mg, 6.80 mmol, 1.2 equiv.) and NaHCO₃ (952 mg, 11.3 mmol, 2.0 equiv.) successively. After being stirred at 25 °C for 12 h, the reaction was diluted (EtOAc) and washed (1 × 10% aqueous citric acid, 1 × saturated aqueous NaHCO₃, and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 0–5% MeOH/CH₂Cl₂, gradient elution) gave the product as a white solid.

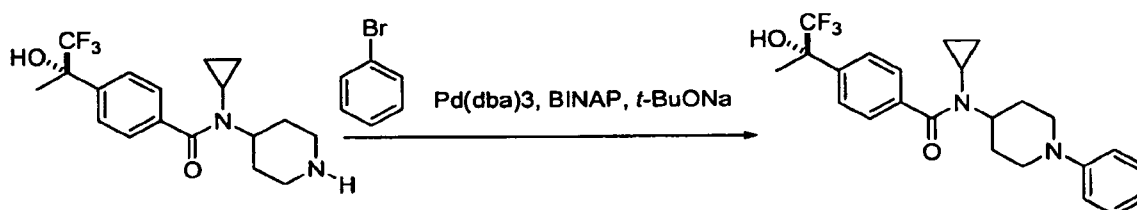
[0227] c). (*S*)-*tert*-butyl 4-[*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamido]piperidine-1-carboxylate prepared above in step b (2.33 g, 5.10 mmol, 1.0 equiv.) was treated with trifluoroacetic acid (19 mL, 260 mmol, 50 equiv.) at 0 °C. After being stirred at 25 °C for 1 h, the reaction was concentrated under reduced pressure, basified (ice-cold 1 N aqueous NaOH) and extracted (5 × 10% MeOH/CH₂Cl₂). The combined organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to provide the product as a pale yellow solid.

[0228] d). (*S*)-*N*-{1-[(1-cyanocyclopropyl)methyl]piperidin-4-yl}-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide. A solution of (*S*)-*N*-cyclopropyl-*N*-(piperidin-4-yl)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide prepared above in step c (200 mg, 0.56 mmol, 1.0 equiv.) and 1-(iodomethyl)cyclopropanecarbonitrile (140 mg, 0.68 mmol, 1.2 equiv.) in CH₃CN (2.8 mL) was treated with *N,N*-diisopropylethylamine (118 µL, 0.68 mmol, 1.2 equiv.). After being stirred for 17 h at 80 °C, the reaction was diluted (EtOAc) and washed (1 × saturated aqueous NaHCO₃, and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 0–5% MeOH/CH₂Cl₂, gradient elution) gave the title compound as a pale yellow solid: ¹H NMR (CDCl₃, 400 MHz) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 4.25–4.15 (m, 1H), 3.15–3.11 (m, 2H), 2.58–2.54 (m, 2H), 2.45 (s, 2H), 2.18–2.04

(m, 4H), 1.88–1.85 (m, 2H), 1.79 (s, 3H), 1.31–1.25 (m, 2H), 0.88–0.85 (m, 2H), 0.62–0.57 (m, 2H), 0.49–0.45 (m, 2H); MS(ESI) 436 [M+H]⁺.

Example 2

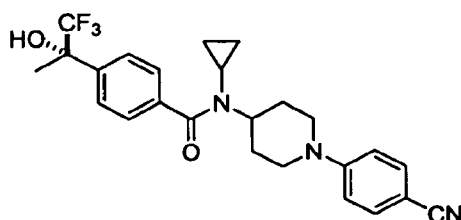
Preparation of (*S*)-*N*-cyclopropyl-*N*-(1-phenylpiperidin-4-yl)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0229] A solution of (*S*)-*N*-cyclopropyl-*N*-(piperidin-4-yl)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide prepared above in step c in Example 1 (43 mg, 0.12 mmol, 1.0 equiv.), bromobenzene (15 μ L, 0.14 mmol, 1.2 equiv.), ($\pm$)-BINAP (6.7 mg, 0.011 mmol, 0.09 equiv.), and *t*-BuONa (28 mg, 0.29 mmol, 2.4 equiv.) in toluene (150 μ L, degassed by Argon for 10 min) was treated with Pd₂(dba)₃ (3.3 mg, 0.0036 mmol, 0.03 equiv.) under Argon. After being stirred for 17 h at 80 °C under argon, the reaction was diluted (EtOAc) and washed (brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 20–50% EtOAc/Hexanes, gradient elution) gave the title compound as a pale yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.28–7.25 (m, 2H), 6.98–6.96 (m, 2H), 6.88–6.85 (m, 1H), 4.35–4.25 (m, 1H), 3.80–3.75 (m, 2H), 2.87–2.82 (m, 2H), 2.62–2.54 (m, 1H), 2.52 (s, 1H), 2.28–2.21 (m, 2H), 2.04–2.00 (m, 2H), 1.80 (s, 3H), 0.60–0.57 (m, 2H), 0.49–0.45 (m, 2H); MS(ESI) 433 [M+H]⁺.

Example 3

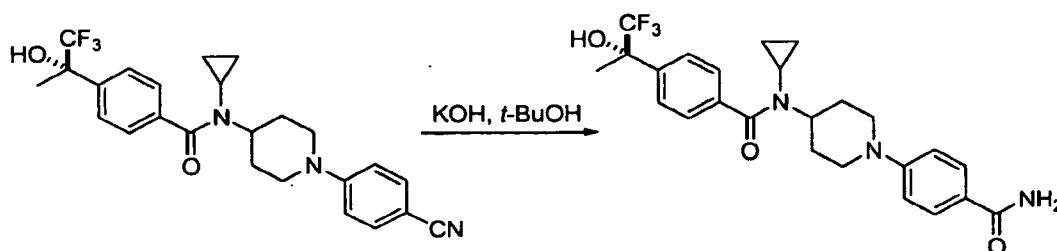
Preparation of (*S*)-*N*-[1-(4-cyanophenyl)piperidin-4-yl]-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0230] Using the methods described above in Example 2, but substituting 4-bromobenzonitrile for bromobenzene, the title compound was prepared: ^1H NMR (CDCl_3 , 500 MHz) δ 7.60 (d, $J = 8.1$ Hz, 2H), 7.50 (d, $J = 8.3$ Hz, 2H), 7.49 (d, $J = 8.9$ Hz, 2H), 6.89 (d, $J = 8.9$ Hz, 2H), 4.42–4.35 (m, 1H), 3.95–3.90 (m, 2H), 3.02–2.95 (m, 2H), 2.62–2.55 (m, 1H), 2.49 (s, 1H), 2.22–2.14 (m, 2H), 2.05–2.00 (m, 2H), 1.80 (s, 3H), 0.59–0.54 (m, 2H), 0.45–0.40 (m, 2H); MS(ESI) 458 $[\text{M}+\text{H}]^+$.

Example 4

Preparation of (*S*)-*N*-[1-(4-carbamoylphenyl)piperidin-4-yl]-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide

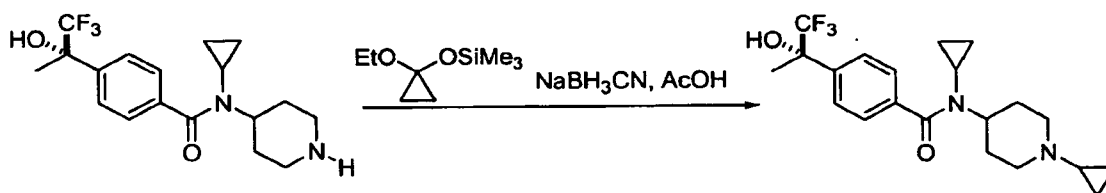


[0231] A solution of (*S*)-*N*-[1-(4-cyanophenyl)piperidin-4-yl]-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide prepared above in Example 3 (29 mg, 0.063 mmol, 1.0 equiv.) in *t*-BuOH (2.0 mL) was treated with KOH (18 mg, 0.32 mmol, 5.0

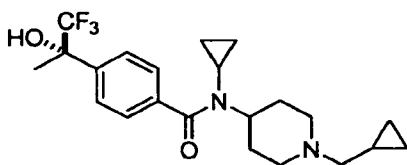
equiv.) and stirred for 17 h at 85 °C. The reaction was concentrated under reduced pressure and purification of the residue by flash chromatography (SiO₂, 0–10% MeOH/CH₂Cl₂, gradient elution) gave the title compound as a white solid: ¹H NMR (CDCl₃, 500 MHz) 7.73 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 4.44–4.35 (m, 1H), 3.97–3.93 (m, 2H), 3.49 (d, *J* = 5.6 Hz, 2H), 3.00–2.94 (m, 2H), 2.58–2.52 (m, 1H), 2.45 (s, 1H), 2.20–2.12 (m, 2H), 2.05–2.00 (m, 2H), 1.80 (s, 3H), 0.59–0.54 (m, 2H), 0.47–0.42 (m, 2H); MS(ESI) 476 [M+H]⁺.

Example 5

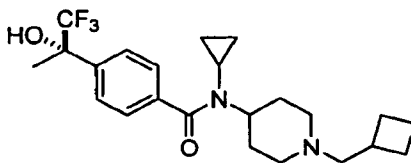
Preparation of (*S*)-*N*-cyclopropyl-*N*-(1-cyclopropylpiperidin-4-yl)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0232] A solution of (*S*)-*N*-cyclopropyl-*N*-(piperidin-4-yl)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide prepared above in step c in Example 1 (120 mg, 0.337 mmol, 1.0 equiv.), (1-ethoxycyclopropoxy)trimethylsilane (404 μL, 2.02 mmol, 6.0 equiv.) and AcOH (193 μL, 3.37 mmol, 10 equiv.) in MeOH (2.0 mL) was treated with NaBH₃CN (95 mg, 1.52 mmol, 4.5 equiv.). After being stirred for 48 h at 25 °C and being refluxed for additional 24 h, the reaction was diluted (EtOAc) and washed (1 × 1 N aqueous NaOH, and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 0–7% MeOH/CH₂Cl₂, gradient elution) gave the title compound as a pale yellow solid: ¹H NMR (CDCl₃, 500 MHz) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 4.22–4.13 (m, 1H), 3.12 (d, *J* = 11.5 Hz, 2H), 2.96 (s, br, 1H), 2.54–2.50 (m, 1H), 2.39–2.22 (m, 2H), 2.12–1.99 (m, 2H), 1.88–1.82 (m, 2H), 1.74 (s, 3H), 1.61–1.57 (m, 1H), 0.88–0.85 (m, 2H), 0.55–0.41 (m, 6H); MS(ESI) 398 [M+H]⁺.

Example 6**Preparation of (S)-N-cyclopropyl-N-[1-(cyclopropylmethyl)piperidin-4-yl]-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide**

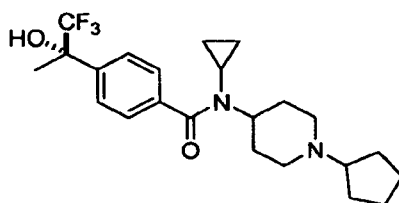
[0233] Using the methods described in step d in Example 1, but substituting (bromomethyl)cyclopropane for 1-(iodomethyl)cyclopropanecarbonitrile, the title compound was prepared: ^1H NMR (CDCl_3 , 500 MHz) δ 7.57 (d, $J = 8.2$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 4.14–4.10 (m, 1H), 3.22–3.18 (m, 2H), 2.80 (s, br, 1H), 2.56–2.52 (m, 1H), 2.32–2.28 (m, 2H), 2.17–2.08 (m, 4H), 1.92–1.87 (m, 2H), 1.78 (s, 3H), 0.94–0.87 (m, 1H), 0.59–0.51 (m, 4H), 0.47–0.42 (m, 2H), 0.14–0.10 (m, 2H); MS(ESI) 411 $[\text{M}+\text{H}]^+$.

Example 7**Preparation of (S)-N-[1-(cyclobutylmethyl)piperidin-4-yl]-N-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide**

[0234] Using the methods described in step d in Example 1, but substituting (bromomethyl)cyclobutane for 1-(iodomethyl)cyclopropanecarbonitrile, the title compound was prepared: ^1H NMR (CDCl_3 , 500 MHz) δ 7.56 (d, $J = 8.2$ Hz, 2H), 7.46 (d, $J = 8.1$ Hz, 2H), 4.15–4.05 (m, 1H), 3.06–2.99 (m, 2H), 2.97 (s, br, 1H), 2.60–2.51 (m, 2H), 2.44–2.41 (m, 2H), 2.17–2.04 (m, 6H), 1.92–1.40 (m, 6H), 1.71 (s, 3H), 0.58–0.53 (m, 2H), 0.47–0.42 (m, 2H); MS(ESI) 425 $[\text{M}+\text{H}]^+$.

Example 8

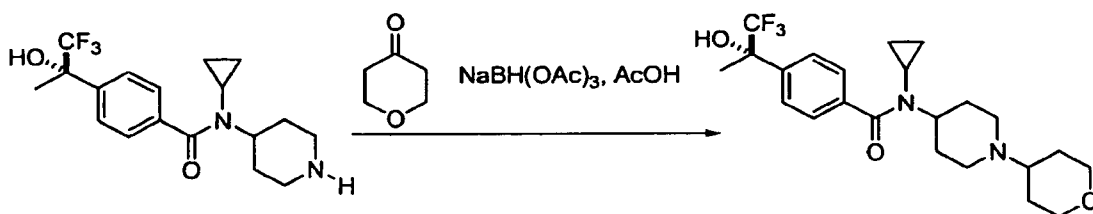
Preparation of (*S*)-*N*-[1-(cyclopentyl)piperidin-4-yl]-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0235] Using the methods described in step d in Example 1, but substituting bromocyclopentane for 1-(iodomethyl)cyclopropanecarbonitrile, the title compound was prepared: ^1H NMR (CDCl_3 , 500 MHz) δ 7.57 (d, $J = 8.2$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 4.33–4.23 (m, 1H), 3.14–3.07 (m, 2H), 2.84 (s, br, 1H), 2.55–2.51 (m, 2H), 2.20–2.00 (m, 4H), 1.92–1.86 (m, 4H), 1.78 (s, 3H), 1.70–1.40 (m, 6H), 0.58–0.53 (m, 2H), 0.47–0.42 (m, 2H); MS(ESI) 425 $[\text{M}+\text{H}]^+$.

Example 9

Preparation of (*S*)-*N*-cyclopropyl-*N*-[1-(tetrahydro-2*H*-pyran-4-yl)piperidin-4-yl]-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide

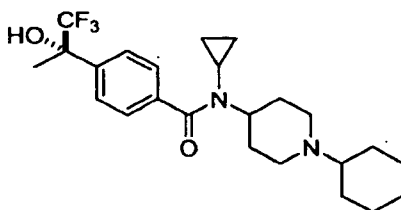


[0236] A solution of (*S*)-*N*-cyclopropyl-*N*-(piperidin-4-yl)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide prepared above in step c in Example 1 (73 mg, 0.20 mmol, 1.0 equiv.), tetrahydro-4*H*-pyran-4-one (65 μL , 7.0 mmol, 3.5 equiv.) and AcOH (23 μL , 0.40 mmol, 2 equiv.) in 1,2-dichloroethane/THF (2/1, 1.5 mL) was treated with $\text{NaBH}(\text{OAc})_3$

(210 mg, 1.00 mmol, 5.0 equiv.). After being stirred for 48 h at 75 °C, the reaction was diluted (EtOAc) and washed (1 × 1 N aqueous NaOH, and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 0–10% MeOH/CH₂Cl₂, gradient elution) gave the title compound as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 4.26–4.20 (m, 1H), 4.06–4.02 (m, 2H), 3.40–3.35 (m, 2H), 3.14–3.07 (m, 2H), 2.55–2.52 (m, 2H), 2.48 (s, br, 1H), 2.39–2.35 (m, 2H), 2.16–2.07 (m, 2H), 1.99–1.93 (m, 2H), 1.79 (s, 3H), 1.80–1.73 (m, 2H), 1.65–1.60 (m, 2H), 0.58–0.53 (m, 2H), 0.47–0.42 (m, 2H); MS(ESI) 441 [M+H]⁺.

Example 10

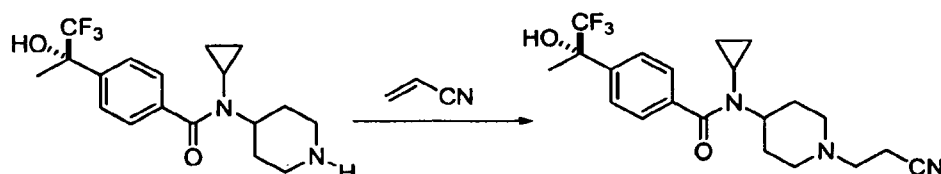
Preparation of (*S*)-*N*-(1-cyclohexylpiperidin-4-yl)-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0237] Using the methods described in Example 9, but substituting cyclohexanone for tetrahydro-4*H*-pyran-4-one, the title compound was prepared: ¹H NMR (CDCl₃, 500 MHz) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 4.30–4.18 (m, 1H), 4.05–3.97 (m, 1H), 3.06–2.97 (m, 2H), 2.62–2.52 (m, 1H), 2.55–2.50 (m, 2H), 2.48–2.32 (m, 2H), 2.18–2.05 (m, 2H), 2.00–1.87 (m, 3H), 1.86–1.80 (m, 2H), 1.79 (s, 3H), 1.27–1.12 (m, 6H), 0.58–0.53 (m, 2H), 0.47–0.42 (m, 2H); MS(ESI) 439 [M+H]⁺.

Example 11

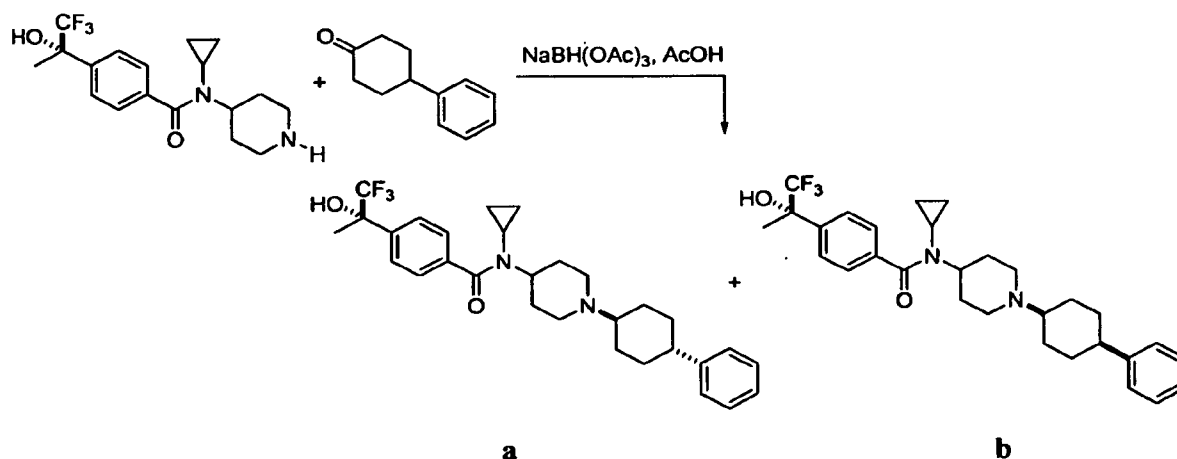
Preparation of (*S*)-*N*-[1-(2-cyanoethyl)piperidin-4-yl]-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0238] A solution of (*S*)-*N*-cyclopropyl-*N*-(piperidin-4-yl)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide prepared above in step c in Example 1 (73 mg, 0.20 mmol, 1.0 equiv.) in THF (0.70 mL) was treated with acrylonitrile (55 μ L, 0.84 mmol, 4.2 equiv.). After being stirred for 24 h at 50 °C, the reaction was diluted (EtOAc) and washed (1 $\times$ 1 N aqueous NaOH, and 1 $\times$ brine). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2 , 0–10% MeOH/ CH_2Cl_2 , gradient elution) gave the title compound as a colorless oil: ^1H NMR (CDCl_3 , 400 MHz) δ 7.58 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 4.16–4.09 (m, 1H), 3.02–2.98 (m, 2H), 2.75–2.70 (m, 3H), 2.57–2.54 (m, 3H), 2.26–2.20 (m, 2H), 2.15–2.08 (m, 2H), 1.92–1.87 (m, 2H), 1.78 (s, 3H), 0.58–0.53 (m, 2H), 0.46–0.42 (m, 2H); MS(ESI) 410 $[\text{M}+\text{H}]^+$.

Example 12

Preparation of *N*-cyclopropyl-*N*-(1-[(1*r*,4*r*)-4-phenylcyclohexyl]piperidin-4-yl)-4-[(*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl]benzamide and *N*-cyclopropyl-*N*-(1-[(1*s*,4*s*)-4-phenylcyclohexyl]piperidin-4-yl)-4-[(*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl]benzamide



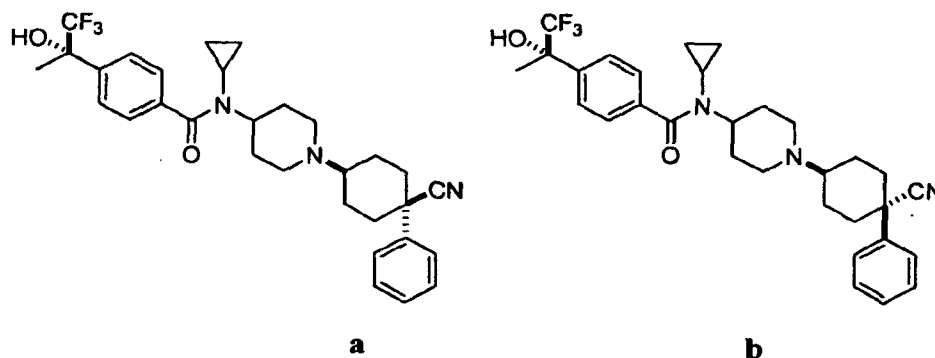
[0239] A solution of (*S*)-*N*-cyclopropyl-*N*-(piperidin-4-yl)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide prepared above in step (c) in Example 1 (73 mg, 0.20 mmol, 1.0 equiv.), 4-phenylcyclohexanone (156 mg, 7.00 mmol, 4.5 equiv.) and AcOH (23 μ L, 0.40 mmol, 2 equiv.) in 1,2-dichloroethane/THF (2/1, 3.0 mL) was treated with NaBH(OAc)₃ (211 mg, 1.00 mmol, 5.0 equiv.). After being stirred for 72 h at 75 °C, the reaction was diluted (EtOAc) and washed (1 $\times$ 1 N aqueous NaOH, and 1 $\times$ brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 60% EtOAc/Hexanes containing 2.5% triethylamine) gave **a** as a white solid and **b** as a white solid.

[0240] **a**: *R_f* = 0.40 (60% EtOAc/hexanes containing 2.5% triethylamine); ¹H NMR (CDCl₃, 500 MHz) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.33–7.27 (m, 4H), 7.19–7.13 (m, 1H), 4.16–4.09 (m, 1H), 3.21–3.15 (m, 2H), 2.79–2.69 (m, 1H), 2.58–2.54 (m, 1H), 2.40–2.30 (m, 1H), 2.17–2.00 (m, 7H), 1.89–1.82 (m, 4H), 1.77 (s, 3H), 1.68–1.55 (m, 4H), 0.60–0.56 (m, 2H), 0.49–0.43 (m, 2H); MS (ESI) 515 [M+H]⁺.

[0241] **b**: *R_f* = 0.25 (60% EtOAc/hexanes containing 2.5% triethylamine); ¹H NMR (CDCl₃, 500 MHz) δ 7.59 (d, *J* = 7.7 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.29–7.26 (m, 2H), 7.23–7.16 (m, 3H), 4.26–4.19 (m, 1H), 3.64 (s, 1H), 3.10–3.02 (m, 2H), 2.60–2.36 (m, 6H), 2.06–1.83 (m, 7H), 1.80 (s, 3H), 1.65–1.55 (m, 4H), 0.62–0.58 (m, 2H), 0.49–0.44 (m, 2H); MS (ESI) 515 [M+H]⁺.

Example 13

Preparation of *N*-{1-[(1*S*,4*S*)-4-cyano-4-phenylcyclohexyl]piperidin-4-yl}-*N*-cyclopropyl-4-[(*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl]benzamide and *N*-{1-[(1*R*,4*R*)-4-cyano-4-phenylcyclohexyl]piperidin-4-yl}-*N*-cyclopropyl-4-[(*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl]benzamide



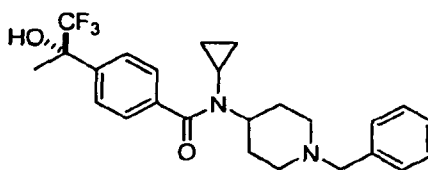
[0242] Using the methods described in Example 13, but substituting 4-cyano-4-phenylcyclohexanone for 4-phenylcyclohexanone, the title compounds were prepared.

a: ^1H NMR (CDCl_3 , 500 MHz) δ 7.58 (d, $J = 8.2$ Hz, 2H), 7.55–7.50 (m, 2H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.42–7.36 (m, 2H), 7.33–7.28 (m, 1H), 4.16–4.09 (m, 1H), 3.60 (s, 1H), 3.15–3.07 (m, 2H), 2.70–2.60 (m, 1H), 2.63–2.58 (m, 1H), 2.43–2.33 (m, 3H), 2.10–1.83 (m, 11H), 1.78 (s, 3H), 0.60–0.56 (m, 2H), 0.49–0.43 (m, 2H); MS (ESI) 540 $[\text{M}+\text{H}]^+$.

b: ^1H NMR (CDCl_3 , 500 MHz) δ 7.63 (d, $J = 9.1$ Hz, 2H), 7.51–7.47 (m, 2H), 7.49 (d, $J = 8.2$ Hz, 2H), 7.42–7.36 (m, 2H), 7.34–7.30 (m, 1H), 4.23–4.15 (m, 1H), 3.10–3.02 (m, 2H), 2.70–2.40 (m, 5H), 2.30–2.25 (m, 2H), 2.13–1.83 (m, 10H), 1.76 (s, 3H), 0.61–0.58 (m, 2H), 0.49–0.45 (m, 2H); MS (ESI) 540 $[\text{M}+\text{H}]^+$.

Example 14

Preparation of (*S*)-*N*-(1-benzylpiperidin-4-yl)-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide

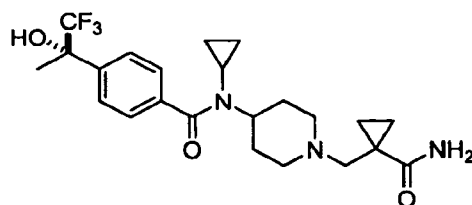


[0243] Using the methods described in step (d) in Example 1, but substituting benzyl bromide for 1-(iodomethyl)cyclopropanecarbonitrile, the title compound was prepared: ^1H NMR (CDCl_3 , 400 MHz) δ 7.58 (d, $J = 8.1$ Hz, 2H), 7.47 (d, $J = 8.2$ Hz, 2H),

7.35–7.27 (m, 5H), 4.22–4.16 (m, 1H), 3.58–3.49 (m, 2H), 3.00–2.96 (m, 2H), 2.56–2.48 (m, 2H), 2.20–2.08 (m, 4H), 1.91–1.80 (m, 2H), 1.79 (s, 3H), 0.59–0.56 (m, 2H), 0.48–0.42 (m, 2H); MS(ESI) 447 [M+H]⁺.

Example 15

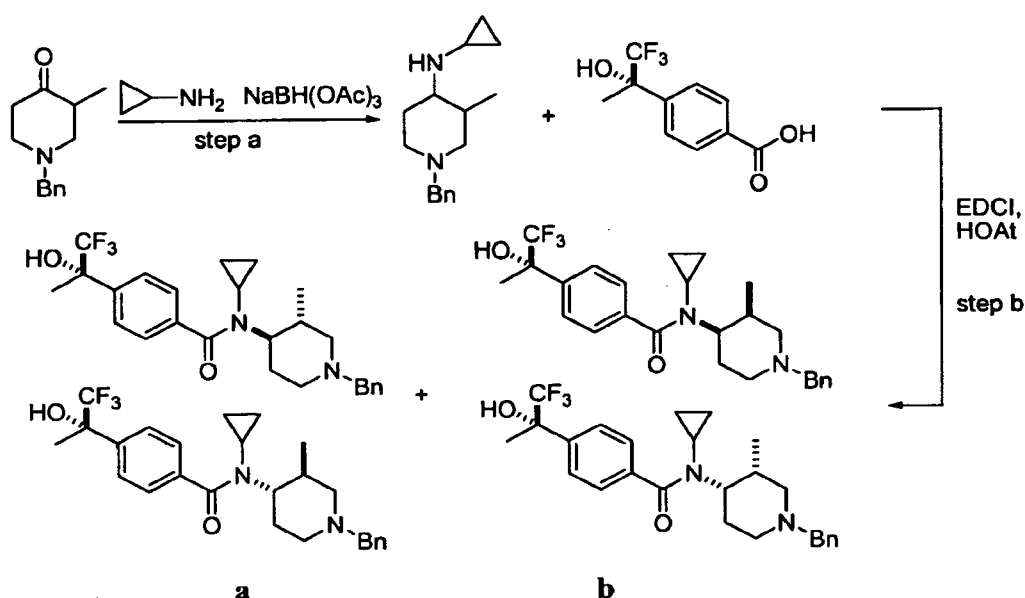
Preparation of (*S*)-*N*-{1-[(1-carbamoylcyclopropyl)methyl]piperidin-4-yl}-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0244] Using the methods described in Example 4, but substituting (*S*)-*N*-{1-[(1-cyanocyclopropyl)methyl]piperidin-4-yl}-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide for (*S*)-*N*-[1-(4-cyanophenyl)piperidin-4-yl]-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide the title compound was prepared: ¹H NMR (CDCl₃, 400 MHz) δ 9.15 (s, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 5.38 (s, 1H), 4.12–4.08 (m, 1H), 3.24–3.19 (m, 2H), 2.68 (s, 1H), 2.61–2.57 (m, 1H), 2.48 (s, 2H), 2.18–2.04 (m, 4H), 1.94–1.89 (m, 2H), 1.79 (s, 3H), 1.32–1.27 (m, 2H), 0.62–0.49 (m, 4H), 0.45–0.42 (m, 2H); MS(ESI) 454 [M+H]⁺.

Example 16

Preparation of a mixture of *N*-[(3*R*,4*R*)-1-benzyl-3-methylpiperidin-4-yl]-*N*-cyclopropyl-4-[(*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl]benzamide and *N*-[(3*S*,4*S*)-1-benzyl-3-methylpiperidin-4-yl]-*N*-cyclopropyl-4-[(*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl]benzamide and a mixture of *N*-[(3*S*,4*R*)-1-benzyl-3-methylpiperidin-4-yl]-*N*-cyclopropyl-4-[(*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl]benzamide and *N*-[(3*R*,4*S*)-1-benzyl-3-methylpiperidin-4-yl]-*N*-cyclopropyl-4-[(*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl]benzamide



[0245] a). A solution of 1-benzyl-3-methyl-4-piperidone (1.01 g, 4.92 mmol, 1.0 equiv.), cyclopropylamine (1.02 mL, 14.8 mmol, 3.0 equiv.) and AcOH (0.84 mL, 14.8 mmol, 3.0 equiv.) in 1,2-dichloroethane (24 mL) was treated at 0 °C with NaBH(OAc)₃ (3.13 g, 14.8 mmol, 3.0 equiv.). After being stirred for 16 h at 25 °C, the reaction was then diluted (EtOAc) and washed (1 × 1 N aqueous NaOH and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to provide the product as a yellow liquid.

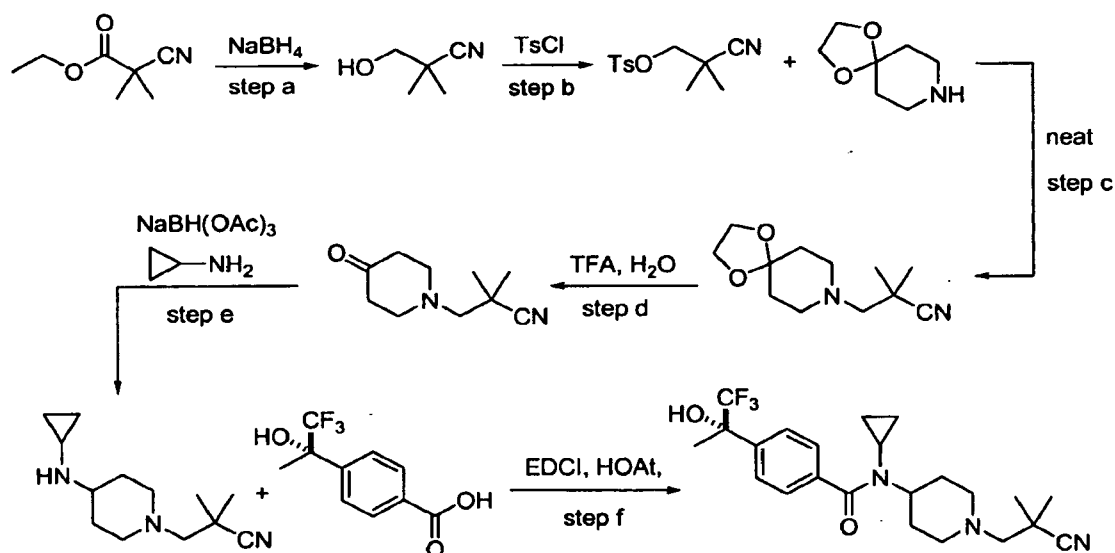
[0246] b). A solution of 1-benzyl-N-cyclopropyl-3-methylpiperidin-4-amine prepared above in step a (312 mg, 1.28 mmol, 1.0 equiv.) and (S)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid (300 mg, 1.28 mmol, 1.0 equiv.) in DMF (3.0 mL) was treated at 0 °C with EDCI (320 mg, 1.66 mmol, 1.3 equiv.), HOAt (226 mg, 1.66 mmol, 1.3 equiv.) and NaHCO₃ (215 mg, 2.56 mmol, 2.0 equiv.) successively. After being stirred at 25 °C for 3 days, 3-dimethylamino-1-propylamine (322 μL, 2.56 mmol, 2.0 equiv.) was added and the reaction was stirred at 25 °C for additionally 10 min. The reaction was then diluted (EtOAc) and washed (1 × 10% aqueous citric acid, 1 × saturated NaHCO₃, and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 0–5% MeOH/CH₂Cl₂, gradient elution) gave **a** as a white solid and **b** as a white solid.

[0247] a: $R_f = 0.30$ (10% MeOH/CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 7.58 (d, $J = 8.1$ Hz, 2H), 7.49 (d, $J = 8.3$ Hz, 2H), 7.33–7.28 (m, 5H), 4.41–4.34 (m, 1H), 3.54–3.40 (m, 2H), 3.03–2.98 (m, 1H), 2.71–2.66 (m, 1H), 2.62–2.57 (m, 1H), 2.56–2.47 (m, 1H), 2.45–2.40 (m, 1H), 2.37–2.32 (m, 1H), 2.27–2.23 (m, 1H), 2.10–2.04 (m, 1H), 1.89–1.82 (m, 1H), 1.79 (s, 3H), 1.21 (d, $J = 6.9$ Hz, 3H), 0.70–0.66 (m, 1H), 0.52–0.46 (m, 2H), 0.35–0.29 (m, 1H); MS (ESI) 461 [M+H]⁺.

[0248] b: $R_f = 0.25$ (10% MeOH/CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 7.63 (d, $J = 8.3$ Hz, 2H), δ 7.57 (d, $J = 8.2$ Hz, 2H), 7.36–7.28 (m, 5H), 4.05–3.70 (s, br, 1H), 3.54–3.47 (m, 2H), 2.98–2.90 (m, 2H), 2.70–2.05 (m, 5H), 1.82–1.68 (m, 2H), 1.79 (s, 3H), 0.93 (d, $J = 6.9$ Hz, 3H), 0.58–0.38 (m, 4H); MS (ESI) 461 [M+H]⁺.

Example 17

Preparation of (S)-N-[1-(2-cyano-2-methylpropyl)piperidin-4-yl]-N-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0249] a). To a solution of cyano-dimethyl-acetic acid ethyl ester (7.00 g, 49.6 mmol, 1.0 equiv.) which was prepared as described in the reference (P.M. O'Brien et al., *J. Med. Chem.* **1996**, *39*, 2354-2366) in 1,2-dimethoxyethane/MeOH (10/1, 100 mL) was added

NaBH₄ (3.77 g, 99.2 mmol, 2.0 equiv.) slowly at 0 °C. After being stirred for 16 h at 25 °C, the reaction was quenched (saturated aqueous NH₄Cl) cautiously and the resulting solution was stirred at 25 °C for additional 1 h. The reaction mixture was then diluted (EtOAc) and washed (1 × H₂O and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to provide the product as a colorless liquid.

[0250] b). A solution of 3-hydroxy-2,2-dimethylpropanenitrile prepared above in step a (300 mg, 3.02 mmol, 1.1 equiv.) in pyridine (6.0 mL) was treated at 0 °C with TsCl (576 mg, 3.02 mmol, 1.0 equiv.). After being stirred at 25 °C for 12 h, the reaction was diluted (EtOAc) and washed (3 × ice-cold 1 N aqueous HCl, 1 × saturated aqueous NaHCO₃, and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 10–20% EtOAc/hexanes, gradient elution) gave the product as a white solid.

[0251] c). A mixture of toluene-4-sulfonic acid 2-cyano-2,2-dimethyl-ethyl ester prepared above in step b (200 mg, 0.79 mmol, 1.0 equiv.) and 1,4-dioxo-8-azaspiro[4,5]decane (237 mg, 1.66 mmol, 2.1 equiv.) was placed in a sealed tube. After being stirred at 125 °C for 12 h, the reaction was diluted (EtOAc) and washed (1 × 1 N aqueous NaOH and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 0–5% MeOH/CH₂Cl₂, gradient elution) gave the product as a yellow film.

[0252] d). 3-(1,4-Dioxo-8-aza-spiro[4,5]dec-8-yl)-2,2-dimethyl-propionitrile prepared above in step c (350 mg, 1.56 mmol, 1.0 equiv.) was dissolved in trifluoroacetic acid (6.0 mL, 78 mmol, 50 equiv.) at 0 °C and the resulting reaction was treated with H₂O (280 µL, 15.6 mmol, 10 equiv.). After being stirred at 25 °C for 48 h, the reaction was concentrated under reduced pressure. The reaction mixture was then basified (ice-cold 1 N aqueous NaOH) and extracted (5 × 10% MeOH/CH₂Cl₂). The combined organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to provide the product as a yellow liquid.

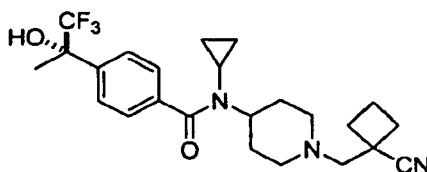
[0253] e). A solution of 2,2-dimethyl-3-(4-oxo-piperidin-1-yl)-propanenitrile prepared above in step d (126 mg, 0.70 mmol, 1.0 equiv.), cyclopropylamine (97 µL, 1.40 mmol, 2.0 equiv.) and AcOH (80 µL, 1.40 mmol, 2.0 equiv.) in 1,2-dichloroethane (3.6 mL)

was treated at 0 °C with NaBH(OAc)₃ (296 mg, 1.40 mmol, 2.0 equiv.). After being stirred for 16 h at 25 °C, the reaction was diluted (CH₂Cl₂), basified (1 N aqueous NaOH and 1 × brine) and extracted (5 × 10% MeOH/CH₂Cl₂). The combined organic layer were dried (Na₂SO₄) and concentrated under reduced pressure to provide the product as a yellow liquid.

[0254] f). (*S*)-*N*-[1-(2-cyano-2-methylpropyl)piperidin-4-yl]-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide. A solution of 3-(4-(cyclopropylamino)piperidin-1-yl)-2,2-dimethylpropanenitrile prepared above in step e (152 mg, 0.69 mmol, 1.1 equiv.) and (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid (146 mg, 0.63 mmol, 1.0 equiv.) in DMF (1.3 mL) was treated at 0 °C with EDCI (240 mg, 1.25 mmol, 2.0 equiv.), HOAt (170 mg, 1.25 mmol, 2.0 equiv.) and NaHCO₃ (105 mg, 1.25 mmol, 2.0 equiv.) successively. After being stirred at 25 °C for 12 h, the reaction was diluted (EtOAc) and washed (1 × saturated NaHCO₃, and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 0–5% MeOH/CH₂Cl₂, gradient elution) gave the title compound as a white solid: ¹H NMR (CDCl₃, 400 MHz) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 4.17–4.11 (m, 1H), 3.24–3.14 (m, 2H), 2.58–2.50 (m, 6H), 2.17–2.04 (m, 2H), 1.90–1.84 (m, 2H), 1.79 (s, 3H), 1.35 (s, 3H), 1.35 (s, 3H), 0.62–0.57 (m, 2H), 0.49–0.45 (m, 2H); MS(ESI) 438 [M+H]⁺.

Example 18

Preparation of (*S*)-*N*-{1-[(1-cyanocyclobutyl)methyl]piperidin-4-yl}-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide

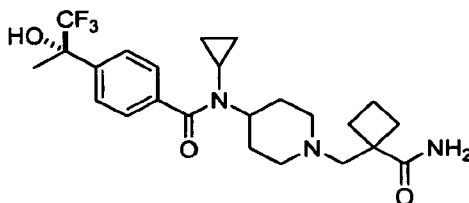


[0255] Using steps a–f described above in Example 17, but substituting 1-cyanocyclobutane-carboxylic acid ethyl ester for cyano-dimethyl-acetic acid ethyl ester in step (a), the title compound was prepared: ¹H NMR (DMSO, 500 MHz) δ 7.61 (d, *J* = 8.1 Hz, 2H),

7.49 (d, $J = 8.0$ Hz, 2H), 6.66 (s, 1H), 3.93–3.88 (m, 1H), 2.98–2.96 (m, 2H), 2.76–2.72 (m, 1H), 2.66 (s, 2H), 2.38–2.35 (m, 2H), 2.19–2.14 (m, 4H), 2.14–2.00 (m, 4H), 1.80–1.77 (m, 2H), 1.71 (s, 3H), 0.51–0.49 (m, 2H), 0.37–0.33 (m, 2H); MS(ESI) 450 $[M+H]^+$.

Example 19

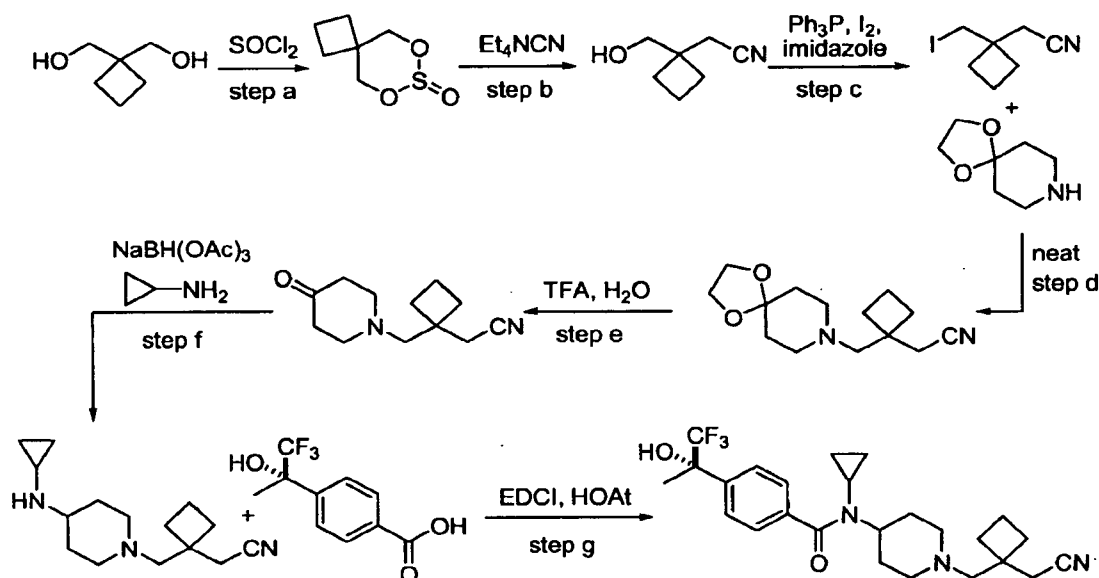
Preparation of (*S*)-*N*-{1-[(1-carbamoylcyclobutyl)methyl]piperidin-4-yl}-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0256] Using the methods described in Example 4, but substituting (*S*)-*N*-{1-[(1-cyanocyclobutyl)methyl]piperidin-4-yl}-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide for (*S*)-*N*-[1-(4-cyanophenyl)piperidin-4-yl]-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide, the title compound was prepared: ^1H NMR (DMSO, 500 MHz) δ 7.66 (d, $J = 8.2$ Hz, 2H), 7.53 (d, $J = 8.2$ Hz, 2H), 7.33 (br, s, 1H), 6.84 (br, s, 1H), 6.72 (s, 1H), 3.95–3.91 (m, 1H), 2.95–2.93 (m, 2H), 2.77–2.71 (m, 1H), 2.70 (s, 2H), 2.35–2.30 (m, 2H), 2.10–1.99 (m, 4H), 1.95–1.90 (m, 2H), 1.85–1.77 (m, 4H), 1.77 (m, 3H), 0.55–0.54 (m, 2H), 0.41–0.37 (m, 2H); MS(ESI) 468 $[M+H]^+$.

Example 20

Preparation of (*S*)-*N*-{1-[[1-(cyanomethyl)cyclobutyl]methyl]piperidin-4-yl}-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0257] a). To a solution of [1-(hydroxymethyl)-cyclobutyl]methanol (2.50 g, 21.5 mmol, 1.0 equiv.) which was prepared as described in the reference (F. X. Tavares et al., *J. Med. Chem.* **2004**, 47, 5057-5068) in CH_2Cl_2 (43 mL) was added SOCl_2 (2.35 mL, 32.3 mmol, 1.5 equiv.) slowly at 0 °C. After being stirred for 2 h at 25 °C, the reaction was diluted (10% MeOH/ CH_2Cl_2) and washed (1 × H_2O and 1 × brine). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide the product as a colorless liquid.

[0258] b). A solution of 6,8-dioxa-7-thia-spiro[3,5]nonane-7-oxide prepared above in step (a) (1.28 g, 7.89 mmol, 1.0 equiv.) in DMF (8.0 mL) was treated with Et_4NCN (2.47 g, 15.8 mmol, 2.0 equiv.). After being stirred at 70 °C for 12 h, the reaction was concentrated under reduced pressure. The reaction mixture was then diluted (10% MeOH/ CH_2Cl_2) and washed (1 × H_2O and 1 × brine). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide the product as a pale red liquid.

[0259] c). A solution of 2-[1-(hydroxymethyl)cyclobutyl]acetonitrile prepared above in step (b) (463 mg, 3.70 mmol, 1.0 equiv.), Ph_3P (1.36 g, 5.18 mmol, 1.4 equiv.), and imidazole (352 mg, 5.18 mmol, 1.4 equiv.) in $\text{CH}_3\text{CN}/\text{Et}_2\text{O}$ (2/1, 18 mL) was treated at 0 °C with I_2 (2.63 g, 10.4 mmol, 2.8 equiv.). After being stirred at 25 °C for 40 min, the reaction was diluted (EtOAc) and washed (1 × 1 M aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and 1 × brine). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the

residue by flash chromatography (SiO₂, 5–10% EtOAc/hexanes, gradient elution) gave the product as a yellow film.

[0260] d). A mixture of 2-[1-(iodomethyl)cyclobutyl]acetonitrile prepared above in step (c) (342 mg, 1.45 mmol, 1.0 equiv.) and 1,4-dioxo-8-azaspiro[4,5]decane (519 mg, 3.63 mmol, 2.5 equiv.) was placed in a sealed tube. After being stirred at 80 °C for 12 h, the reaction was diluted (EtOAc) and washed (1 × 1 N aqueous NaOH and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 0–5% MeOH/CH₂Cl₂, gradient elution) gave the product as a colorless liquid.

[0261] e). [1-(1,4-dioxo-8-aza-spiro[4,5]dec-8-ylmethyl)-cyclobutyl]-acetonitrile prepared above in step (d) (265 mg, 1.06 mmol, 1.0 equiv.) was dissolved in trifluoroacetic acid (8.2 mL, 110 mmol, 100 equiv.) at 0 °C and the resulting reaction was treated with H₂O (380 µL, 21.2 mmol, 20 equiv.). After being stirred at 25 °C for 5 days, the reaction was concentrated under reduced pressure. The reaction mixture was then basified (ice-cold 1N aqueous NaOH) and extracted (5 × 10% MeOH/CH₂Cl₂). The combined organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to provide the product as a yellow liquid.

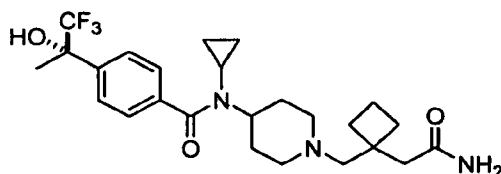
[0262] f). A solution of 2-{1-[(4-oxopiperidin-1-yl)methyl]cyclobutyl} acetonitrile prepared above in step (f) (200 mg, 0.97 mmol, 1.0 equiv.), cyclopropylamine (134 µL, 1.94 mmol, 2.0 equiv.) and AcOH (111 µL, 1.94 mmol, 2.0 equiv.) in 1,2-dichloroethane (5.0 mL) was treated at 0 °C with NaBH(OAc)₃ (411 mg, 1.94 mmol, 2.0 equiv.). After being stirred for 16 h at 25 °C, the reaction was diluted (CH₂Cl₂), basified (1 N aqueous NaOH and 1 × brine) and extracted (5 × 10% MeOH/CH₂Cl₂). The combined organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to provide the product as a yellow liquid.

[0263] g). (*S*)-*N*-(1-{[1-(cyanomethyl)cyclobutyl]methyl}piperidin-4-yl)-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide. A solution of 2-(1-{[4-(cyclopropylamino)piperidin-1-yl]methyl}cyclobutyl)acetonitrile prepared above in step (f) (247 mg, 0.97 mmol, 1.1 equiv.) and (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid (206 mg, 0.88 mmol, 1.0 equiv.) in DMF (1.3 mL) was treated at 0 °C with EDCI (338 mg, 1.76 mmol, 2.0 equiv.), HOAt (240 mg, 1.76 mmol, 2.0 equiv.) and NaHCO₃ (148 mg,

1.76 mmol, 2.0 equiv.) successively. After being stirred at 25 °C for 12 h, the reaction was diluted (EtOAc) and washed (1 × saturated NaHCO₃, and 1 × brine). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, 0–5% MeOH/CH₂Cl₂, gradient elution) gave the title compound as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 4.86–4.84 (m, 1H), 2.88–2.84 (m, 2H), 2.70–2.67 (m, 3H), 2.58–2.54 (m, 1H), 2.48 (s, 2H), 2.24–2.19 (m, 2H), 2.14–1.89 (m, 8H), 1.88–1.78 (m, 2H), 1.81 (s, 3H), 0.62–0.57 (m, 2H), 0.49–0.45 (m, 2H); MS(ESI) 464 [M+H]⁺.

Example 21

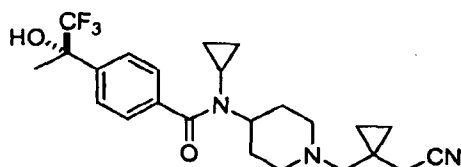
Preparation of (*S*)-*N*-(1-{{1-(2-amino-2-oxoethyl)cyclobutyl}methyl}piperidin-4-yl)-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0264] Using the methods described in Example 4, but substituting (*S*)-*N*-(1-{{1-(cyanomethyl)cyclobutyl}methyl}piperidin-4-yl)-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide for (*S*)-*N*-[1-(4-cyanophenyl)piperidin-4-yl]-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide, the title compound was prepared: ¹H NMR (CD₃OD, 500 MHz) δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 4.04–3.98 (m, 1H), 2.98–2.88 (m, 2H), 2.80–2.70 (m, 1H), 2.62–2.48 (m, 4H), 2.27–2.10 (m, 4H), 2.07–1.80 (m, 8H), 1.77 (s, 3H), 0.64–0.62 (m, 2H), 0.50–0.44 (m, 2H); MS(ESI) 482 [M+H]⁺.

Example 22

Preparation of (*S*)-*N*-(1-{{1-(cyanomethyl)cyclopropyl}methyl}piperidin-4-yl)-*N*-cyclopropyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzamide



[0265] Using steps (a) through (g) described above in Example 20, but substituting [1-(hydroxymethyl)-cyclopropyl]methanol for [1-(hydroxymethyl)-cyclobutyl]methanol in step (a), the title compound was prepared: ^1H NMR (CD_3OD , 400 MHz) δ 7.58 (d, $J = 8.1$ Hz, 2H), 7.48 (d, $J = 8.3$ Hz, 2H), 4.19–4.14 (m, 1H), 3.11–3.05 (m, 2H), 2.58–2.50 (m, 4H), 2.29 (s, 2H), 2.19–2.3 (m, 4H), 1.93–1.87 (m, 2H), 1.79 (s, 3H), 0.63–0.56 (m, 4H), 0.49–0.45 (m, 4H); MS(ESI) 450 $[\text{M}+\text{H}]^+$.

Biological Examples

Procedures Useful For The Biological Evaluation Of The Benzamide Derivatives

[0266] In addition to the extensive literature disclosing the role of HSDs in various diseases and disorders, described herein are assays useful for testing the Benzamide Derivatives of the present invention.

Assays

In vitro 11 β -HSD1 (hydroxysteroid dehydrogenase 1) activity inhibitory action

[0267] The 11 β -HSD1 inhibitory activity was examined by quantitative determination by an SPA (scintillation proximity assay) system of the suppressive action on the conversion from cortisone to cortisol using human 11 β -HSD1 (hereinafter recombinant 11 β -HSD1) expressed using a baculo-virus system as an enzyme source. For the reaction, a reagent was added to a 96 well plate (96 well Opti-platesTM-96 (Packard)) to the following final concentration and a volume of 100 μl was reacted at room temperature for 90 min. The reaction solution used was 0.1 $\mu\text{g}/\text{ml}$ recombinant 11 β -HSD1, 500 μM NADPH, 16 nM ^3H cortisone (Amersham Biosciences, 1.78 Tbq/mol) dissolved in 0.1% BSA (Sigma)-containing PBS and the test drug was 2 μl of a compound solution (dissolved in DMSO). After 90 min, the reaction was stopped by adding PBS (40 μl , containing 0.1% BSA (Sigma)) containing 0.08 μg of anti-cortisol mouse monoclonal antibody (East Coast Biologics), 365 μg SPA

PVT mouse antibody-binding beads (Amersham Biosciences) and 175 μ M carbenoxolone (Sigma) to the reaction solution. After the completion of the reaction, the plate was incubated overnight at room temperature and the radioactivity was measured by Topcount (Packard). For control, the value (0% inhibition) of the well containing 2 μ L of DMSO instead of the test drug was used, and for positive control, the value (100% inhibition) of the well containing carbenoxolone instead of the test drug at the final concentration of 50 μ M was used. The inhibition (%) of the test drug was calculated by $((\text{value of control} - \text{value of test drug}) / (\text{value of control} - \text{value of positive control})) \times 100$ (%). The IC_{50} value was analyzed using a computer-based curve fitting software.

[0268] This example provides assays that are useful in evaluating and selecting a compound that modulates 11 β -HSD1.

Biochemical 11 β -HSD1 assay by SPA

[0269] Recombinant human, mouse and rat 11 β -HSD1 were expressed in baculovirus expression system, isolated by affinity purification and used as the enzyme sources for cortisone to cortisol conversion *in vitro*. ^3H -Cortisone (Amersham Bioscience, 1.78 Tbq/mol. 49 Ci/mmol) was used as the substrate, and a monoclonal anti-cortisol antibody and the scintillation proximity assay (SPA) system were used to detect the product of the 11 β -HSD1-catalyzed reaction, ^3H -cortisol. Reactions took place at room temperature for 90 min. in 96-well Opti-platesTM-96 (Packard) in 100 μ L volume with 2 μ L test compounds or control in DMSO, 0.1 μ g/mL 11 β -HSD1 protein, 500 μ M NADPH and 16 nM radioactive cortisone, in PBS buffer supplemented with 0.1% BSA (Sigma). Reaction was stopped with the addition of 40 μ L buffer containing 0.08 μ g anti-cortisol monoclonal antibody (East Coast Biologics), 365 μ g SPA PVT antibody-binding beads (Amersham Biosciences) and 175 μ M carbenoxolone (Sigma).

[0270] Plates were incubated at room temperature overnight before being read on a Topcount (Packard). The point of 50% inhibition of 11 β -HSD1 enzyme activity (IC_{50}) was determined by computer-based curve fitting.

Cell-based 11 β -HSD1 assay by SPA

[0271] This cell-based assay measures the conversion of ^3H -cortisone to ^3H -cortisol in a HEK-293 cell line stably overexpressing human recombinant 11 β -HSD1. HEK-293 cells were grown in DMEM/F12 supplemented with 10% fetal bovine serum, and plated onto poly-D-lysine-coated 96-well assay plates (Costar 3903), 100,000 cells per well in 50 μL assay media (phenol free DMEM/F12 (Invitrogen) + 0.2% BSA + 1% antibiotic-antimycotic solutions). The solution was incubated at 37 $^{\circ}\text{C}$ for 24 h, and the reaction was initiated by the addition of 25 μL of assay media containing compounds of desired concentration and 25 μL of assay media containing 40 nM of ^3H -cortisone to each well. The reaction mixture was incubated at 37 $^{\circ}\text{C}$ for 90 min. and the reaction terminated by the addition of 25 μL of assay media containing 0.2 μg of anti-cortisol monoclonal antibody (East Coast Biologics), 500 μg SPA PVT antibody-binding beads (Amersham Biosciences) and 500 μM carbenoxolone (Sigma).

[0272] Plates were incubated at room temperature for at least 2 h before being read on Topcount (Packard). The point of 50% inhibition of 11 β -HSD1 enzyme activity (IC_{50}) was determined by computer-based curve fitting.

Scintillation Proximity Assay

[0273] [1, 2(n) - ^3H]-cortisone was purchased from Amersham Pharmacia Biotech. Anti-cortisol monoclonal mouse antibody, clone 6D6.7 was obtained from Immunotech and Scintillation proximity assay (SPA) beads coated with monoclonal antimouse antibodies were from Amersham Pharmacia Biotech. NADPH, tetrasodium salt was from Calbiochem and glucose-6-phosphate (G-6-P) was supplied by Sigma. The human 11- β -hydroxysteroid dehydrogenase type-1 enzyme (11- β -HSD $_1$) was expressed in *Pichia pastoris*. 18- β -glycyrrhetic acid (GA) was obtained from Sigma. The serial dilutions of the compounds were performed on a Tecan Genesis RSP 150. Compounds to be tested were dissolved in DMSO (1 mM) and diluted in 50 mM Tris-HCl, pH 7.2 containing 1 mM EDTA.

[0274] The multiplication of plates was done on a WallacQuadra. The amount of the product [^3H]-cortisol, bound to the beads was determined in a Packard, Top Count microplate liquid scintillation counter.

[0275] The 11- β -HSD₁ enzyme assay was carried out in 96 well microtiter plates (Packard, Optiplate) in a total well volume of 220 μ L and contained 30 mM Tris-HCl, pH 7.2 with 1 mM EDTA, a substrate mixture tritiated Cortisone/NADPH (175 nM / 181 μ M), G-6-P (1 mM) and inhibitors in serial dilutions (9 to 0.15 μ M). Reactions were initiated by the addition of human 11- β -HSD₁, either as *Pichia pastoris* cell homogenate or microsomes prepared from *Pichia pastoris* (the final amount of enzyme used was varied between 0.057 to 0.11 mg/mL). Following mixing, the plates were shaken for 30 to 45 minutes at room temperature. The reactions were terminated with 10 μ L 1 mM GA stop solution. Monoclonal mouse antibody was then added (10 μ L of 4 μ M) followed by 100 μ L of SPA beads (suspended according to the manufacturers instructions). Appropriate controls were set up by omitting the 11- β -HSD₁ to obtain the non-specific binding (NSB) value.

[0276] The plates were covered with plastic film and incubated on a shaker for 30 minutes, at room temperature, before counting. The amount of [³H]-cortisol, bound to the beads was determined in a microplate liquid scintillation counter. The calculation of the K_i values for the inhibitors was performed by use of Activity Base. The K_i value is calculated from IC₅₀ and the K_m value is calculated using the Cheng Prushoff equation (with reversible inhibition that follows the Michaelis-Menten equation): $K_i = IC_{50}(1+[S]/K_m)$ [Cheng, Y.C.; Prushoff, W.H. Biochem. Pharmacol. 1973, 22, 3099-3108]. The IC₅₀ is measured experimentally in an assay wherein the decrease of the turnover of cortisone to cortisol is dependent on the inhibition potential of each substance.

Cloning, Expression and Purification of 11 β -HSD1

[0277] The expression and purification of the murine enzyme is described by J. Zhang, et al. Biochemistry, 44, 2005, pp 6948-57. The expression and purification of the human enzyme is similar to that of the murine sequence.

Enzyme Assay:

[0278] The IC₅₀ and K_i of the compounds are determined by the following method:

[0279] 1. Prepare an Assay Buffer, (pH 7.2, 50 mM Tris-HCL, 1 mM EDTA) fresh each week.

[0280] 2. Prepare the following solutions:

NADPH (Sigma, 200 μ M)

3 H-Cortisone(Amersham Biosciences, 45 Ci/mmol, 200 nM)

Enzyme Prep (20 nM for human, 10 nM for mouse)

Cortisol Antibody (East Coast Biologicals, (1:50 dilution)

Anti-mouse SPA beads (Amersham Biosciences, 15 mg/ml)

18 β -Glycyrrhetic acid ("GA")(Aldrich, 1 μ M)

Compound Stock Solution(10mM in DMSO), serially diluted in assay buffer. Each compound is tested at six different concentrations usually (10 μ M to 0.1 nM). All of the solutions and dilutions are made in the Assay Buffer.

[0281] 3. Assay is run using white/white, 96-well assay plates (Corning) in a total volume of 100 μ L.

[0282] 4. Into each well of a 96-well plate is added Assay Buffer (30 μ L), compound (10 μ L) NADPH (10 μ L), and 3 H-cortisone (10 μ L).

[0283] 5. Initiate reaction by adding 40 μ L of HSD-1 enzyme prep to the wells.

[0284] 6. The plate is covered with tape and incubated on an orbital shaker for 1 h at RT.

[0285] 7. After 1 h, the tape is removed and anti-cortisol antibody (10 μ L), GA solution (10 μ L), and SPA bead preparation (100 μ L) is added.

[0286] 8. The plate is incubated (30 min) on an orbital shaker at RT.

[0287] 9. The counts are read on a TopCount NXT reader.

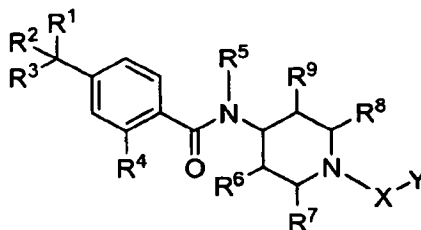
[0288] 10. A dose-response curve is first plotted using the Graphpad Prism software, to generate the IC₅₀ values.

[0289] With this IC₅₀ value and the known K_m value for the substrate and HSD1 enzyme, an estimated K_i can be calculated with the Chen and Prusoff equation $\{K_i = IC_{50} / [1 + (substrate/K_m)]\}$.

[0290] The compounds of the present invention all show 11 β -HSD1 enzyme activity (IC₅₀) in the assays ranging from 1000 nM to < 1 nM.

WHAT IS CLAIMED IS:

1. A compound having the formula (I):



(I)

or pharmaceutically acceptable salts, solvates, stereoisomers or prodrugs thereof,
wherein:

R¹ is a member selected from the group consisting of -OH, halogen and (C₁-C₈)haloalkyl;

R² and R³ are members independently selected from the group consisting of halogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₁-C₈)haloalkyl, (C₂-C₈)hydroxyalkyl and (C₃-C₈)cycloalkyl, wherein no more than two of R¹, R² and R³ are halogen;

R⁴ is a member selected from the group consisting of hydrogen, halogen, (C₁-C₈)alkyl and (C₃-C₈)cycloalkyl;

R⁵ is selected from the group consisting of (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, (C₂-C₈)hydroxyalkyl, (C₃-C₈)cycloalkyl, and (C₃-C₈)heterocycloalkyl, wherein any cycloalkyl or heterocycloalkyl portion is optionally substituted with from one to two members selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₂-C₄)hydroxyalkyl, and (C₁-C₄)alkoxy;

X is selected from the group consisting of a bond, (C₁-C₈)alkylene, (C₀-C₈)alkylene-SO₂, and (C₀-C₈)alkylene-C(O);

Y is selected from the group consisting of H, -CN, -N(R')₂, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)haloalkyl, (C₂-C₈)hydroxyalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, heteroaryl, and aryl, wherein any cycloalkyl portion, heterocycloalkyl

portion, aryl portion or heteroaryl portion is optionally substituted with from one to four members selected from the group consisting of halogen, -CN, -NO₂, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, =O, (C₁-C₈)haloalkyl, (C₂-C₈)hydroxyalkyl, aryl, heteroaryl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, (C₃-C₈)heterocycloalkyl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl or aryl(C₁-C₆)alkyl, -C(O)R', -C(O)OR', -NR'C(O)OR', -OR', -SR', -OC(O)R', -C(O)N(R')₂, -S(O)R', -SO₂R', -SO₂N(R')₂, -N(R')₂, -NR'C(O)R', -NR'SO₂R', -Z-C(O)R', -Z-CN, -Z-C(O)OR', -Z-NR'C(O)OR', -Z-OR', -Z-OC(O)R', -Z-C(O)N(R')₂, -Z-S(O)R', -Z-SO₂R', -Z-SO₂N(R')₂, -Z-N(R')₂ and -Z-NR'C(O)R';

R⁶ to R⁹ are members independently selected from hydrogen and (C₁-C₈)alkyl;

Z is a branched or straight chain (C₁-C₈)alkylene group;

each occurrence of R' is independently H or an unsubstituted member selected from the group consisting of (C₁-C₈)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkyl, (C₁-C₈)haloalkyl, (C₂-C₈)hydroxyalkyl, or two R' groups, when attached to the same nitrogen atom, can be combined with the nitrogen atom to which they are attached to form a heterocycle or heteroaryl group.

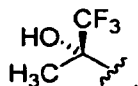
2. The compound of claim 1, wherein R¹ is -OH, R² is (C₁-C₃)alkyl, R³ is (C₁-C₃)haloalkyl, and

R⁵ is selected from (C₁-C₈)alkyl, (C₁-C₈)haloalkyl, and (C₃-C₆)cycloalkyl.

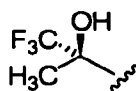
3. The compound of claim 2, wherein R⁵ is cyclopropyl.

4. The compound of claim 1, wherein R¹ is -OH, R² is methyl, and R³ is trifluoromethyl.

5. The compound according to claim 4, wherein R¹, R², and R³, together with the carbon atom to which they are attached, are an (*S*)-trifluoromethyl carbinol group of the formula:



6. The compound according to claim 4, wherein R^1 , R^2 , and R^3 , together with the carbon atom to which they are attached, are an (*R*)-trifluoromethyl carbinol group of the formula:



7. A pharmaceutical composition comprising the compound of claim 1, and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition comprising the compound of claim 1, and an additional therapeutic agent.

9. A method of treating a disease or condition selected from the group consisting of diabetes, obesity, dyslipidemia, hyperinsulinemia, glaucoma, osteoporosis, cognitive disorders, atherosclerosis, immune disorders, hypertension and wound healing in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the compound of claim 1.

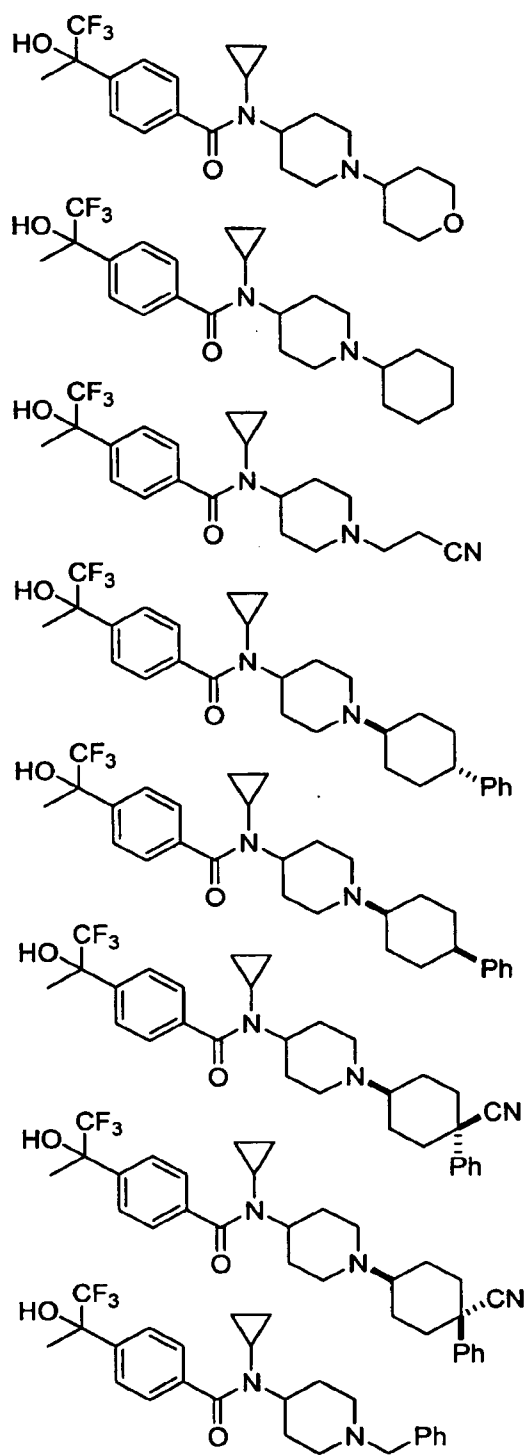
10. The method according to claim 9, wherein the disease or condition is diabetes, obesity, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, low level of high-density lipoprotein, hyperinsulinemia, or atherosclerosis.

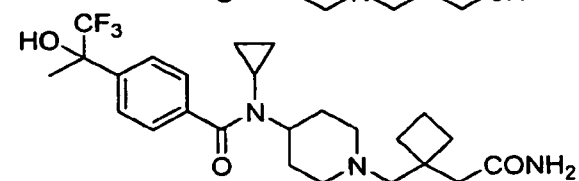
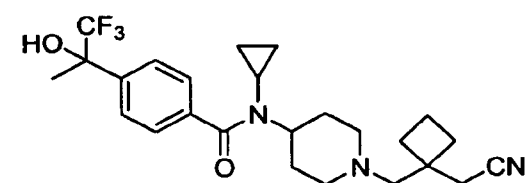
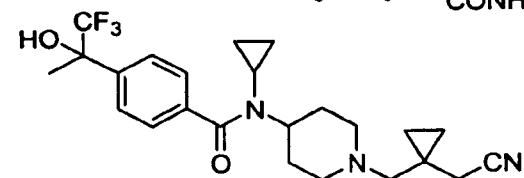
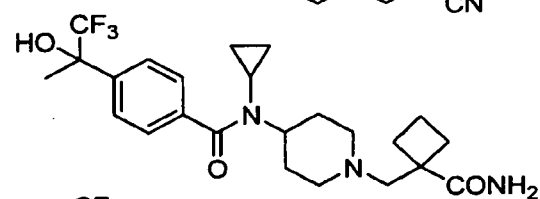
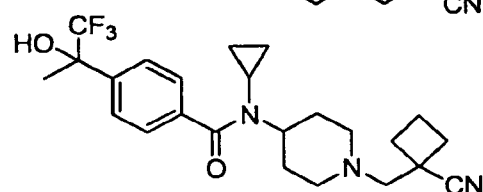
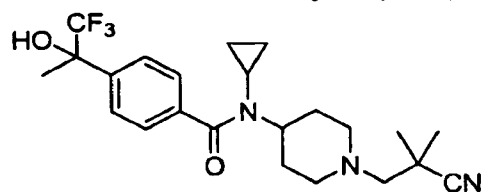
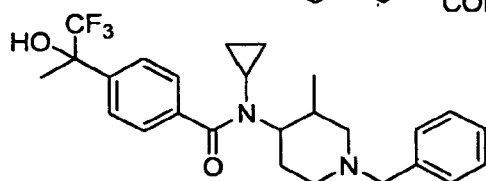
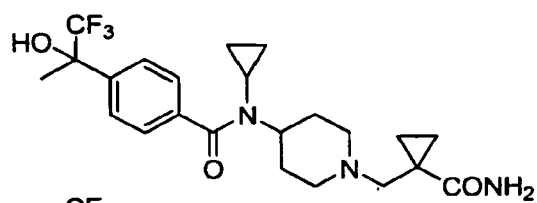
11. The method of claim 10, wherein the condition or disorder is diabetes or obesity.

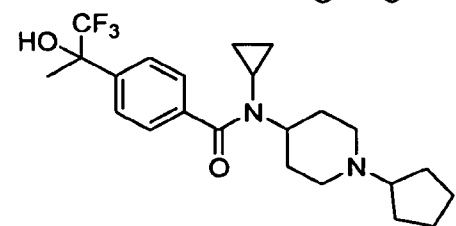
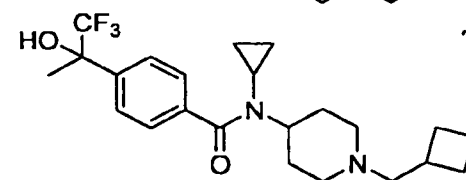
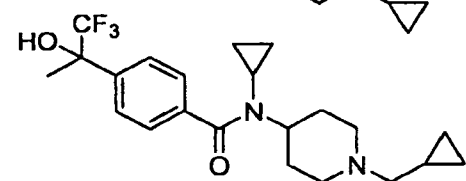
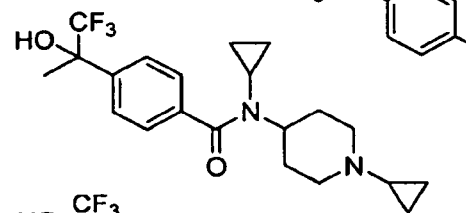
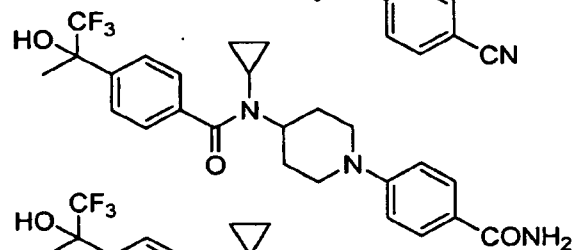
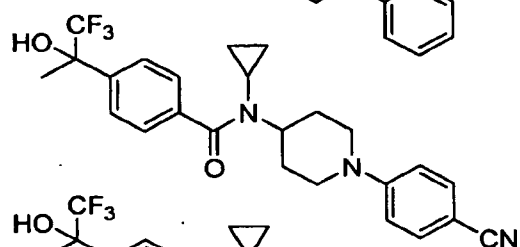
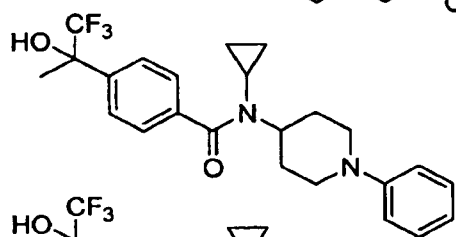
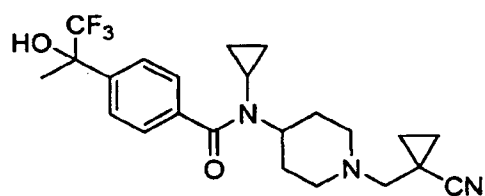
12. A method of treating a condition or disorder responsive to the modulation of a hydroxysteroid dehydrogenase, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1.

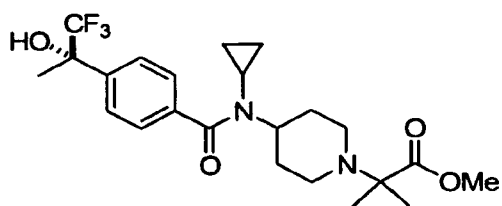
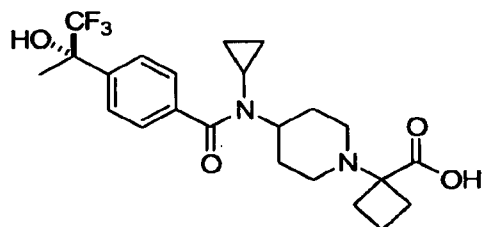
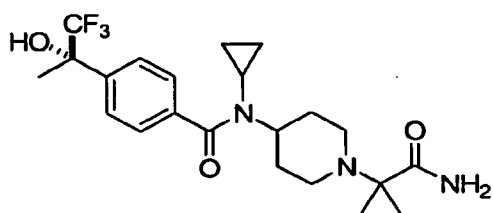
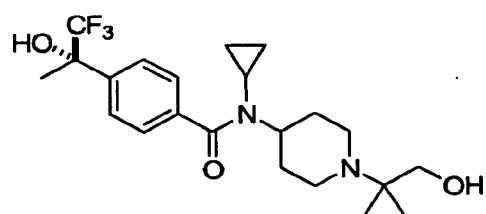
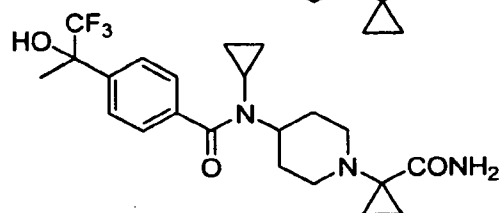
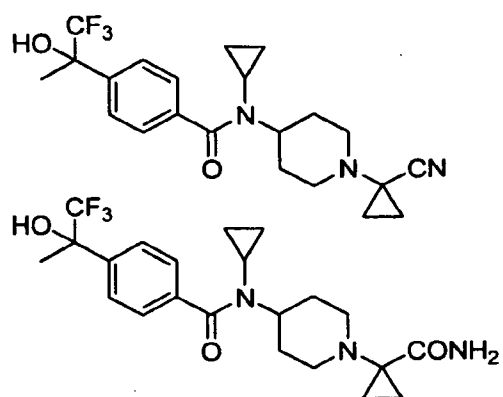
13. The method of claim 12, wherein said hydroxysteroid dehydrogenase is selected from the group consisting of 11 β -HSD1, 11 β -HSD2 and 17 β -HSD3.

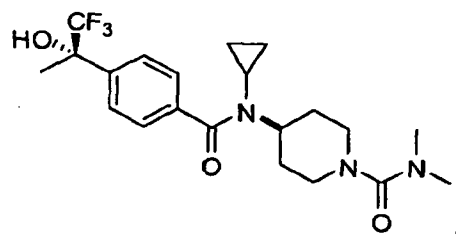
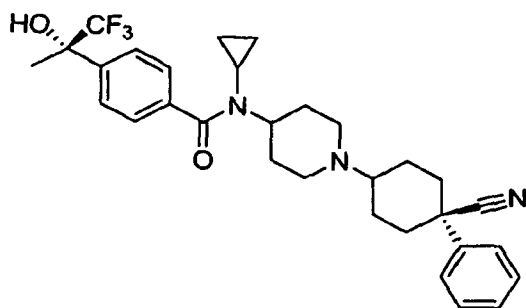
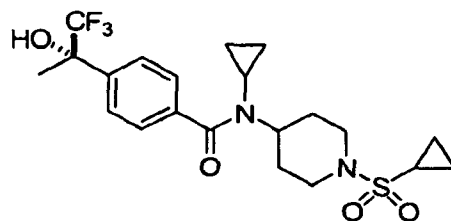
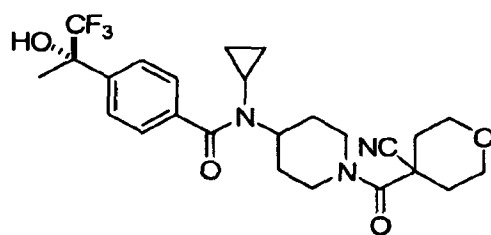
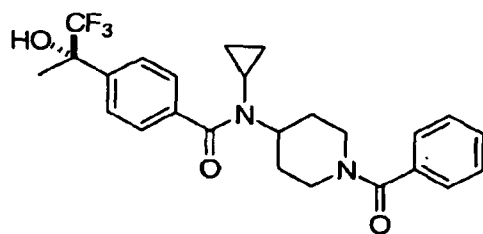
14. A compound selected from the group consisting of:











or a pharmaceutically acceptable salt, solvate, stereoisomer or prodrug thereof.