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(54) Title: AMIDO COMPOUNDS AND THEIR USE AS PHARMACEUTICALS

(57) Abstract: The present invention relates to inhibitors of 11-β hydroxyl steroid dehydrogenase type 1, antagonists of the mineralocorticoid receptor (MR), and pharmaceutical compositions thereof. The compounds of the invention can be useful in the treatment of various diseases associated with expression of activity of 11-β hydroxyl steroid dehydrogenase type 1 and/or diseases associated with aldosterone excess.

AMIDO COMPOUNDS AND THEIR USE AS PHARMACEUTICALS

FIELD OF THE INVENTION

The present invention relates to modulators of 11-β hydroxyl steroid dehydrogenase type 1 (11βHSD1) and/or mineralocorticoid receptor (MR), compositions thereof and methods of using the same.

BACKGROUND OF THE INVENTION

Glucocorticoids are steroid hormones that regulate fat metabolism, function and distribution. In vertebrates, glucocorticoids also have profound and diverse physiological effects on development, neurobiology, inflammation, blood pressure, metabolism and programmed cell death. In humans, the primary endogenously-produced glucocorticoid is cortisol. Cortisol is synthesized in the zona fasciculate of the adrenal cortex under the control of a short-term neuroendocrine feedback circuit called the hypothalamic-pituitary-adrenal (HPA) axis. Adrenal production of cortisol proceeds under the control of adrenocorticotrophic hormone (ACTH), a factor produced and secreted by the anterior pituitary. Production of ACTH in the anterior pituitary is itself highly regulated, driven by corticotropin releasing hormone (CRH) produced by the paraventricular nucleus of the hypothalamus. The HPA axis maintains circulating cortisol concentrations within restricted limits, with forward drive at the diurnal maximum or during periods of stress, and is rapidly attenuated by a negative feedback loop resulting from the ability of cortisol to suppress ACTH production in the anterior pituitary and CRH production in the hypothalamus.

Aldosterone is another hormone produced by the adrenal cortex; aldosterone regulates sodium and potassium homeostasis. Fifty years ago, a role for aldosterone excess in human disease was reported in a description of the syndrome of primary aldosteronism (Conn, (1955), J. Lab. Clin. Med. 45: 6-17). It is now clear that elevated levels of aldosterone are associated with deleterious effects on the heart and kidneys, and are a major contributing factor to morbidity and mortality in both heart failure and hypertension.

Two members of the nuclear hormone receptor superfamily, glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), mediate cortisol function *in vivo*, while the primary intracellular receptor for aldosterone is the MR. These receptors are also referred to as 'ligand-dependent transcription factors,' because their functionality is dependent on the receptor being bound to its

ligand (for example, cortisol); upon ligand-binding these receptors directly modulate transcription via DNA-binding zinc finger domains and transcriptional activation domains.

Historically, the major determinants of glucocorticoid action were attributed to three primary factors: 1) circulating levels of glucocorticoid (driven primarily by the HPA axis), 2) protein binding of glucocorticoids in circulation, and 3) intracellular receptor density inside target tissues. Recently, a fourth determinant of glucocorticoid function was identified: tissue-specific pre-receptor metabolism by glucocorticoid-activating and -inactivating enzymes. These 11-beta-hydroxysteroid dehydrogenase (11-β-HSD) enzymes act as pre-receptor control enzymes that modulate activation of the GR and MR by regulation of glucocorticoid hormones. To date, two distinct isozymes of 11-beta-HSD have been cloned and characterized: 11βHSD1(also known as 11-beta-HSD type 1, 11betaHSD1, HSD11B1, HDL, and HSD11L) and 11βHSD2. 11βHSD1 and 11βHSD2 catalyze the interconversion of hormonally active cortisol (corticosterone in rodents) and inactive cortisone (11-dehydrocorticosterone in rodents). 11βHSD1 is widely distributed in rat and human tissues; expression of the enzyme and corresponding mRNA have been detected in lung, testis, and most abundantly in liver and adipose tissue. 11βHSD1 catalyzes both 11-beta-dehydrogenation and the reverse 11-oxoreduction reaction, although 11βHSD1 acts predominantly as a NADPH-dependent oxoreductase in intact cells and tissues, catalyzing the activation of cortisol from inert cortisone (Low et al. (1994) J. Mol. Endocrin. 13: 167-174) and has been reported to regulate glucocorticoid access to the GR. Conversely, 11βHSD2 expression is found mainly in mineralocorticoid target tissues such as kidney, placenta, colon and salivary gland, acts as an NAD-dependent dehydrogenase catalyzing the inactivation of cortisol to cortisone (Albiston et al. (1994) Mol. Cell. Endocrin. 105: R11-R17), and has been found to protect the MR from glucocorticoid excess, such as high levels of receptor-active cortisol (Blum, et al., (2003) Prog. Nucl. Acid Res. Mol. Biol. 75:173-216).

In vitro, the MR binds cortisol and aldosterone with equal affinity. The tissue specificity of aldosterone activity, however, is conferred by the expression of 11βHSD2 (Funder et al. (1988), Science 242: 583-585). The inactivation of cortisol to cortisone by 11βHSD2 at the site of the MR enables aldosterone to bind to this receptor *in vivo*. The binding of aldosterone to the MR results in dissociation of the ligand-activated MR from a multiprotein complex containing chaperone proteins, translocation of the MR into the nucleus, and its binding to hormone response elements in regulatory regions of target gene promoters. Within the distal nephron of the kidney, induction of serum and glucocorticoid inducible kinase-1 (sgk-1) expression leads to the absorption of Na^+ ions and water through the epithelial sodium channel, as well as potassium excretion with subsequent volume expansion and hypertension (Bhargava et al., (2001), Endo 142: 1587-1594).

In humans, elevated aldosterone concentrations are associated with endothelial dysfunction, myocardial infarction, left ventricular atrophy, and death. In attempts to modulate these ill effects, multiple intervention strategies have been adopted to control aldosterone overactivity and attenuate the resultant hypertension and its associated cardiovascular consequences. Inhibition of angiotensin-

converting enzyme (ACE) and blockade of the angiotensin type 1 receptor (AT1R) are two strategies that directly impact the rennin-angiotensin-aldosterone system (RAAS). However, although ACE inhibition and AT1R antagonism initially reduce aldosterone concentrations, circulating concentrations of this hormone return to baseline levels with chronic therapy (known as 'aldosterone escape'). Importantly, co-administration of the MR antagonist Spironolactone or Eplerenone directly blocks the deleterious effects of this escape mechanism and dramatically reduces patient mortality (Pitt et al., New England J. Med. (1999), 341: 709-719; Pitt et al., New England J. Med. (2003), 348: 1309-1321). Therefore, MR antagonism may be an important treatment strategy for many patients with hypertension and cardiovascular disease, particularly those hypertensive patients at risk for target-organ damage.

Mutations in either of the genes encoding the 11-beta-HSD enzymes are associated with human pathology. For example, 11βHSD2 is expressed in aldosterone-sensitive tissues such as the distal nephron, salivary gland, and colonic mucosa where its cortisol dehydrogenase activity serves to protect the intrinsically non-selective MR from illicit occupation by cortisol (Edwards et al. (1988) Lancet 2: 986-989). Individuals with mutations in 11βHSD2 are deficient in this cortisol-inactivation activity and, as a result, present with a syndrome of apparent mineralocorticoid excess (also referred to as 'SAME') characterized by hypertension, hypokalemia, and sodium retention (Wilson et al. (1998) Proc. Natl. Acad. Sci. 95: 10200-10205). Likewise, mutations in 11βHSD1, a primary regulator of tissue-specific glucocorticoid bioavailability, and in the gene encoding a co-localized NADPH-generating enzyme, hexose 6-phosphate dehydrogenase (H6PD), can result in cortisone reductase deficiency (CRD), in which activation of cortisone to cortisol does not occur, resulting in adrenocorticotropin-mediated androgen excess. CRD patients excrete virtually all glucocorticoids as cortisone metabolites (tetrahydrocortisone) with low or absent cortisol metabolites (tetrahydrocortisols). When challenged with oral cortisone, CRD patients exhibit abnormally low plasma cortisol concentrations. These individuals present with ACTH-mediated androgen excess (hirsutism, menstrual irregularity, hyperandrogenism), a phenotype resembling polycystic ovary syndrome (PCOS) (Draper et al. (2003) Nat. Genet. 34: 434-439).

The importance of the HPA axis in controlling glucocorticoid excursions is evident from the fact that disruption of homeostasis in the HPA axis by either excess or deficient secretion or action results in Cushing's syndrome or Addison's disease, respectively (Miller and Chrousos (2001) Endocrinology and Metabolism, eds. Felig and Frohman (McGraw-Hill, New York), 4th Ed.: 387-524). Patients with Cushing's syndrome (a rare disease characterized by systemic glucocorticoid excess originating from the adrenal or pituitary tumors) or receiving glucocorticoid therapy develop reversible visceral fat obesity. Interestingly, the phenotype of Cushing's syndrome patients closely resembles that of Reaven's metabolic syndrome (also known as Syndrome X or insulin resistance syndrome) the symptoms of which include visceral obesity, glucose intolerance, insulin resistance, hypertension, type 2 diabetes and hyperlipidemia (Reaven (1993) Ann. Rev. Med. 44: 121-131).

However, the role of glucocorticoids in prevalent forms of human obesity has remained obscure because circulating glucocorticoid concentrations are not elevated in the majority of metabolic syndrome patients. In fact, glucocorticoid action on target tissue depends not only on circulating levels but also on intracellular concentration, locally enhanced action of glucocorticoids in adipose tissue and skeletal muscle has been demonstrated in metabolic syndrome. Evidence has accumulated that enzyme activity of 11βHSD1, which regenerates active glucocorticoids from inactive forms and plays a central role in regulating intracellular glucocorticoid concentration, is commonly elevated in fat depots from obese individuals. This suggests a role for local glucocorticoid reactivation in obesity and metabolic syndrome.

Given the ability of 11βHSD1 to regenerate cortisol from inert circulating cortisone, considerable attention has been given to its role in the amplification of glucocorticoid function. 11βHSD1 is expressed in many key GR-rich tissues, including tissues of considerable metabolic importance such as liver, adipose, and skeletal muscle, and, as such, has been postulated to aid in the tissue-specific potentiation of glucocorticoid-mediated antagonism of insulin function. Considering a) the phenotypic similarity between glucocorticoid excess (Cushing's syndrome) and the metabolic syndrome with normal circulating glucocorticoids in the latter, as well as b) the ability of 11βHSD1 to generate active cortisol from inactive cortisone in a tissue-specific manner, it has been suggested that central obesity and the associated metabolic complications in syndrome X result from increased activity of 11βHSD1 within adipose tissue, resulting in 'Cushing's disease of the omentum' (Bujalska et al. (1997) Lancet 349: 1210-1213). Indeed, 11βHSD1 has been shown to be upregulated in adipose tissue of obese rodents and humans (Livingstone et al. (2000) Endocrinology 131: 560-563; Rask et al. (2001) J. Clin. Endocrinol. Metab. 86: 1418-1421; Lindsay et al. (2003) J. Clin. Endocrinol. Metab. 88: 2738-2744; Wake et al. (2003) J. Clin. Endocrinol. Metab. 88: 3983-3988).

Additional support for this notion has come from studies in mouse transgenic models. Adipose-specific overexpression of 11βHSD1 under the control of the aP2 promoter in mouse produces a phenotype remarkably reminiscent of human metabolic syndrome (Masuzaki et al. (2001) Science 294: 2166-2170; Masuzaki et al. (2003) J. Clinical Invest. 112: 83-90). Importantly, this phenotype occurs without an increase in total circulating corticosterone, but rather is driven by a local production of corticosterone within the adipose depots. The increased activity of 11βHSD1 in these mice (2-3 fold) is very similar to that observed in human obesity (Rask et al. (2001) J. Clin. Endocrinol. Metab. 86: 1418-1421). This suggests that local 11βHSD1-mediated conversion of inert glucocorticoid to active glucocorticoid can have profound influences whole body insulin sensitivity.

Based on this data, it would be predicted that the loss of 11βHSD1 would lead to an increase in insulin sensitivity and glucose tolerance due to a tissue-specific deficiency in active glucocorticoid levels. This is, in fact, the case as shown in studies with 11βHSD1-deficient mice produced by homologous recombination (Kotelevstev et al. (1997) Proc. Natl. Acad. Sci. 94: 14924-14929; Morton et al. (2001) J. Biol. Chem. 276: 41293-41300; Morton et al. (2004) Diabetes 53: 931-938). These

mice are completely devoid of 11-keto reductase activity, confirming that 11βHSD1 encodes the only activity capable of generating active corticosterone from inert 11-dehydrocorticosterone. 11βHSD1-deficient mice are resistant to diet- and stress-induced hyperglycemia, exhibit attenuated induction of hepatic gluconeogenic enzymes (PEPCK, G6P), show increased insulin sensitivity within adipose, and have an improved lipid profile (decreased triglycerides and increased cardio-protective HDL). Additionally, these animals show resistance to high fat diet-induced obesity. Taken together, these transgenic mouse studies confirm a role for local reactivation of glucocorticoids in controlling hepatic and peripheral insulin sensitivity, and suggest that inhibition of 11βHSD1 activity may prove beneficial in treating a number of glucocorticoid-related disorders, including obesity, insulin resistance, hyperglycemia, and hyperlipidemia.

Data in support of this hypothesis has been published. Recently, it was reported that 11βHSD1 plays a role in the pathogenesis of central obesity and the appearance of the metabolic syndrome in humans. Increased expression of the 11βHSD1 gene is associated with metabolic abnormalities in obese women and that increased expression of this gene is suspected to contribute to the increased local conversion of cortisone to cortisol in adipose tissue of obese individuals (Engeli, et al., (2004) Obes. Res. 12: 9-17).

A new class of 11βHSD1 inhibitors, the arylsulfonamidothiazoles, was shown to improve hepatic insulin sensitivity and reduce blood glucose levels in hyperglycemic strains of mice (Barf et al. (2002) J. Med. Chem. 45: 3813-3815; Alberts et al. Endocrinology (2003) 144: 4755-4762). Furthermore, it was recently reported that selective inhibitors of 11βHSD1 can ameliorate severe hyperglycemia in genetically diabetic obese mice. Thus, 11βHSD1 is a promising pharmaceutical target for the treatment of the Metabolic Syndrome (Masuzaki, et al., (2003) Curr. Drug Targets Immune Endocr. Metabol. Disord. 3: 255-62).

A. Obesity and metabolic syndrome

As described above, multiple lines of evidence suggest that inhibition of 11βHSD1 activity can be effective in combating obesity and/or aspects of the metabolic syndrome cluster, including glucose intolerance, insulin resistance, hyperglycemia, hypertension, and/or hyperlipidemia. Glucocorticoids are known antagonists of insulin action, and reductions in local glucocorticoid levels by inhibition of intracellular cortisone to cortisol conversion should increase hepatic and/or peripheral insulin sensitivity and potentially reduce visceral adiposity. As described above, 11βHSD1 knockout mice are resistant to hyperglycemia, exhibit attenuated induction of key hepatic gluconeogenic enzymes, show markedly increased insulin sensitivity within adipose, and have an improved lipid profile. Additionally, these animals show resistance to high fat diet-induced obesity (Kotelevstev et al. (1997) Proc. Natl. Acad. Sci. 94: 14924-14929; Morton et al. (2001) J. Biol. Chem. 276: 41293-41300; Morton et al. (2004) Diabetes 53: 931-938). Thus, inhibition of 11βHSD1 is predicted to have

multiple beneficial effects in the liver, adipose, and/or skeletal muscle, particularly related to alleviation of component(s) of the metabolic syndrome and/or obesity.

B. Pancreatic function

Glucocorticoids are known to inhibit the glucose-stimulated secretion of insulin from pancreatic beta-cells (Billaudel and Sutter (1979) Horm. Metab. Res. 11: 555-560). In both Cushing's syndrome and diabetic Zucker *fa/fa* rats, glucose-stimulated insulin secretion is markedly reduced (Ogawa et al. (1992) J. Clin. Invest. 90: 497-504). 11βHSD1 mRNA and activity has been reported in the pancreatic islet cells of ob/ob mice and inhibition of this activity with carbenoxolone, an 11βHSD1 inhibitor, improves glucose-stimulated insulin release (Davani et al. (2000) J. Biol. Chem. 275: 34841-34844). Thus, inhibition of 11βHSD1 is predicted to have beneficial effects on the pancreas, including the enhancement of glucose-stimulated insulin release.

C. Cognition and dementia

Mild cognitive impairment is a common feature of aging that may be ultimately related to the progression of dementia. In both aged animals and humans, inter-individual differences in general cognitive function have been linked to variability in the long-term exposure to glucocorticoids (Lupien et al. (1998) Nat. Neurosci. 1: 69-73). Further, dysregulation of the HPA axis resulting in chronic exposure to glucocorticoid excess in certain brain subregions has been proposed to contribute to the decline of cognitive function (McEwen and Sapolsky (1995) Curr. Opin. Neurobiol. 5: 205-216). 11βHSD1 is abundant in the brain, and is expressed in multiple subregions including the hippocampus, frontal cortex, and cerebellum (Sandeep et al. (2004) Proc. Natl. Acad. Sci. Early Edition: 1-6). Treatment of primary hippocampal cells with the 11βHSD1 inhibitor carbenoxolone protects the cells from glucocorticoid-mediated exacerbation of excitatory amino acid neurotoxicity (Rajan et al. (1996) J. Neurosci. 16: 65-70). Additionally, 11βHSD1-deficient mice are protected from glucocorticoid-associated hippocampal dysfunction that is associated with aging (Yau et al. (2001) Proc. Natl. Acad. Sci. 98: 4716-4721). In two randomized, double-blind, placebo-controlled crossover studies, administration of carbenoxolone improved verbal fluency and verbal memory (Sandeep et al. (2004) Proc. Natl. Acad. Sci. Early Edition: 1-6). Thus, inhibition of 11βHSD1 is predicted to reduce exposure to glucocorticoids in the brain and protect against deleterious glucocorticoid effects on neuronal function, including cognitive impairment, dementia, and/or depression.

D. Intra-ocular pressure

Glucocorticoids can be used topically and systemically for a wide range of conditions in clinical ophthalmology. One particular complication with these treatment regimens is corticosteroid-induced glaucoma. This pathology is characterized by a significant increase in intra-ocular pressure

(IOP). In its most advanced and untreated form, IOP can lead to partial visual field loss and eventually blindness. IOP is produced by the relationship between aqueous humour production and drainage. Aqueous humour production occurs in the non-pigmented epithelial cells (NPE) and its drainage is through the cells of the trabecular meshwork. 11βHSD1 has been localized to NPE cells (Stokes et al. (2000) Invest. Ophthalmol. Vis. Sci. 41: 1629-1683; Rauz et al. (2001) Invest. Ophthalmol. Vis. Sci. 42: 2037-2042) and its function is likely relevant to the amplification of glucocorticoid activity within these cells. This notion has been confirmed by the observation that free cortisol concentration greatly exceeds that of cortisone in the aqueous humour (14:1 ratio). The functional significance of 11βHSD1 in the eye has been evaluated using the inhibitor carbenoxolone in healthy volunteers (Rauz et al. (2001) Invest. Ophthalmol. Vis. Sci. 42: 2037-2042). After seven days of carbenoxolone treatment, IOP was reduced by 18%. Thus, inhibition of 11βHSD1 in the eye is predicted to reduce local glucocorticoid concentrations and IOP, producing beneficial effects in the management of glaucoma and other visual disorders.

E. Hypertension

Adipocyte-derived hypertensive substances such as leptin and angiotensinogen have been proposed to be involved in the pathogenesis of obesity-related hypertension (Matsuzawa et al. (1999) Ann. N.Y. Acad. Sci. 892: 146-154; Wajchenberg (2000) Endocr. Rev. 21: 697-738). Leptin, which is secreted in excess in aP2-11βHSD1 transgenic mice (Masuzaki et al. (2003) J. Clinical Invest. 112: 83-90), can activate various sympathetic nervous system pathways, including those that regulate blood pressure (Matsuzawa et al. (1999) Ann. N.Y. Acad. Sci. 892: 146-154). Additionally, the renin-angiotensin system (RAS) has been shown to be a major determinant of blood pressure (Walker et al. (1979) Hypertension 1: 287-291). Angiotensinogen, which is produced in liver and adipose tissue, is the key substrate for renin and drives RAS activation. Plasma angiotensinogen levels are markedly elevated in aP2-11βHSD1 transgenic mice, as are angiotensin II and aldosterone (Masuzaki et al. (2003) J. Clinical Invest. 112: 83-90). These forces likely drive the elevated blood pressure observed in aP2-11βHSD1 transgenic mice. Treatment of these mice with low doses of an angiotensin II receptor antagonist abolishes this hypertension (Masuzaki et al. (2003) J. Clinical Invest. 112: 83-90). This data illustrates the importance of local glucocorticoid reactivation in adipose tissue and liver, and suggests that hypertension may be caused or exacerbated by 11βHSD1 activity. Thus, inhibition of 11βHSD1 and reduction in adipose and/or hepatic glucocorticoid levels is predicted to have beneficial effects on hypertension and hypertension-related cardiovascular disorders.

F. Bone disease

Glucocorticoids can have adverse effects on skeletal tissues. Continued exposure to even moderate glucocorticoid doses can result in osteoporosis (Cannalis (1996) J. Clin. Endocrinol. Metab. 81: 3441-3447) and increased risk for fractures. Experiments *in vitro* confirm the deleterious effects

of glucocorticoids on both bone-resorbing cells (also known as osteoclasts) and bone forming cells (osteoblasts). 11βHSD1 has been shown to be present in cultures of human primary osteoblasts as well as cells from adult bone, likely a mixture of osteoclasts and osteoblasts (Cooper et al. (2000) Bone 27: 375-381), and the 11βHSD1 inhibitor carbenoxolone has been shown to attenuate the negative effects of glucocorticoids on bone nodule formation (Bellows et al. (1998) Bone 23: 119-125). Thus, inhibition of 11βHSD1 is predicted to decrease the local glucocorticoid concentration within osteoblasts and osteoclasts, producing beneficial effects in various forms of bone disease, including osteoporosis.

Small molecule inhibitors of 11βHSD1 are currently being developed to treat or prevent 11βHSD1-related diseases such as those described above. For example, certain amide-based inhibitors are reported in WO 2004/089470, WO 2004/089896, WO 2004/056745, and WO 2004/065351.

Antagonists of 11βHSD1 have been evaluated in human clinical trials (Kurukulasuriya , et al., (2003) Curr. Med. Chem. 10: 123-53).

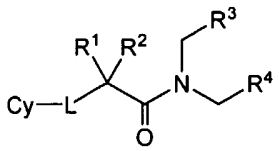
In light of the experimental data indicating a role for 11βHSD1 in glucocorticoid-related disorders, metabolic syndrome, hypertension, obesity, insulin resistance, hyperglycemia, hyperlipidemia, type 2 diabetes, androgen excess (hirsutism, menstrual irregularity, hyperandrogenism) and polycystic ovary syndrome (PCOS), therapeutic agents aimed at augmentation or suppression of these metabolic pathways, by modulating glucocorticoid signal transduction at the level of 11βHSD1 are desirable.

Furthermore, because the MR binds to aldosterone (its natural ligand) and cortisol with equal affinities, compounds that are designed to interact with the active site of 11βHSD1 (which binds to cortisone/cortisol) may also interact with the MR and act as antagonists. Because the MR is implicated in heart failure, hypertension, and related pathologies including atherosclerosis, arteriosclerosis, coronary artery disease, thrombosis, angina, peripheral vascular disease, vascular wall damage, and stroke, MR antagonists are desirable and may also be useful in treating complex cardiovascular, renal, and inflammatory pathologies including disorders of lipid metabolism including dyslipidemia or hyperlipoproteinaemia, diabetic dyslipidemia, mixed dyslipidemia, hypercholesterolemia, hypertriglyceridemia, as well as those associated with type 1 diabetes, type 2 diabetes, obesity, metabolic syndrome, and insulin resistance, and general aldosterone-related target-organ damage.

As evidenced herein, there is a continuing need for new and improved drugs that target 11βHSD1 and/or MR. The compounds, compositions and methods described herein help meet this and other needs.

SUMMARY OF THE INVENTION

The present invention provides, *inter alia*, compounds of Formulas I, II, IIa, IIb, IIc, IId, IIe, IIf, IIg, III, IIIa and IIIb:



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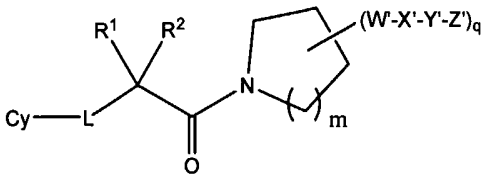

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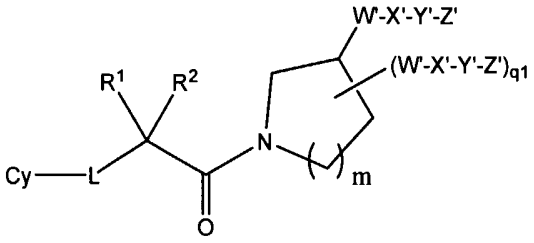

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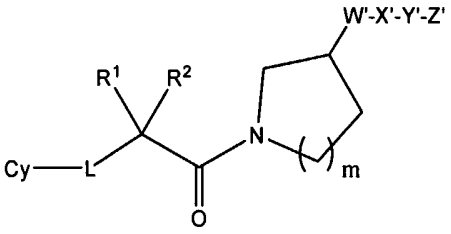

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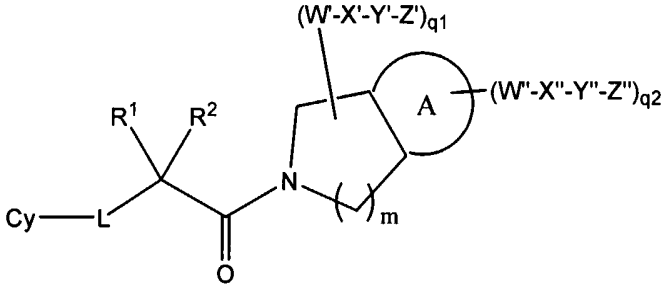

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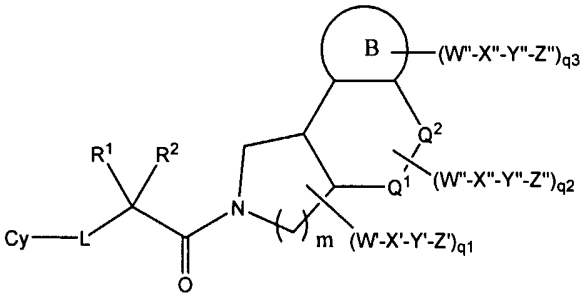

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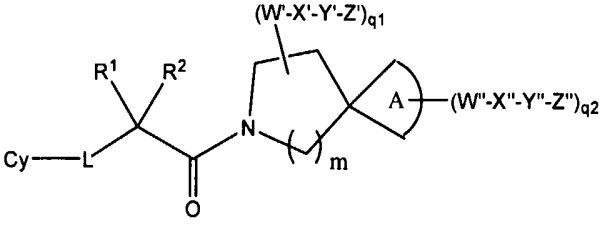

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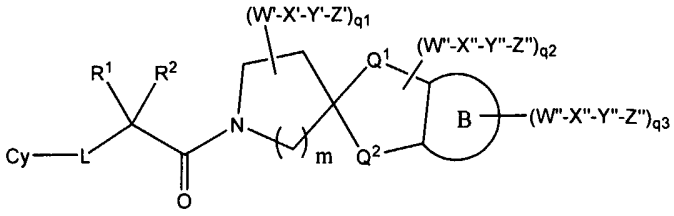

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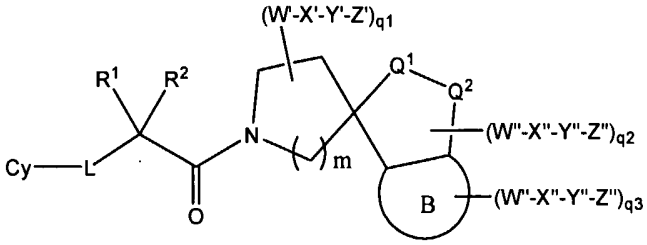

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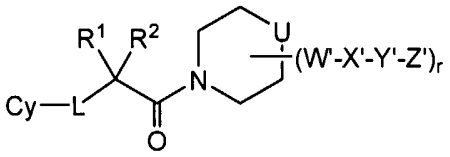
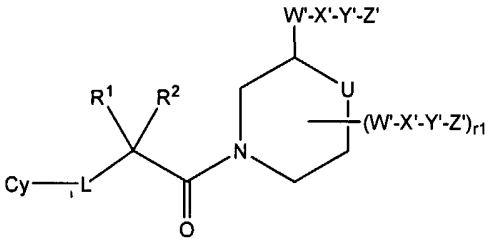
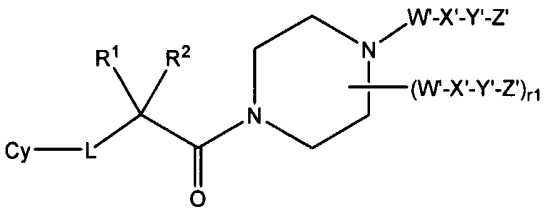


III



IIIa



IIIb

or pharmaceutically acceptable salts or prodrugs thereof, wherein constituent members are defined herein.

The present invention further provides compositions comprising compounds of the invention and a pharmaceutically acceptable carrier.

The present invention further provides methods of modulating 11βHSD1 or MR by contacting 11βHSD1 or MR with a compound of the invention.

The present invention further provides methods of inhibiting 11βHSD1 or MR by contacting 11βHSD1 or MR with a compound of the invention.

The present invention further provides methods of inhibiting the conversion of cortisone to cortisol in a cell by contacting the cell with a compound of the invention.

The present invention further provides methods of inhibiting the production of cortisol in a cell by contacting the cell with a compound of the invention.

The present invention further provides methods of increasing insulin sensitivity in a cell.

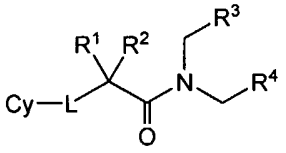
The present invention further provides methods of treating diseases associated with activity or expression of 11βHSD1 or MR.

The present invention further provides the compounds and compositions of the invention for use in therapy.

The present invention further provides the compounds and compositions of the invention for the preparation of a medicament for use in therapy.

DETAILED DESCRIPTION

The present invention provides, *inter alia*, compounds of Formula I:



I

or pharmaceutically acceptable salt or prodrug thereof, wherein:

Cy is aryl, heteroaryl, cycloalkyl or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z;

L is CH_2, O, S, SO or SO_2;

R^1 and R^2 together with the C atom to which they are attached form cyclopropyl or cyclobutyl, each optionally substituted by 1, 2 or 3 R^5;

R^3 and R^4, together with the two C atoms to which they are attached, and together with the N atom to which said two C atoms are attached, form a 3-20 membered heterocycloalkyl group optionally substituted by 1, 2, 3, 4 or 5 –W'-X'-Y'-Z';

R^5 is halo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl, said C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl is optionally substituted by one or more halo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl;

W, W' and W'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, O, S, NR^e, CO, COO, $CONR^e$, SO, SO_2, $SONR^e$, or NR^eCONR^f, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl are each optionally substituted by 1, 2 or 3 halo, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

X, X' and X'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, cycloalkyl, heteroaryl or heterocycloalkyl is optionally substituted by one or more halo, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

Y, Y' and Y'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, O, S, NR^e, CO, COO, $CONR^e$, SO, SO_2, $SONR^e$, or NR^eCONR^f, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl are each optionally substituted by 1, 2 or 3 halo, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

Z, Z' and Z'' are each, independently, H, halo, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl is optionally substituted by 1, 2 or 3 halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, or $S(O)_2NR^cR^d$;

wherein two –W-X-Y-Z together with the atom to which they are both attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W-X-Y-Z together with the C atom to which they are both attached optionally form a carbonyl;

wherein two –W-X-Y-Z together with two adjacent atoms to which they are attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W-X-Y-Z together with two adjacent atoms to which they are attached optionally form a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

wherein two –W'-X'-Y'-Z' together with the atom to which they are both attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W'-X'-Y'-Z' together with the C atom to which they are both attached optionally form a carbonyl;

wherein two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

wherein –W-X-Y-Z is other than H;

wherein –W'-X'-Y'-Z' is other than H;

wherein –W''-X''-Y''-Z'' is other than H;

R^a is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl;

R^b is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl;

R^c and R^d are each, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, arylalkyl, or cycloalkylalkyl;

or R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group; and

R^e and R^f are each, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, arylalkyl, or cycloalkylalkyl;

or R^e and R^f together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group.

In some embodiments, when L is SO_2, then Cy is other than phenyl optionally substituted by 1, 2, 3, 4 or 5 C_{1-4} alkyl or halo.

In some embodiments, Cy is aryl optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z.

In some embodiments, Cy is phenyl optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z.

In some embodiments, Cy is phenyl.

In some embodiments, L is O, SO_2 or S.

In some embodiments, L is O or S.

In some embodiments, L is S.

In some embodiments, R^1 and R^2 together with the C atom to which they are attached form cyclopropyl or cyclobutyl optionally substituted by 1, 2 or 3 halo, C_{1-4} alkyl, or C_{1-4} haloalkyl.

In some embodiments, R^1 and R^2 together with the C atom to which they are attached form cyclopropyl or cyclobutyl.

In some embodiments, R^1 and R^2 together with the C atom to which they are attached form cyclopropyl.

In some embodiments, R^3 and R^4, together with the two C atoms to which they are attached, and together with the N atom to which said two C atoms are attached, form piperidinyl, piperrazinyl,

pyrrolidinyl, 1,2,3,4-tetrahydro-isoquinolinyl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridinyl, 2,3,3a,4,5,9b-hexahydro-1H-benzo[e]isoindole, 3H-spiro[2-benzofuran-1,3'-pyrrolidinyl]-3-one, 3H-spiro[2-benzofuran-1,3'-pyrrolidinyl], 3a,4,5,6,7,7a-hexahydro-thieno[2,3-c]pyridinyl, decahydro-isoquinyl, or 1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrolyl, each optionally substituted by 1, 2 or 3 –W'-X'-Y'-Z'.

In some embodiments, –W-X-Y-Z is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH. C_{1-4} alkoxy, C_{1-4} haloalkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl.

In some embodiments, –W-X-Y-Z is halo.

In some embodiments, –W'-X'-Y'-Z' is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkoxy substituted by OH, C_{1-4} hydroxyalkyl, alkoxyalkyl, aryl, heteroaryl, aryl substituted by halo, or heteroaryl substituted by halo.

In some embodiments:

Cy is phenyl optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z;

L is S;

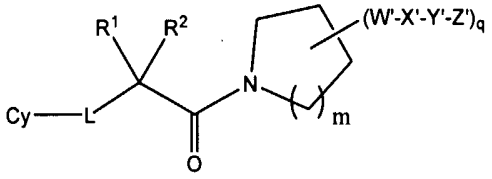
R^1 and R^2 together with the C atom to which they are attached form cyclopropyl;

R^3 and R^4, together with the two C atoms to which they are attached, and together with the N atom to which said two C atoms are attached, form piperidinyl, piperrazinyl, pyrrolidinyl, 1,2,3,4-tetrahydro-isoquinolinyl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridinyl, 2,3,3a,4,5,9b-hexahydro-1H-benzo[e]isoindole, 3H-spiro[2-benzofuran-1,3'-pyrrolidinyl]-3-one, 3H-spiro[2-benzofuran-1,3'-pyrrolidinyl], 3a,4,5,6,7,7a-hexahydro-thieno[2,3-c]pyridinyl, decahydro-isoquinyl, or 1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrolyl, each optionally substituted by 1, 2 or 3 –W'-X'-Y'-Z';

–W-X-Y-Z is halo; and

–W'-X'-Y'-Z' is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkoxy substituted by OH, C_{1-4} hydroxyalkyl, alkoxyalkyl, aryl, heteroaryl, aryl substituted by halo, or heteroaryl substituted by halo.

In some embodiments, the compounds of the invention have Formula II:



II

including pharmaceutically acceptable salt or prodrug thereof, wherein constituent variables are defined as above, m is 1 or 2, and q is 0, 1, 2, 3, 4 or 5.

In some embodiments, Cy is aryl optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z.

In some embodiments, Cy is phenyl optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z.

In some embodiments, Cy is phenyl.

In some embodiments, m is 1.

In some embodiments, m is 2.

In some embodiments, q is 1, 2, 3, 4 or 5.

In some embidments, q is 1.

In some embodiments, q is 2, 3 or 4.

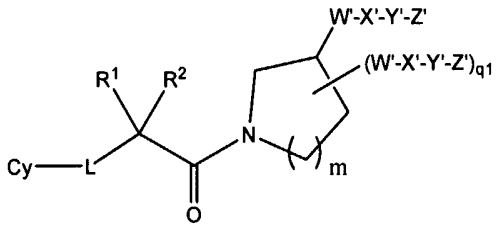
In some embodiments, –W'-X'-Y'-Z' is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkoxy substituted by OH, C_{1-4} hydroxyalkyl, alkoxyalkyl, aryl, heteroaryl, aryl substituted by halo, or heteroaryl substituted by halo.

In some embodiments, two –W'-X'-Y'-Z' together with the atom to which they are both attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z''.

In some embodiments, two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

In some embodiments, two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

The present invention further provides compounds of Formula IIa:



IIa

or pharmaceutically acceptable salt or prodrug thereof, wherein constituent variables are defined as above; and q1 is 0, 1, 2, or 3.

In some embodiments, m is 1.

In some embodiments, m is 2.

In some embodiments, q1 is 0 or 1.

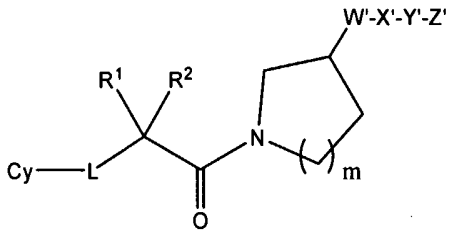
In some embodiments, –W'-X'-Y'-Z' is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkoxy substituted by OH, C_{1-4} hydroxyalkyl, alkoxyalkyl, aryl, heteroaryl, aryl substituted by halo, or heteroaryl substituted by halo.

In some embodiments, two –W'-X'-Y'-Z' together with the atom to which they are both attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z''.

In some embodiments, two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

In some embodiments, two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

The present invention further provides compounds of Formula IIb:



IIb

or pharmaceutically acceptable salts or prodrugs thereof, wherein constituent variables are defined as above.

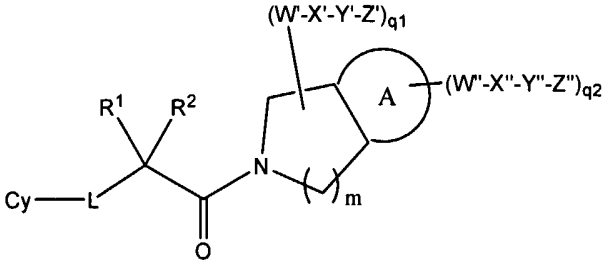
In some embodiemtns, –W'-X'-Y'-Z' is aryl or heteroaryl, each optionally substituted by one or more halo.

In some embodiments, –W'-X'-Y'-Z' is aryl optionally substituted by one or more halo.

In some embodiments, –W'-X'-Y'-Z' is phenyl.

In some embodiments, –W'-X'-Y'-Z' is phenyl substituted by one halo.

The present invention further provides compounds of Formula IIc:



IIc

or pharmaceutically acceptable salts or prodrugs thereof, wherein constituent variables are defined as above and:

ring A is a fused 5- or 6- membered aryl, fused 5- or 6- membered heteroaryl group; a fused 3-14 membered cycloalkyl group, or a fused 3-14 membered heterocycloalkyl group;

q1 is 0, 1 or 2;

q2 is 0, 1 or 2; and

the sum of q1 and q2 is 0, 1, 2 or 3.

In some embodiments, ring A is a fused 5- or 6- membered aryl or heteroaryl group.

In some embodiments, ring A is a fused phenyl or thienyl.

In some embodiments, q1 is 0.

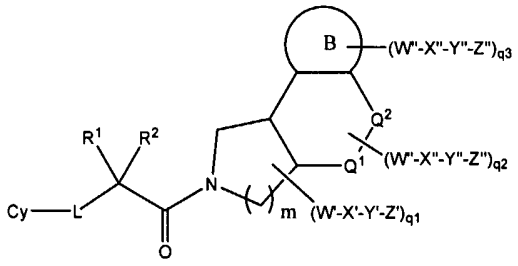
In some embodiments, q2 is 0.

In some embodiments, q1 is 0 and q2 is 0.

In some embodiments, q1 is 1.

In some embodiments, –W''-X''-Y''-Z'' is, independently, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkoxy substituted by OH, C_{1-4} hydroxyalkyl, alkoxyalkyl, aryl, heteroaryl, aryl substituted by halo, or heteroaryl substituted by halo.

The present invention further provides compounds of Formula IId:



IId

or pharmaceutically acceptable salt or prodrug thereof, wherein constituent variables are defined as above:

Q^1 is O, S, NH, CH_2, CO, CS, SO, SO_2, OCH_2, SCH_2, $NHCH_2$, CH_2CH_2, $COCH_2$, CONH, COO, $SOCH_2$, SONH, SO_2CH_2, or SO_2NH;

Q^2 is O, S, NH, CH_2, CO, CS, SO, SO_2, OCH_2, SCH_2, $NHCH_2$, CH_2CH_2, $COCH_2$, CONH, COO, $SOCH_2$, SONH, SO_2CH_2, or SO_2NH;

ring B is a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group;

q1 is 0, 1 or 2;

q2 is 0, 1 or 2;

q3 is 0, 1, or 2; and

the sum of q1, q2 and q3 is 0, 1, 2 or 3.

In some embodiments, Q^1 and Q^2 together form a moiety having 2 or 3 ring-forming atoms. In further embodiments, Q^1 and Q^2 when bonded together form a moiety having other than an O-O or O-S ring-forming bond.

In some embodiments, Q^1 is O, S, NH, CH_2 or CO, wherein each of said NH and CH_2 is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, Q^2 is O, S, NH, CH_2, CO, or SO_2, wherein each of said NH and CH_2 is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, one of Q^1 and Q^2 is CH_2 and the other is O, S, NH, or CH_2, and wherein each of said NH and CH_2 is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, one of Q^1 and Q^2 is CH_2.

In some embodiments, Q^1 and Q^2 are both CH_2.

In some embodiments, m is 0.

In some embodiments, q1 is 0.

In some embodiments, q2 is 0.

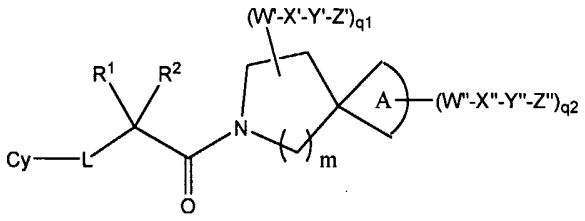
In some embodiments, q3 is 0.

In some embodiments, q1, q2 and q3 are each 0.

In some embodiments, ring B is a fused 5- or 6- membered aryl group.

In some embodiments, ring B is a fused benzene ring.

The present invention further provides compounds of Formula IIe



IIe

or pharmaceutically acceptable salt or prodrug thereof, wherein constituent variables are defined as above.

In some embodiments:

ring A is a 3-14 membered cycloalkyl group or a 3-14 membered heterocycloalkyl group;

q1 is 0, 1 or 2;

q2 is 0, 1 or 2; and

the sum of q1 and q2 is 0, 1, 2, or 3.

In some embodiments, m is 0.

In some embodiments, m is 1.

In some embodiments, q1 is 0 or 1.

In some embodiments, q1 is 0.

In some embodiments, q2 is 0 or 1.

In some embodiments, q2 is 0.

In some embodiments, q1 is 0 and q2 is 0.

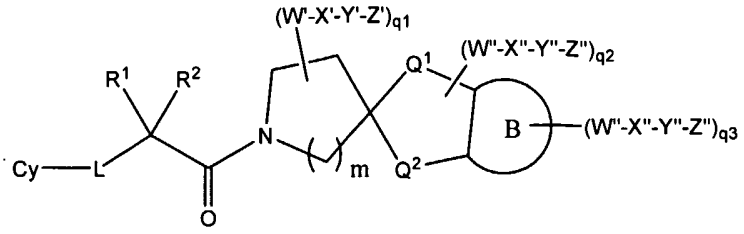
In some embodiments, ring A is a 6-14 membered cycloalkyl group or a 6-14 membered heterocycloalkyl group.

In some embodiments, ring A is a 6-14 membered cycloalkyl group.

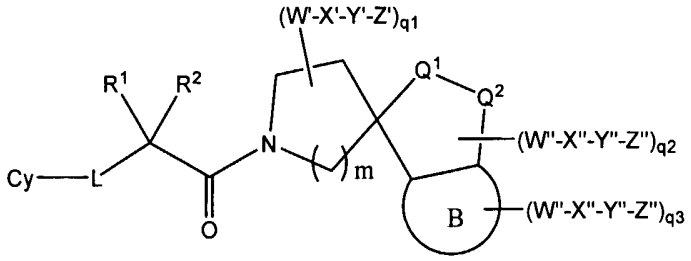
In some embodiments, ring A is a 6-14 membered heterocycloalkyl group.

In some embodiments, ring A is bicyclic.

The present invention further provides compounds of Formula IIf or IIg:



IIf



IIg

or pharmaceutically acceptable salts or prodrugs thereof, wherein constituent variables are defined as above.

In some embodiments:

Q^1 is O, S, NH, CH_2, CO, CS, SO, SO_2, OCH_2, SCH_2, $NHCH_2$, CH_2CH_2, $COCH_2$, CONH, COO, $SOCH_2$, SONH, SO_2CH_2, or SO_2NH;

Q^2 is O, S, NH, CH_2, CO, CS, SO, SO_2, OCH_2, SCH_2, $NHCH_2$, CH_2CH_2, $COCH_2$, CONH, COO, $SOCH_2$, SONH, SO_2CH_2, or SO_2NH;

ring B is a fused 5- or 6- membered aryl or 5- or 6- membered heteroaryl group;

q1 is 0, 1 or 2;

q2 is 0, 1 or 2;

q3 is 0, 1, or 2; and

the sum of q1, q2 and q3 is 0, 1, 2 or 3.

In some embodiments, Q^1 and Q^2 together have 1, 2, or 3 ring-forming atoms. In further embodiments, Q^1 and Q^2 when bonded together form a moiety having other than an O-O or O-S ring-forming bond.

In some embodiments, Q^1 is O, S, NH, CH_2 or CO, wherein each of said NH and CH_2 is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, Q^1 is O, NH, CH_2 or CO, wherein each of said NH and CH_2 is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, Q^2 is O, S, NH, CH_2, CO, or SO_2, wherein each of said NH and CH_2 is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, one of Q^1 and Q^2 is O and the other is CO or CONH, wherein said CONH is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, one of Q^1 and Q^2 is CO and the other is O, NH, or CH_2, and wherein each of said NH and CH_2 is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, one of Q^1 and Q^2 is CH_2 and the other is O, S, NH, or CH_2, and wherein each of said NH and CH_2 is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, one of Q^1 and Q^2 is CO.

In some embodiments, one of Q^1 and Q^2 is O.

In some embodiments, one of Q^1 and Q^2 is CH_2.

In some embodiments, the compound has Formula IIf wherein one of Q^1 and Q^2 is CH_2 and the other is O, S, NH, or CH_2, and wherein each of said NH and CH_2 is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, the compound has Formula IIg wherein one of Q^1 and Q^2 is CO and the other is O, NH, or CH_2, and wherein each of said NH and CH_2 is optionally substituted by –W"-X"-Y"-Z".

In some embodiments, the compound has Formula IIg wherein one of Q^1 and Q^2 is CO.

In some embodiments, the compound has Formula IIf.

In some embodiments, the compound has Formula IIg.

In some embodiments, ring B is a fused 5- or 6- membered aryl group.

In some embodiments, ring B is phenyl.

In some embodiments, m is 0.

In some embodiments, m is 1.

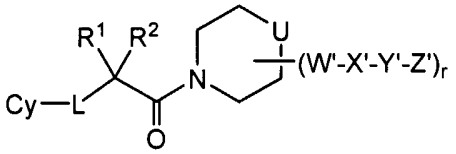
In some embodiments, q1 is 0 or 1.

In some embodiments, q2 is 0 or 1.

In some embodiments, q3 is 0 or 1.

In some embodiments, q1, q2 and q3 are all 0.

The present invention further provides compounds of Formula III:



III

or pharmaceutically acceptable salts or prodrugs thereof, wherein constituent variables are defined as above, U is NH, CH_2 or O; and r is 0, 1, 2, 3 or 4.

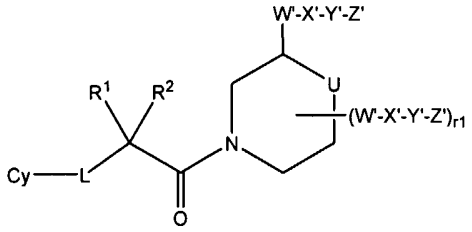
In some embodiments, U is O or NH, wherein said NH is optionally substituted by –W'-X'-Y'-Z'.

In some embodiments, U is NH or CH_2, wherein each of said NH and CH_2 is optionally substituted by –W'-X'-Y'-Z'.

In some embodiments, r is 1, 2, 3 or 4.

In some embodiments, –W'-X'-Y'-Z' is independently C_{1-4} alkyl, C_{3-7} cycloalkyl, aryl or heteroaryl, wherein each said C_{1-4} alkyl, C_{3-7} cycloalkyl, aryl and heteroaryl is optionally substituted by up to five sbustituents independently selected from the group consisting of halo, OH, C_{1-4} alkoxy, C_{1-4} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, aryl substituted by halo, or heteroaryl substituted by halo.

The present invention further provides compounds of Formula IIIa:



IIIa

or pharmaceutically acceptable salt or prodrug thereof, wherein constituent variables are defined as above.

In some embodiments:

U is O or NH; and

r1 is 0, 1, 2 or 3.

In some embodiments, U is NH, wherein said NH is optionally substituted by –W'-X'-Y'-Z'.

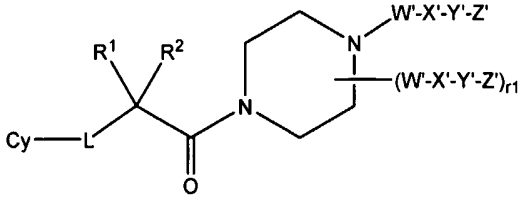
In some embodiments, U is NH, wherein said NH is substituted by –W'-X'-Y'-Z'.

In some embodiments, r1 is 1, 2, or 3.

In some embodiments, r1 is 1 or 2.

In some embodiments, –W'-X'-Y'-Z' is independently C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, aryl, heteroaryl, aryl substituted by halo, or heteroaryl substituted by halo.

The present invention further provides compounds of Formula IIIb:



IIIb

or pharmaceutically acceptable salt or prodrug thereof, wherein constituent variables are defined as above.

In some embodiments, r1 is 1, 2 or 3.

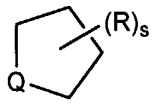
In some embodiments, r1 is 1 or 2.

In some embodiments, r1 is 1.

In some embodiments, –W'-X'-Y'-Z' is independently C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, aryl, heteroaryl, aryl substituted by halo, or heteroaryl substituted by halo.

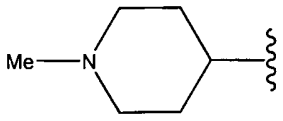
At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

For compounds of the invention in which a variable appears more than once, each variable can be a different moiety selected from the Markush group defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound; the two R groups can represent different moieties selected from the Markush group defined for R. In another example, when an optionally multiple substituent is designated in the form:

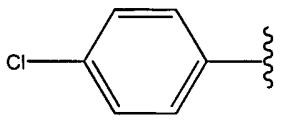


then it is understood that substituent R can occur *s* number of times on the ring, and R can be a different moiety at each occurrence. Further, in the above example, should the variable Q be defined to include hydrogens, such as when Q is said to be CH_2, NH, etc., any floating substituent such as R in the above example, can replace a hydrogen of the Q variable as well as a hydrogen in any other non-variable component of the ring.

As used herein, the terms "substituted" or "substitution" refer the replacement of a hydrogen atom with a substituent other than H. For example, an "N-substituted piperidin-4-yl" refers to replacement of the H atom of the piperdinyl NH with a non-hydrogen substituent, such as alkyl. In another example, a "4-substituted phenyl" refers to replacement of the H atom on the 4-position of the phenyl with a non-hydrogen substituent, such as chloro.



N-methylpiperidin-4-yl



4-chlorophenyl

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

As used herein, the term "alkyl" is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. Example alkyl groups include methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, neopentyl), and the like. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms. The term "alkylenyl" refers to a divalent alkyl linking group.

As used herein, "alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds. Example alkenyl groups include ethenyl, propenyl, and the like. The term "alkenylenyl" refers to a divalent linking alkenyl group.

As used herein, "alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds. Example alkynyl groups include ethynyl, propynyl, and the like. The term "alkynylenyl" refers to a divalent linking alkynyl group.

As used herein, "haloalkyl" refers to an alkyl group having one or more halogen substituents. Example haloalkyl groups include CF_3, C_2F_5, CHF_2, CCl_3, $CHCl_2$, C_2Cl_5, and the like.

As used herein, "aryl" refers to monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms.

As used herein, "cycloalkyl" refers to non-aromatic cyclic hydrocarbons including cyclized alkyl, alkenyl, and alkynyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) ring systems as well as spiro ring systems. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo or sulfido. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings (can be aryl or heteroaryl) fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of pentane, pentene, hexane, and the like.

As used herein, "heteroaryl" groups refer to an aromatic heterocycle having at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, and the like. In some embodiments, the heteroaryl

group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

As used herein, "heterocycloalkyl" refers to non-aromatic heterocycles including cyclized alkyl, alkenyl, and alkynyl groups where one or more of the ring-forming carbon atoms is replaced by a heteroatom such as an O, N, or S atom. Heterocycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) ring systems as well as spiro ring systems. Example "heterocycloalkyl" groups include morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxole, benzo-1,4-dioxane, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, and the like. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by oxo or sulfido. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings (can be aryl or heteroaryl) fused (i.e., having a bond in common with) to the nonaromatic heterocyclic ring, for example phthalimidyl, naphthalimidyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridinyl, and benzo derivatives of heterocycles such as 1,2,3,4-tetrahydroisoquinyl, indolene and isoindolene groups. In some embodiments, the heterocycloalkyl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heterocycloalkyl group contains 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 triple bonds.

As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

As used herein, "alkoxy" refers to an -O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), t-butoxy, and the like.

As used here, "haloalkoxy" refers to an –O-haloalkyl group. An example haloalkoxy group is OCF_3.

As used herein, "arylalkyl" refers to alkyl substituted by aryl and "cycloalkylalkyl" refers to alkyl substituted by cycloalkyl. An example arylalkyl group is benzyl.

As used herein, "amino" refers to NH_2.

As used herein, "alkylamino" refers to an amino group substituted by an alkyl group.

As used herein, "dialkylamino" refers to an amino group substituted by two alkyl groups.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or

by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallizaion using a "chiral resolving acid" which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (e.g., *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention also include tautomeric forms, such as keto-enol tautomers.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting

the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

The present invention also includes prodrugs of the compounds described herein. As used herein, "prodrugs" refer to any covalently bonded carriers which release the active parent drug when administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention. Preparation and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

Synthesis

The novel compounds of the present invention can be prepared in a variety of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods as hereinafter described below, together with synthetic methods known in the art of synthetic organic chemistry or variations thereon as appreciated by those skilled in the art.

The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given; other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C) infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatograpy (HPLC) or thin layer chromatography.

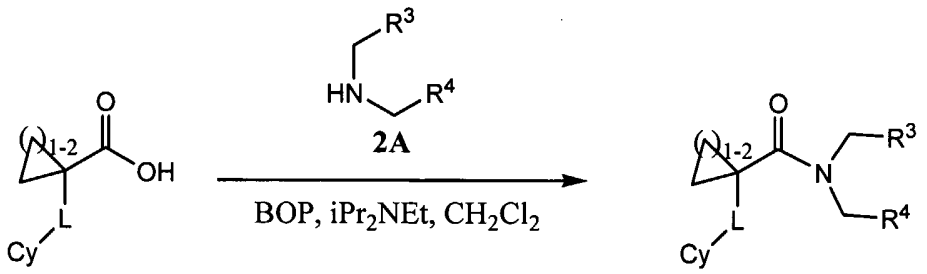
Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene, et al., *Protective Groups in Organic Synthesis*, 2d. Ed., Wiley & Sons, 1991, which is incorporated herein by reference in its entirety.

The reactions of the processes described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.

The compounds of the invention can be prepared, for example, using the reaction pathways and techniques as described below.

A series of cyclopropanecarboxamides and cyclobutanecarboxamides of formula **2** are prepared by the method outlined in Scheme 1. Cyclopropane or cyclobutanecarboxylic acids **1** can be coupled to an amine having the structure of formula **2A** using a coupling reagent such as BOP to provide the desired products **2**.

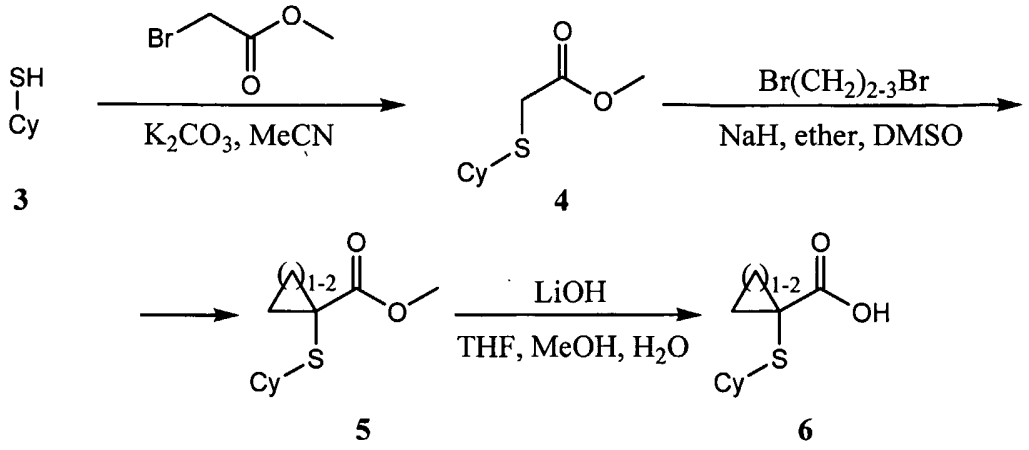
Scheme 1



1 **2**

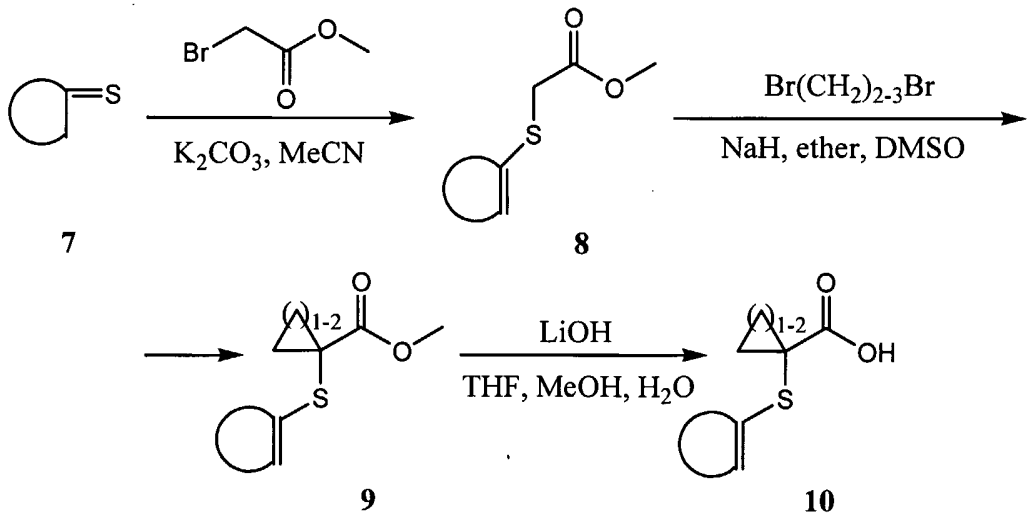
A series of cyclopropane- and cyclobutane-carboxylic acids of formula **6** (wherein Cy is a cyclic moiety such as aryl) can be prepared according to the method outlined in Scheme 2. Reaction of an appropriate thiol **3** with methyl bromoacetate in the presence of a base such as potassium or sodium carbonate, triethylamine or sodium hydride in a solvent such as tetrahydrofuran, acetonitrile or dichloromethane provides thioethers **4**. Treatment of **4** with 1,2-dibromoethane or 1,3-dibromopropane in the presence of a suitable base such as sodium hydride, in as solvent such as a mixture of ether and DMSO provides methyl esters **5**, which upon basic hydrolysis yield the desired carboxylic acids **6**.

Scheme 2



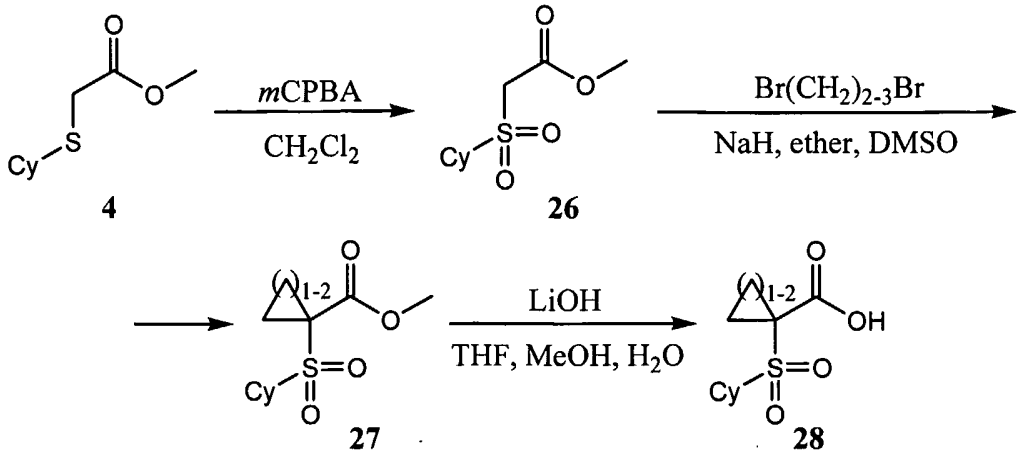
Alternatively, starting with an appropriate cyclic (such as heterocycloalkyl) thioketone **7** and following Scheme 3, a series of carboxylic acids of formula **10** can be prepared.

Scheme 3



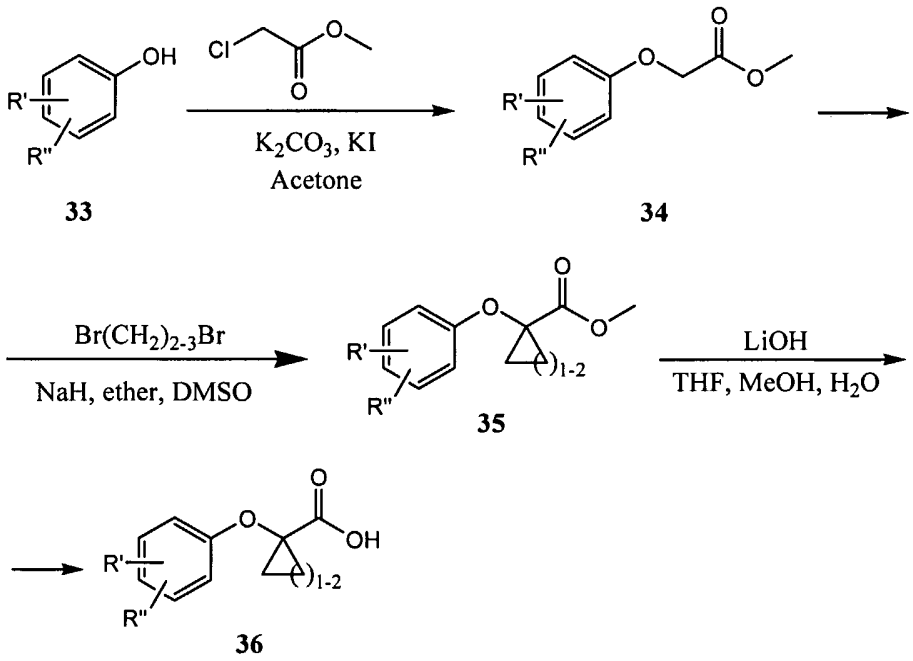
As shown in Scheme 7, thioether **4** can be oxidized to the corresponding sulfone **26** with 3-chloroperoxybenzoic acid. Following Scheme 7, a series of carboxylic acids of formula **28** can be prepared. The same sequence (conversion of the thioether to a sulfone) can be employed in all the schemes described earlier.

Scheme 7



A series of carboxylic acids of formula **36** can be prepared according to Scheme 9 (R' and R'' each can be H, alkyl, halo, haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl and the like). Reaction of a suitable phenol such as **33** with 2-chloromethyl acetate in the presence of KI and K_2CO_3 in refluxing acetone provides methyl esters **34**, which can be converted to the desired carboxylic acids **36** in the standard fashion, as depicted in Scheme 9.

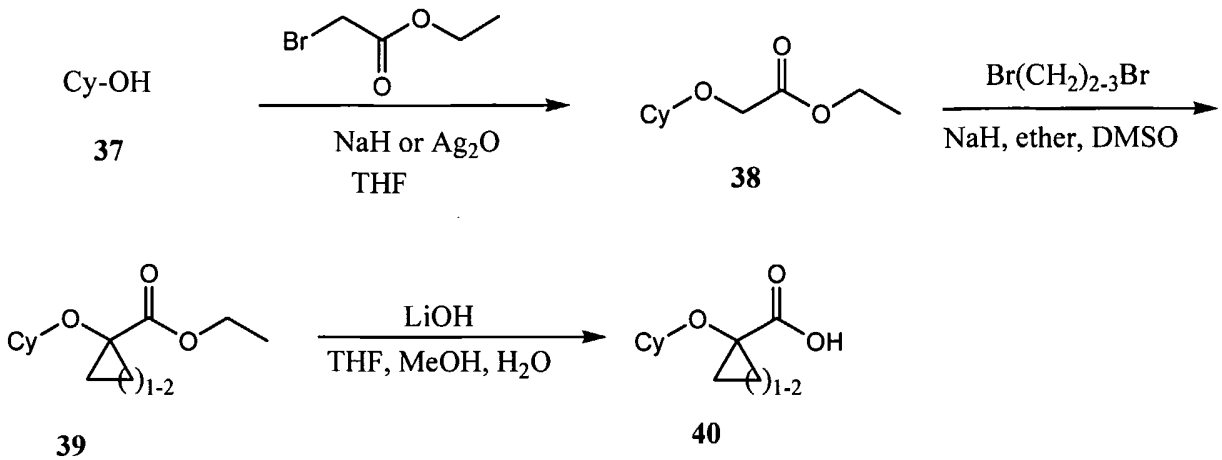
Scheme 9



A series of carboxylic acids of formula **40** can be prepared according to Scheme 10. An ether **38** can be prepared from an alcohol **37** of Cy^1OH (wherein Cy is a cyclic moiety such as aryl or heteroaryl) and ethyl bromoacetate utilizing standard Williamson ether synthesis conditions. Treatment of **38** with either 1,2-dibromoethane or 1,3-dibromopropane under any of the basic reaction

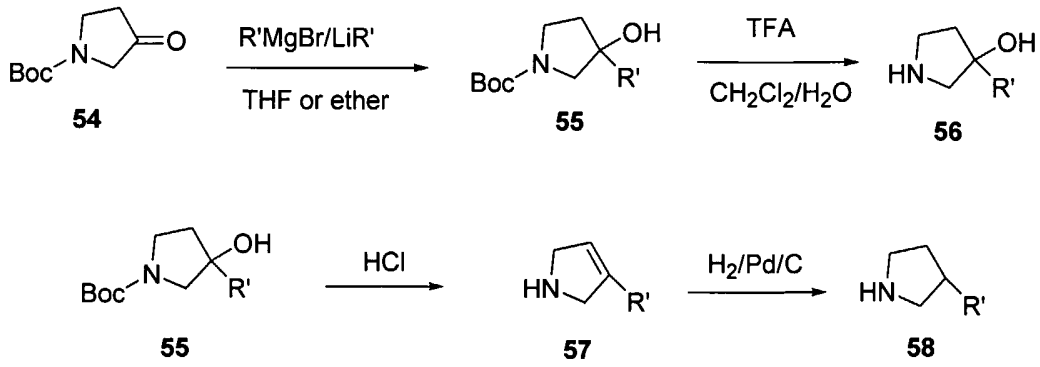
conditions described herein such depicted in scheme 10 affords the corresponding cyclopropane- or cyclobutane- esters **39**, which upon basic hydrolysis provide the desired carboxylic acids **40**.

Scheme 10



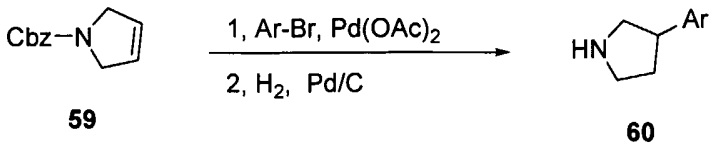
A series of 3-substituted pyrrolidine **56** and **58** can be prepared by the method outlined in Scheme 14 (R' is, e.g., alkyl, cycloalkyl, etc.). Compound **54** can be treated with an organolithium or a Grinard reagent to provide alcohol **55**. The Boc protecting group of **55** can be removed by treatment with TFA to give 3-substituted pyrrolidine **56**. Alternatively, **55** can be treated with HCl to provide the alkene **57**, followed by hydrogenation to give 3-substituted pyrrolidine **58**.

Scheme 14



A series of 3-substituted pyrrolidines **60** can be prepared by the method outlined in Scheme 15 (Ar can be, for example, aryl or heteroaryl). A sequence of a Pd catalyzed coupling reaction of alkene **59** with aryl bromides or heteroaryl bromides, followed by hydrogenation provides the desired 3-substituted pyrrolindines **60**.

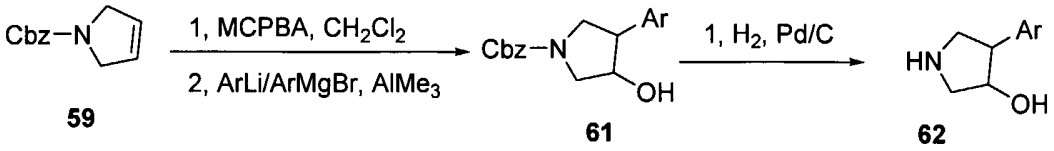
Scheme 15



59 **60**

A series of 3-hydroxyl-4-substituted pyrrolidines **62** can be prepared by the method outlined in Scheme 16 (Ar can be, for example, aryl or heteroaryl). Alkene **59** can react with *m*CPBA to provide the corresponding epoxide, which upon treatment with an organolithium or a Grignard reagent in the presence of $Al(Me)_3$ or other Lewis acid gives the desired alcohols **61**. Finally, hydrogenation provides the desired 3-hydroxyl-4-substituted pyrrolindines **62**.

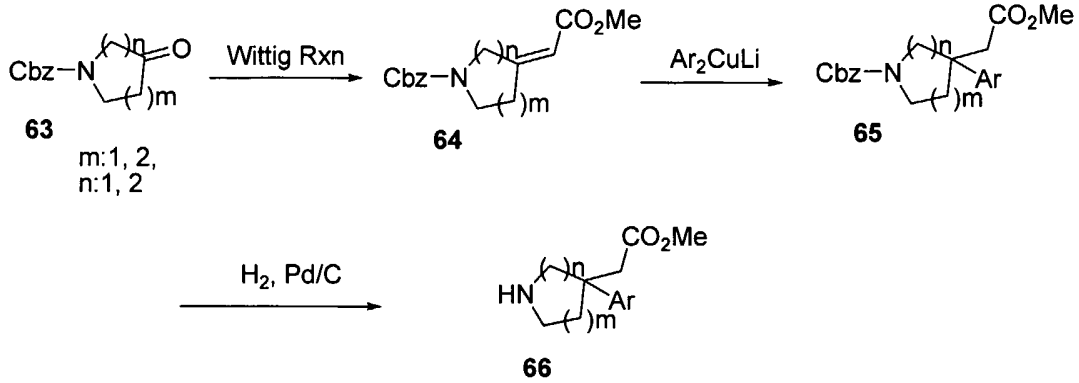
Scheme 16



59 **61** **62**

A series of 3,3-disubstituted pyrrolidines or piperidines **66** can be prepared by the method outlined in Scheme 17 (Ar is, for example, aryl or heteroaryl; n is 1 or 2 and m is 1 or 2). Ketone **63** can be treated with the appropriate Wittig reagent to provide olefinic compounds **64**. Reaction of **64** with an organocuprate Ar_2CuLi provides the corresponding 1,4 addition products **65**. The Cbz protecting group of **65** can be cleaved by hydrogenation to provide the desired 3,3-disubstituted pyrrolidines or 3,3-disubstituted piperidines **66**.

Scheme 17

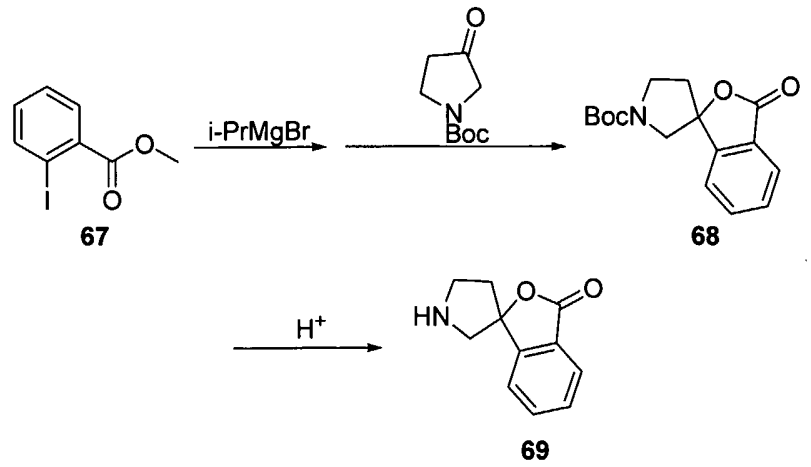


63 m:1, 2, n:1, 2 **64** **65**

66

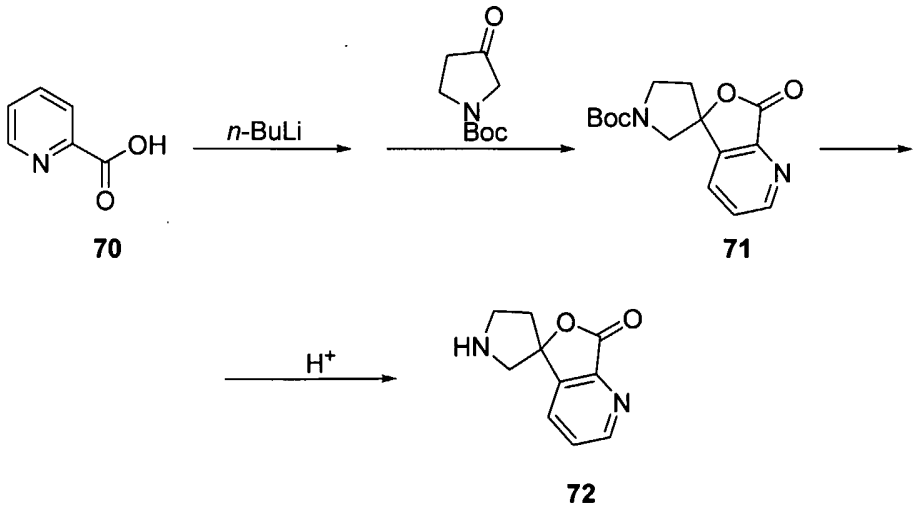
Pyrrolidine **69** can be prepared according to Scheme 18. Halogen metal exchange between aryl iodide **67** and isopropylmagnesium bromide followed by reaction with *N*-Boc-3-oxo-pyrrolidine provides spiral lactone **68** which upon acidic cleavage of the Boc group yields the desired pyrrolidine **69**.

Scheme 18



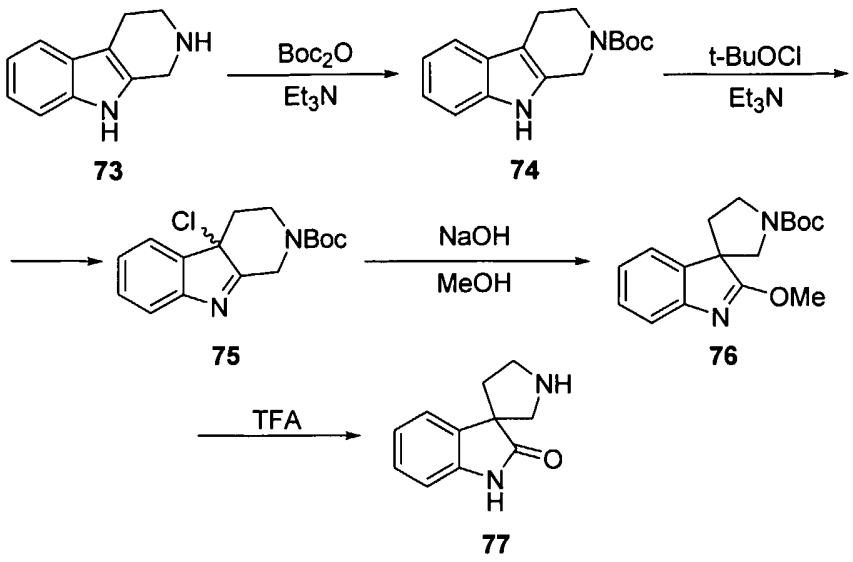
Alternatively, pyrrolidine **72** can be prepared according to Scheme 19. *Ortho* lithiation of carboxylic acid **70**, followed by reaction of the resulting organolithium with *N*-Boc-3-oxo-pyrrolidine yields spiral lactone **71**, which upon acidic cleavage of the Boc group provides the desired pyrrolidine **72**.

Scheme 19



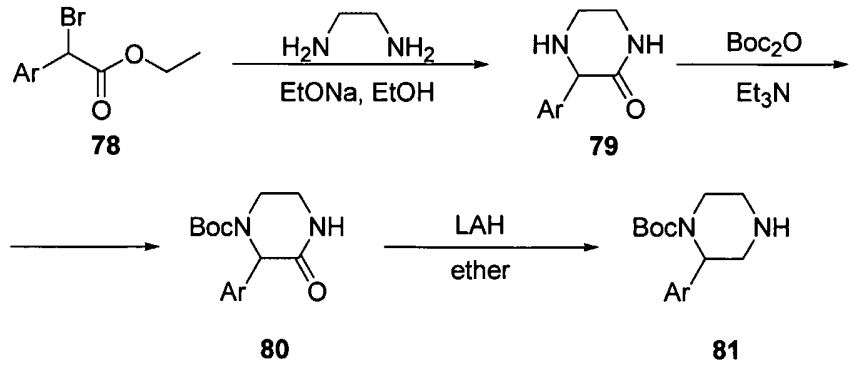
Pyrrolidine **77** can be prepared according to the method outlined in Scheme 20. The protection of the nitrogen on compound **73** affords Boc-protected compound **74**, which undergo chlorination yield compound **75**. Under basic condition, compound 75 undergoes rearrangement to yield compound 76, which affords pyrrolidine **77** under acidic condition when the Boc group is cleaved.

Scheme 20



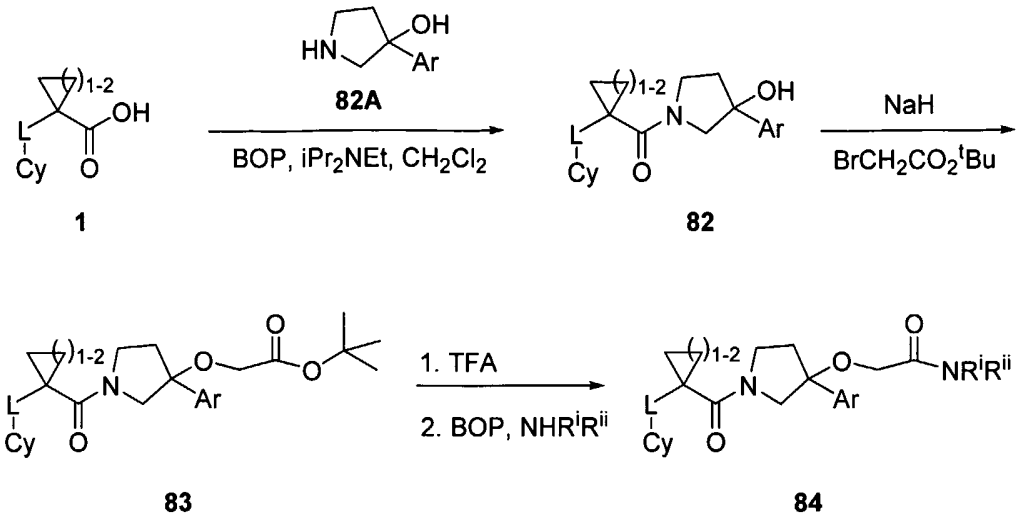
N-Boc-2-Arylpiperazines of formula **81** can be prepared according to Scheme 21 (Ar is an aromatic moiety such as phenyl). α-Bromo esters **78** react with ethylenediamine in the presence of a suitable base such as EtONa to provide 2-aryl-3-oxo-piperazines **79**. Protection with Boc_2O followed by LAH reduction yields the desired monoprotected 2-arylpiperazines **81**.

Scheme 21



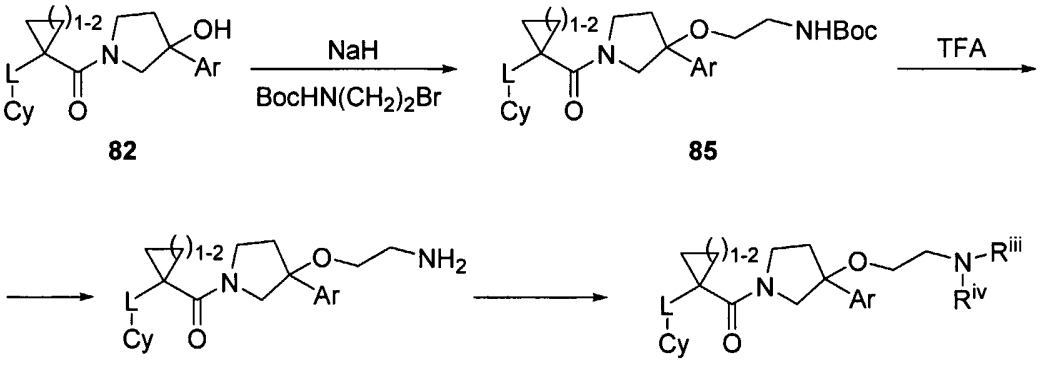
A series of compounds **84** can be prepared by the method outlined in Scheme 22 (Ar is, for example, aryl or heteroaryl; and $R^iR^{ii}NH$ is, for example, amine, alkylamine, dialkylamine or derivatives thereof; R^i and R^{ii} is, e.g., H, alkyl, cycloalkyl, etc.). Carboxylic acids **1** can couple with an amine having the structure of forumula **82A** using BOP or any other coupling reagent to provide an amido **82**. The hydroxyl group of **82** can be alkylated with 2-bromoacetate to give compounds **83**. Hydrolysis of the *t*-butyl ester with TFA, followed by the standard coupling reaction with a variety of amines yields compounds **84**.

Scheme 22



According to Scheme 23 (Ar is, for example, aryl or heteroaryl), the hydroxyl group of compound **82** can be alkylated with N-Boc-protected 2-amino ethyl bromide to give compounds **85**. The *N*-Boc group of **85** can be removed by TFA. The resulting free amino group of compounds **86** can be converted into a variety of analogs of formula **87** by routine methods.

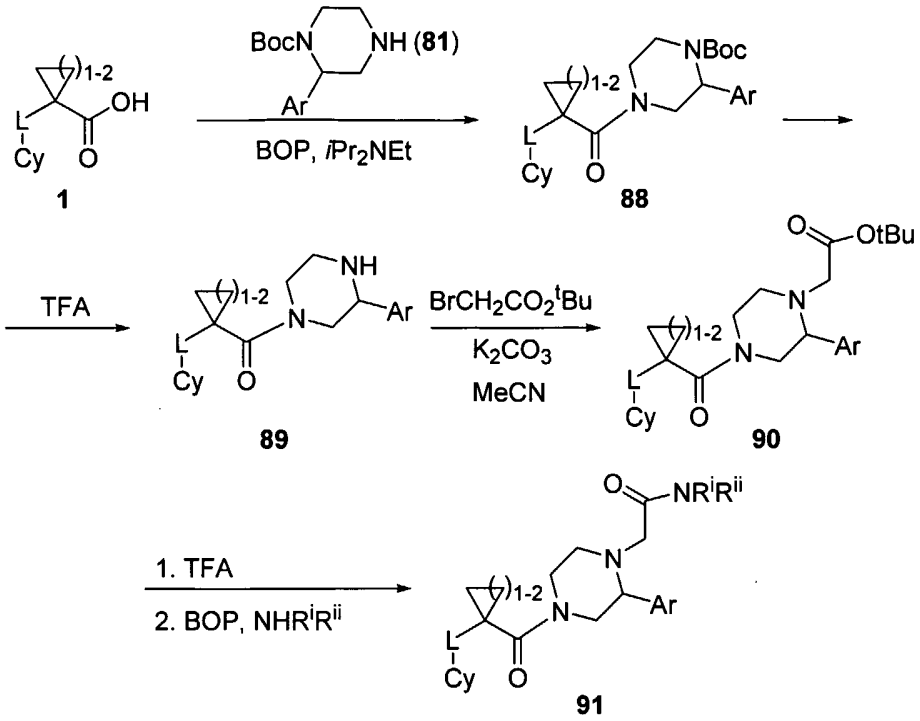
Scheme 23



A series of compounds **91** can be prepared by the method outlined in Scheme 24 (Ar can be an aromatic moiety such as phenyl; R^i and R^{ii} can be, e.g., H, alkyl, cycloalkyl, etc.) Carboxylic acids **1** can couple with 2-arylpiperazine **81** using BOP or any other coupling reagent to provide compounds **88**. Compounds **89**, obtained after the removal of the Boc group, can be alkylated with 2-bromoacetate to give compounds **90**. Hydrolysis of the *t*-butyl ester with TFA, followed by the

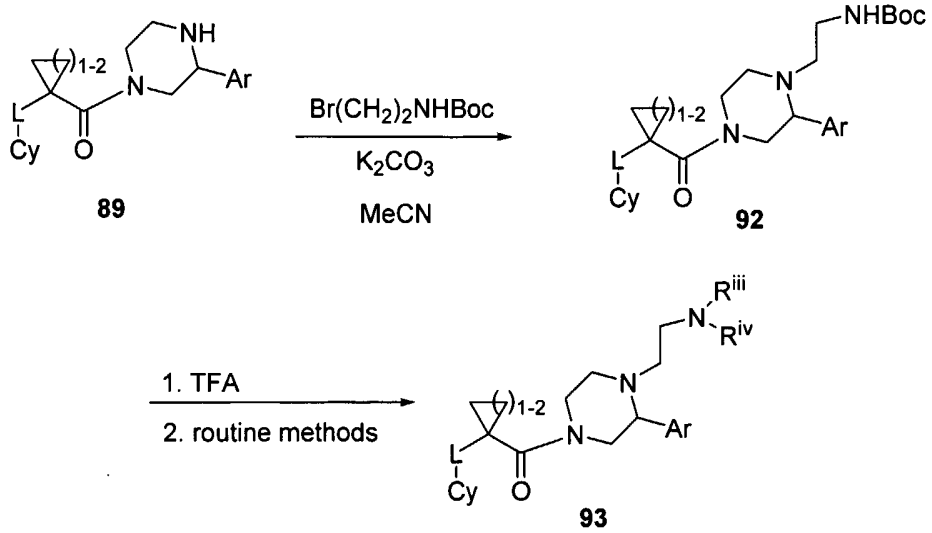
standard coupling reaction with a variety of amines will yield compounds **91** (wherein R^i and R^{ii} can be, e.g., H, alkyl, cycloalkyl, etc).

Scheme 24



According to the method outlined in Scheme 25 (R^{iii} and R^{iv} can be H, alkyl, cycloalkyl, aryl, heteroaryl, etc.), compound **89** can be alkylated with *N*-Boc-protected 2-amino ethyl bromide to provide compounds **92**. The *N*-Boc group of **92** can be removed with TFA. The resulting free amino group of compounds **92** can be converted into a variety of analogs of formula **93** by routine methods.

Scheme 25



Methods

Compounds of the invention can modulate activity of 11βHSD1 and/or MR. The term "modulate" is meant to refer to an ability to increase or decrease activity of an enzyme or receptor. Accordingly, compounds of the invention can be used in methods of modulating 11βHSD1 and/or MR by contacting the enzyme or receptor with any one or more of the compounds or compositions described herein. In some embodiments, compounds of the present invention can act as inhibitors of 11βHSD1 and/or MR. In further embodiments, the compounds of the invention can be used to modulate activity of 11βHSD1 and/or MR in an individual in need of modulation of the enzyme or receptor by administering a modulating amount of a compound of the invention.

The present invention further provides methods of inhibiting the conversion of cortisone to cortisol in a cell, or inhibiting the production of cortisol in a cell, where conversion to or production of cortisol is mediated, at least in part, by 11βHSD1 activity. Methods of measuring conversion rates of cortisone to cortisol and vice versa, as well as methods for measuring levels of cortisone and cortisol in cells, are routine in the art.

The present invention further provides methods of increasing insulin sensitivity of a cell by contacting the cell with a compound of the invention. Methods of measuring insulin sensitivity are routine in the art.

The present invention further provides methods of treating disease associated with activity or expression, including abnormal activity and overexpression, of 11βHSD1 and/or MR in an individual (e.g., patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of a compound of the present invention or a pharmaceutical composition thereof. Example diseases can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the enzyme or receptor. An 11βHSD1-associated disease can also include any disease, disorder or condition that can be prevented, ameliorated, or cured by modulating enzyme activity.

Examples of 11βHSD1-associated diseases include obesity, diabetes, glucose intolerance, insulin resistance, hyperglycemia, hypertension, hyperlipidemia, cognitive impairment, dementia, glaucoma, cardiovascular disorders, osteoporosis, and inflammation. Further examples of 11βHSD1-associated diseases include metabolic syndrome, type 2 diabetes, androgen excess (hirsutism, menstrual irregularity, hyperandrogenism) and polycystic ovary syndrome (PCOS).

The present invention further provides methods of modulating MR activity by contacting the MR with a compound of the invention, pharmaceutically acceptable salt, prodrug, or composition thereof. In some embodiments, the modulation can be inhibition. In further embodiments, methods of inhibiting aldosterone binding to the MR (optionally in a cell) are provided. Methods of measuring MR activity and inhibition of aldosterone binding are routine in the art.

The present invention further provides methods of treating a disease associated with activity or expression of the MR. Examples of diseases associated with activity or expression of the MR include, but are not limited to hypertension, as well as cardiovascular, renal, and inflammatory pathologies such as heart failure, atherosclerosis, arteriosclerosis, coronary artery disease, thrombosis, angina, peripheral vascular disease, vascular wall damage, stroke, dyslipidemia, hyperlipoproteinaemia, diabetic dyslipidemia, mixed dyslipidemia, hypercholesterolemia, hypertriglyceridemia, and those associated with type 1 diabetes, type 2 diabetes, obesity metabolic syndrome, insulin resistance and general aldosterone-related target organ damage.

As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, *ex vivo* or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal. In some embodiments, the cell is an adipocyte, a pancreatic cell, a hepatocyte, neuron, or cell comprising the eye.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" the 11βHSD1 enzyme with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having 11βHSD1, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the 11βHSD1 enzyme.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease (non-limiting examples are preventing metabolic syndrome, hypertension, obesity, insulin resistance, hyperglycemia, hyperlipidemia, type 2 diabetes, androgen excess (hirsutism, menstrual irregularity, hyperandrogenism) and polycystic ovary syndrome (PCOS);

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology) such as inhibiting the development of metabolic syndrome, hypertension, obesity, insulin resistance,

hyperglycemia, hyperlipidemia, type 2 diabetes, androgen excess (hirsutism, menstrual irregularity, hyperandrogenism) or polycystic ovary syndrome (PCOS), stabilizing viral load in the case of a viral infection; and

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of metabolic syndrome, hypertension, obesity, insulin resistance, hyperglycemia, hyperlipidemia, type 2 diabetes, androgen excess (hirsutism, menstrual irregularity, hyperandrogenism) and polycystic ovary syndrome (PCOS), or lowering viral load in the case of a viral infection.

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds of Formula I can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), ocular, oral or parenteral. Methods for ocular delivery can include topical administration (eye drops), subconjunctival, periocular or intravitreal injection or introduction by balloon catheter or ophthalmic inserts surgically placed in the conjunctival sac. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the invention above in combination with one or more pharmaceutically acceptable carriers. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10 % by weight of the active compound,

soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope

over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary

depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral adminstration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compounds of the invention can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as anti-viral agents, antibodies, immune suppressants, anti-inflammatory agents and the like.

Labeled Compounds and Assay Methods

Another aspect of the present invention relates to radio-labeled compounds of the invention that would be useful not only in radio-imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating the enzyme in tissue samples, including human, and for identifying ligands by inhibition binding of a radio-labeled compound. Accordingly, the present invention includes enzyme assays that contain such radio-labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* receptor labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I , ^{131}I, ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

It is understood that a "radio-labeled " or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I , ^{35}S and ^{82}Br.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art.

A radio-labeled compound of the invention can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the radio-labeled compound of the invention to the enzyme. Accordingly, the ability of a test compound to compete with the radio-labeled compound for binding to the enzyme directly correlates to its binding affinity.

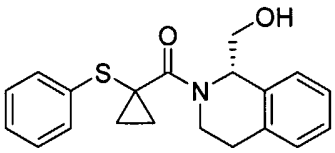
Kits

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of 11βHSD1-associated or MR-associated diseases or disorders, obesity, diabetes and other diseases referred to herein which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results. The compounds of the example section were found to be inhibitors or antagonists of 11βHSD1 or MR according to one or more of the assays provided herein.

EXAMPLES

Example 1

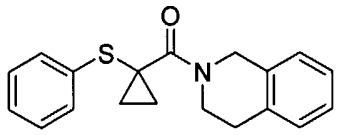


((1S)-2-{[1-(Phenylthio)cyclopropyl]carbonyl}-1,2,3,4-tetrahydroisoquinolin-1-yl)methanol

BOP (200 μL, 0.25 M in DMF, 50 μmol) was added to a solution of the 2-methyl-2-(phenylthio)propanoic acid (200 μL, 0.25 M in DMF, 50 μmol) at RT, followed by addition of N-methyl morpholine (40 μL). The mixture was stirred at RT for 15 min, then a solution of (1S)-1,2,3,4-tetrahydroisoquinolin-1-ylmethanol in DMF (200 μL, 0.25 M in DMF, 50 μmol) was added. The resulting mixture was stirred at RT for 3 h, and then was adjusted by TFA to pH 2.0, and diluted with DMSO (1100 μL). The resulting solution was purified by prep.-HPLC to afford the desired product

((1S)-2-{[1-(phenylthio)cyclopropyl]carbonyl}-1,2,3,4-tetrahydroisoquinolin-1-yl)methanol. LCMS: $(M+H)^+ = 340.1$.

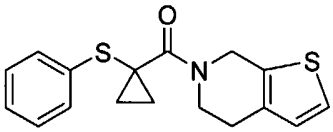
Example 2



2-{[1-(Phenylthio)cyclopropyl]carbonyl}-1,2,3,4-tetrahydroisoquinoline

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 310.0$.

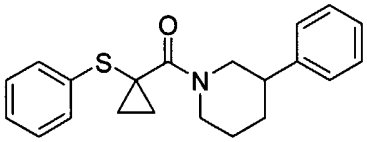
Example 3



6-{[1-(Phenylthio)cyclopropyl]carbonyl}-4,5,6,7-tetrahydrothieno[2,3-c]pyridine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 316.0$.

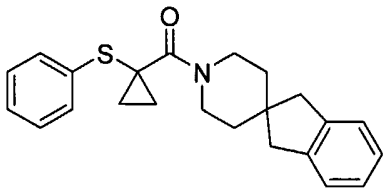
Example 4



3-Phenyl-1-{[1-(phenylthio)cyclopropyl]carbonyl}piperidine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 338.0$.

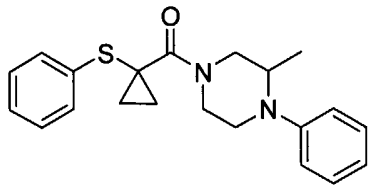
Example 5



1'-{[1-(Phenylthio)cyclopropyl]carbonyl}-1,3-dihydrospiro[indene-2,4'-piperidine]

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 364.1$.

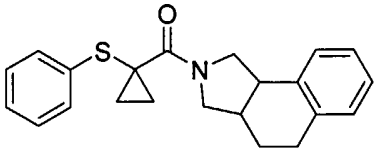
Example 6



2-Methyl-1-phenyl-4-{[1-(phenylthio)cyclopropyl]carbonyl}piperazine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 353.0$.

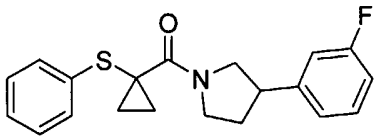
Example 7



2-{[1-(Phenylthio)cyclopropyl]carbonyl}-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]isoindole

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 350.0$.

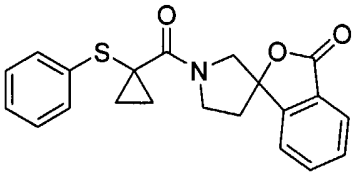
Example 8



3-(3-Fluorophenyl)-1-{[1-(phenylthio)cyclopropyl]carbonyl}pyrrolidine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 342.0$.

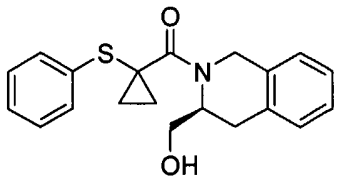
Example 9



1'-{[1-(Phenylthio)cyclopropyl]carbonyl}-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 366.0$.

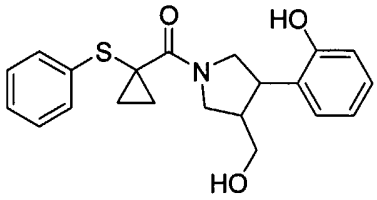
Example 10



((3S)-2-{[1-(Phenylthio)cyclopropyl]carbonyl}-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 340.1$.

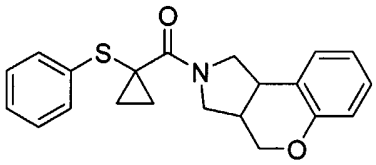
Example 11



2-(4-(Hydroxymethyl)-1-{[1-(phenylthio)cyclopropyl]carbonyl}pyrrolidin-3-yl)phenol

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 370.2$.

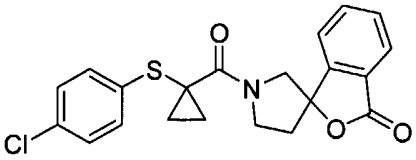
Example 12



2-{[1-(Phenylthio)cyclopropyl]carbonyl}-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole

A mixture of 2-(4-(hydroxymethyl)-1-{[1-(phenylthio)cyclopropyl]carbonyl} pyrrolidin-3-yl)phenol (14.0 mg, 0.0000379 mol, prepared as example 11), triphenylphosphine (20.0 mg, 0.0000762 mol) and diisopropyl azodicarboxylate (15.0 μL, 0.0000762 mol) in tetrahydrofuran (1.0 mL, 0.012 mol) was stirred at rt for 4 h. The mixture was diluted with methanol (0.80 mL) and the crude material was purified by prep-HPLC to give the desired product. $(M+H)^+ = 352.2$.

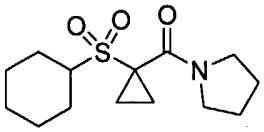
Example 13



1'-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 400.5/402.5$.

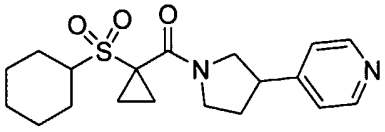
Example 14



1-{[1-(Cyclohexylsulfonyl)cyclopropyl]carbonyl}pyrrolidine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 286.2$.

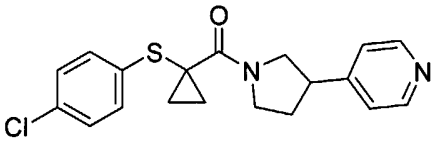
Example 15



4-(1-{[1-(Cyclohexylsulfonyl)cyclopropyl]carbonyl}pyrrolidin-3-yl)pyridine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 363.2$.

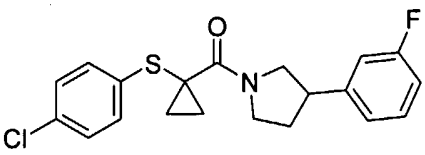
Example 16



4-[1-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)pyrrolidin-3-yl]pyridine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 359.7/361.7$.

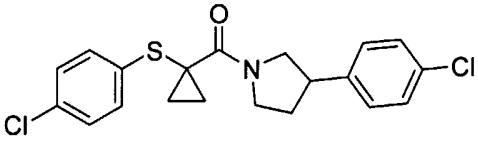
Example 17



1-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)-3-(3-fluorophenyl)pyrrolidine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 376.1/378.1$.

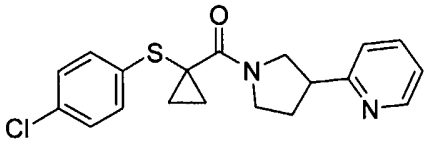
Example 18



3-(4-Chlorophenyl)-1-({1-[(4-chlorophenyl)thio]cyclopropyl}carbonyl)pyrrolidine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+$ = 392.1/394.2.

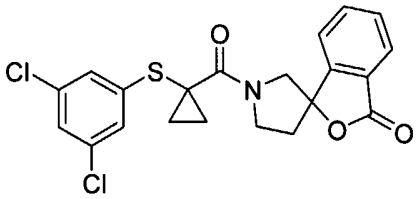
Example 19



2-[1-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)pyrrolidin-3-yl]pyridine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+$ = 359.1/361.2.

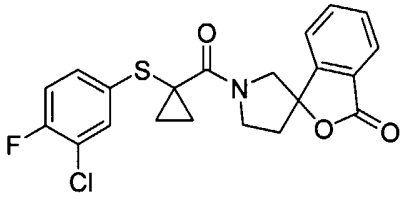
Example 20



1'-({1-[(3,5-Dichlorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+$ = 434.1/436.2.

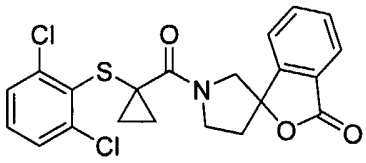
Example 21



1'-({1-[(3-Chloro-4-fluorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+$ = 418.1/420.2.

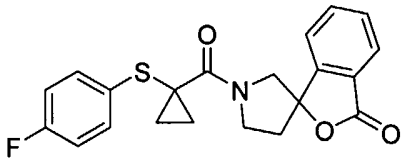
Example 22



1'-({1-[(2,6-Dichlorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+$ = 434.1/436.2.

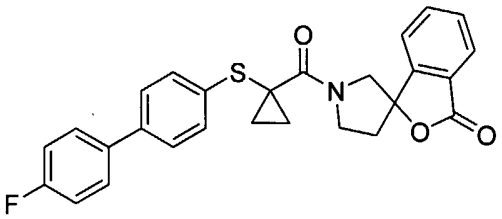
Example 23



1'-({1-[(4-Fluorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+$ = 384.2.

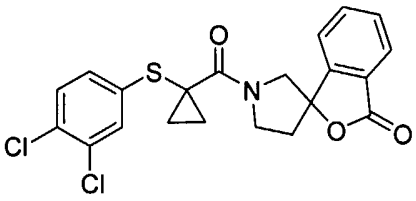
Example 24



1'-({1-[(4'-Fluorobiphenyl-4-yl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+$ = 460.0.

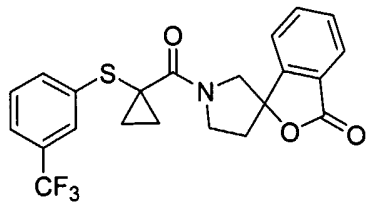
Example 25



1'-({1-[(3,4-Dichlorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+$ = 435.0/437.0.

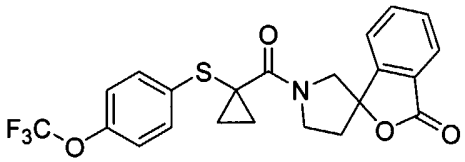
Example 26



1'-[(1-{[3-(Trifluoromethyl)phenyl]thio}cyclopropyl)carbonyl]-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 434.2$.

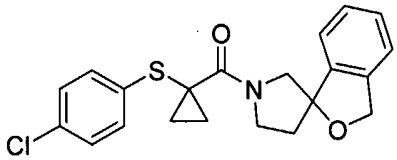
Example 27



1'-[(1-{[4-(Trifluoromethoxy)phenyl]thio}cyclopropyl)carbonyl]-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 450.2$.

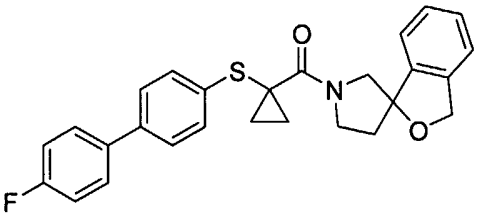
Example 28



1'-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidine]

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 386.1/388.1$.

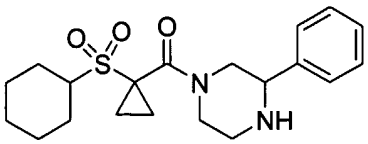
Example 29



1'-({1-[(4'-Fluorobiphenyl-4-yl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidine]

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 446.1$.

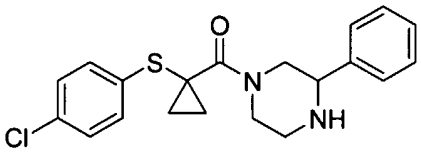
Example 30



1-{[1-(Cyclohexylsulfonyl)cyclopropyl]carbonyl}-3-phenylpiperazine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 377.2$.

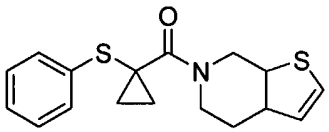
Example 31



1-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)-3-phenylpiperazine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 373.1/375.1$.

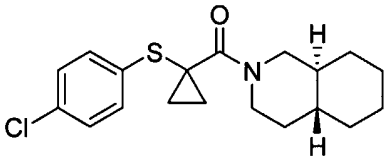
Example 32



6-{[1-(Phenylthio)cyclopropyl]carbonyl}-3a,4,5,6,7,7a-hexahydrothieno[2,3-c]pyridine

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 318.1$.

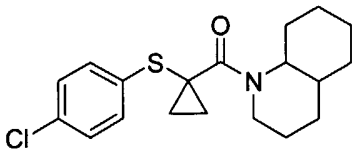
Example 33



(4aR,8aS)-2-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)decahydroisoquinoline

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 350.1/352.1$.

Example 34



1-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)decahydroquinoline

This compound was prepared using procedures analogous to those for example 1. LCMS: $(M+H)^+ = 350.1/352.1$.

Example A

Enzymatic assay of 11βHSD1

All *in vitro* assays were performed with clarified lysates as the source of 11βHSD1 activity. HEK-293 transient transfectants expressing an epitope-tagged version of full-length human 11βHSD1 were harvested by centrifugation. Roughly 2 x 10^7 cells were resuspended in 40 mL of lysis buffer (25 mM Tris-HCl, pH 7.5, 0.1M NaCl, 1 mM $MgCl_2$ and 250mM sucrose) and lysed in a microfluidizer. Lysates were clarified by centrifugation and the supernatants were aliquoted and frozen.

Inhibition of 11βHSD1 by test compounds was assessed *in vitro* by a Scintillation Proximity Assay (SPA). Dry test compounds were dissolved at 5 mM in DMSO. These were diluted in DMSO to suitable concentrations for the SPA assay. 0.8 μL of 2-fold serial dilutions of compounds were dotted on 384 well plates in DMSO such that 3 logs of compound concentration were covered. 20 μL of clarified lysate was added to each well. Reactions were initiated by addition of 20 μL of substrate-cofactor mix in assay buffer (25 mM Tris-HCl, pH 7.5, 0.1M NaCl, 1 mM $MgCl_2$) to final concentrations of 400 μM NADPH, 25 nM ^{3}H-cortisone and 0.007% Triton X-100. Plates were incubated at 37 °C for one hour. Reactions were quenched by addition of 40 μL of anti-mouse coated SPA beads that had been pre-incubated with 10 μM carbenoxolone and a cortisol-specific monoclonal antibody. Quenched plates were incubated for a minimum of 30 minutes at RT prior to reading on a Topcount scintillation counter. Controls with no lysate, inhibited lysate, and with no mAb were run routinely. Roughly 30% of input cortisone is reduced by 11βHSD1 in the uninhibited reaction under these conditions.

Test compounds having an IC_{50} value less than about 20 μM according to this assay were considered active.

Example B

Cell-based assays for HSD activity

Peripheral blood mononuclear cells (PBMCs) were isolated from normal human volunteers by Ficoll density centrifugation. Cells were plated at 4x10^5 cells/well in 200 μL of AIM V (Gibco-BRL) media in 96 well plates. The cells were stimulated overnight with 50 ng/mL recombinant

human IL-4 (R&D Systems). The following morning, 200 nM cortisone (Sigma) was added in the presence or absence of various concentrations of compound. The cells were incubated for 48 hours and then supernatants were harvested. Conversion of cortisone to cortisol was determined by a commercially available ELISA (Assay Design).

Test compounds having an IC_{50} value less than about 20 μM according to this assay were considered active.

Example C

Cellular assay to evaluate MR antagonism

Assays for MR antagonism can be performed essentially as described (Jausons-Loffreda et al. J Biolumin and Chemilumin, 1994, 9: 217-221). Briefly, HEK293/MSR cells (Invitrogen Corp.) are co-transfected with three plasmids: 1) one designed to express a fusion protein of the GAL4 DNA binding domain and the mineralocorticoid receptor ligand binding domain, 2) one containing the GAL4 upstream activation sequence positioned upstream of a firefly luciferase reporter gene (pFR-LUC, Stratagene, Inc.), and 3) one containing the Renilla luciferase reporter gene cloned downstream of a thymidine kinase promoter (Promega). Transfections are performed using the FuGENE6 reagent (Roche). Transfected cells are typically ready for use in subsequent assays 24 hours post-transfection.

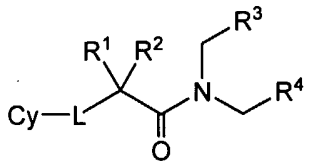
In order to evaluate a compound's ability to antagonize the MR, test compounds are diluted in cell culture medium (E-MEM, 10% charcoal-stripped FBS, 2 mM L-glutamine) supplemented with 1 nM aldosterone and applied to the transfected cells for 16-18 hours. After the incubation of the cells with the test compound and aldosterone, the activity of firefly luciferase (indicative of MR agonism by aldosterone) and Renilla luciferase (normalization control) are determined using the Dual-Glo Luciferae Assay System (Promega). Antagonism of the mineralocorticoid receptor is determined by monitoring the ability of a test compound to attenuate the aldosterone-induced firefly luciferase activity.

Compounds having an IC_{50} of 100 μM or less are considered active.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A compound of Formula I:



I

or pharmaceutically acceptable salt or prodrug thereof, wherein:

Cy is aryl, heteroaryl, cycloalkyl or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z;

L is CH_2, O, S or SO_2;

R^1 and R^2 together with the C atom to which they are attached form cyclopropyl or cyclobutyl, each optionally substituted by 1, 2 or 3 R^5;

R^3 and R^4, together with the two C atoms to which they are attached, and together with the N atom to which said two C atoms are attached, form a 3-20 membered heterocycloalkyl group optionally substituted by 1, 2, 3, 4 or 5 –W'-X'-Y'-Z';

R^5 is halo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl, said C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl is optionally substituted by one or more halo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl;

W, W' and W'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, O, S, NR^e, CO, COO, $CONR^e$, SO, SO_2, $SONR^e$, or NR^eCONR^f, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl are each optionally substituted by 1, 2 or 3 halo, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

X, X' and X'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, cycloalkyl, heteroaryl or heterocycloalkyl is optionally substituted by one or more halo, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

Y, Y' and Y'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, O, S, NR^e, CO, COO, $CONR^e$, SO, SO_2, $SONR^e$, or NR^eCONR^f, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl are each optionally substituted by 1, 2 or 3 halo, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

Z, Z' and Z'' are each, independently, H, halo, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl is optionally substituted by 1, 2 or 3 halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$,

$C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, or $S(O)_2NR^cR^d$;

wherein two –W-X-Y-Z together with the atom to which they are both attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W-X-Y-Z together with the C atom to which they are both attached optionally form a carbonyl;

wherein two –W-X-Y-Z together with two adjacent atoms to which they are attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W-X-Y-Z together with two adjacent atoms to which they are attached optionally form a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

wherein two –W'-X'-Y'-Z' together with the atom to which they are both attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W'-X'-Y'-Z' together with the C atom to which they are both attached optionally form a carbonyl;

wherein two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

wherein –W-X-Y-Z is other than H;

wherein –W'-X'-Y'-Z' is other than H;

wherein –W''-X''-Y''-Z'' is other than H;

R^a is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl;

R^b is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl;

R^c and R^d are each, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, arylalkyl, or cycloalkylalkyl;

or R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group; and

R^e and R^f are each, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, arylalkyl, or cycloalkylalkyl;

or R^e and R^f together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

provided when L is SO_2, then Cy is other than phenyl optionally substituted by 1, 2, 3, 4 or 5 C_{1-4} alkyl or halo.

2. The compound of claim 1 wherein Cy is aryl optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z.

3. The compound of claim 1 wherein Cy is phenyl optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z.

4. The compound of claim 1 wherein Cy is phenyl.

5. The compound of claim 1 wherein L is O, SO_2 or S.

6. The compound of claim 1 wherein L is S.

7. The compound of claim 1 wherein R^1 and R^2 together with the C atom to which they are attached form cyclopropyl or clycobutyl optionally substituted by 1, 2 or 3 halo, C_{1-4} alkyl, or C_{1-4} haloalkyl.

8. The compound of claim 1 wherein R^1 and R^2 together with the C atom to which they are attached form cyclopropyl or cyclobutyl.

9. The compound of claim 1 wherein R^1 and R^2 together with the C atom to which they are attached form cyclopropyl.

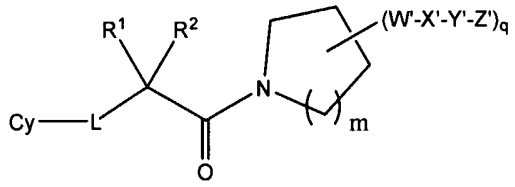
10. The compound of claim 1 wherien R^3 and R^4, together with the two C atoms to which they are attached, and together with the N atom to which said two C atoms are attached, form piperidinyl, piperrazinyl, pyrrolidinyl, 1,2,3,4-tetrahydro-isoquinolinyl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridinyl, 2,3,3a,4,5,9b-hexahydro-1H-benzo[e]isoindole, 3H-spiro[2-benzofuran-1,3'-pyrrolidinyl]-3-one, 3H-spiro[2-benzofuran-1,3'-pyrrolidinyl], 3a,4,5,6,7,7a-hexahydro-thieno[2,3-c]pyridinyl, decahydro-isoquinyl, or 1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrolyl, each optionally substituted by 1, 2 or 3 –W'-X'-Y'-Z'.

11. The compound of claim 1 wherein –W-X-Y-Z is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH. C_{1-4} alkoxy, C_{1-4} haloalkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl.

12. The compound of claim 1 wherein –W-X-Y-Z is halo.

13. The compound of claim 1 wherein –W'-X'-Y'-Z' is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkoxy substituted by OH, C_{1-4} hydroxyalkyl, alkoxyalkyl, aryl, heteroaryl, aryl substituted by halo, or heteroaryl substituted by halo.

14. A compound of Formula II:



II

or pharmaceutically acceptable salt or prodrug thereof, wherein:

Cy is aryl, heteroaryl, cycloalkyl or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z;

L is CH_2, O or S;

R^1 and R^2 together with the C atom to which they are attached form cyclopropyl or cyclobutyl, each optionally substituted by 1, 2 or 3 R^5;

R^5 is halo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl, wherein said C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl is optionally substituted by one or more halo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl;

W, W' and W'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, O, S, NR^e, CO, COO, $CONR^e$, SO, SO_2, $SONR^e$, or NR^eCONR^f, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl are each optionally substituted by 1, 2 or 3 halo, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

X, X' and X'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, cycloalkyl, heteroaryl or heterocycloalkyl is optionally substituted by one or more halo, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

Y, Y' and Y'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, O, S, NR^e, CO, COO, $CONR^e$, SO, SO_2, $SONR^e$, or NR^eCONR^f, wherein said C_{1-6}

alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl are each optionally substituted by 1, 2 or 3 halo, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

Z, Z' and Z'' are each, independently, absent, H, halo, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl is optionally substituted by 1, 2 or 3 halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, or $S(O)_2NR^cR^d$;

wherein two –W-X-Y-Z together with the atom to which they are both attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W-X-Y-Z together with the C atom to which they are both attached optionally form a carbonyl;

wherein two –W-X-Y-Z together with two adjacent atoms to which they are attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W-X-Y-Z together with two adjacent atoms to which they are attached optionally form a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

wherein two –W'-X'-Y'-Z' together with the atom to which they are both attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W'-X'-Y'-Z' together with the C atom to which they are both attached optionally form a carbonyl;

wherein two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

wherein –W-X-Y-Z is other than H;

wherein –W'-X'-Y'-Z' is other than H;

wherein –W''-X''-Y''-Z'' is other than H;

R^a is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl;

R^b is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl;

R^c and R^d are each, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, arylalkyl, or cycloalkylalkyl;

or R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

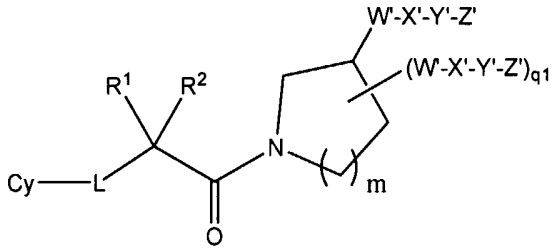
R^e and R^f are each, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, arylalkyl, or cycloalkylalkyl;

or R^e and R^f together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

q is 0, 1, 2, 3, 4 or 5; and

m is 1 or 2.

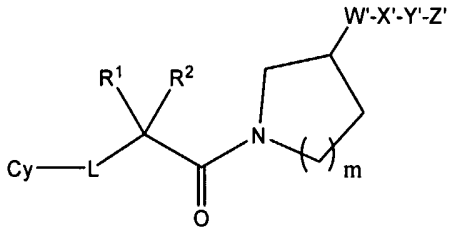
15. The compound of claim 14 having Formula IIa:



IIa

wherein q1 is 0, 1, 2 or 3.

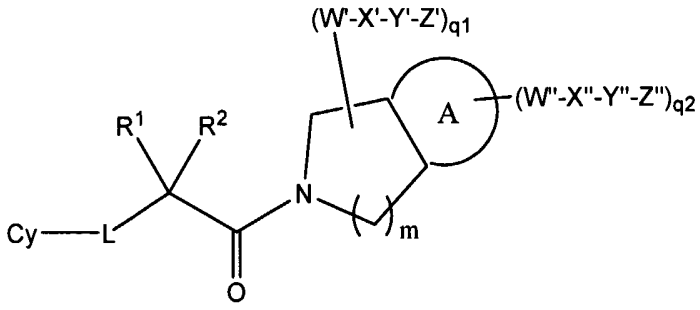
16. The compound of claim 14 having Formula IIb:



IIb

wherein –W'-X'-Y'-Z' is aryl or heteroaryl, each optionally substituted by one or more halo.

17. The compound of claim 14 having Formula IIc:



IIc

wherein:

ring A is a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group;

or ring A is a fused 3-14 membered cycloalkyl group or a fused 3-14 membered heterocycloalkyl group;

q1 is 0, 1 or 2;

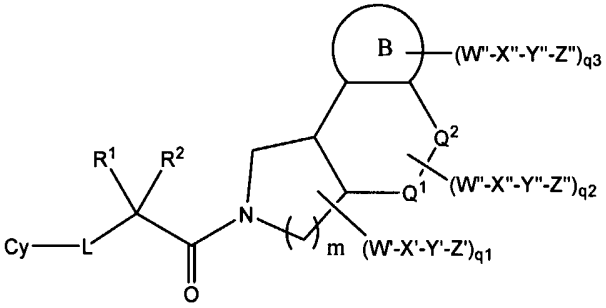
q2 is 0, 1 or 2; and

the sum of q1 and q2 is 0, 1, 2 or 3.

18. The compound of claim 17 wherein ring A is a fused 5- or 6- membered aryl or a fused 5- or 6- membered heteroaryl group.

19. The compound of claim 17 wherein ring A is a fused phenyl or thienyl.

20. The compound of claim 14 having Formula IId:



IId

wherein:

Q^1 is O, S, NH, CH_2, CO, CS, SO, SO_2, OCH_2, SCH_2, $NHCH_2$, CH_2CH_2, $COCH_2$, CONH, COO, $SOCH_2$, SONH, SO_2CH_2, or SO_2NH;

Q^2 is O, S, NH, CH_2, CO, CS, SO, SO_2, OCH_2, SCH_2, $NHCH_2$, CH_2CH_2, $COCH_2$, CONH, COO, $SOCH_2$, SONH, SO_2CH_2, or SO_2NH;

ring B is a fused 5- or 6- membered aryl or a fused 5- or 6- membered heteroaryl group;

q1 is 0, 1 or 2;

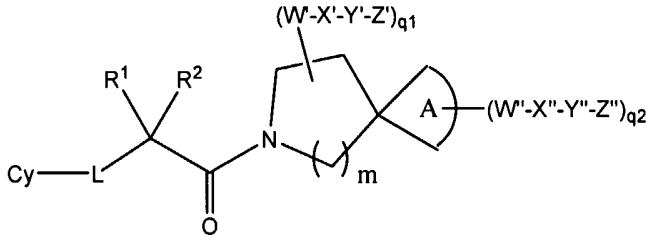
q2 is 0, 1 or 2;

q3 is 0, 1, or 2; and

the sum of q1, q2 and q3 is 0, 1, 2 or 3.

21. The compound of claim 20 wherein Q^1 and Q^2 are CH_2.

22. The compound of claim 14 having Formula IIe:



IIe

wherein:

ring A is a 3-14 membered cycloalkyl group or a 3-14 membered heterocycloalkyl group;

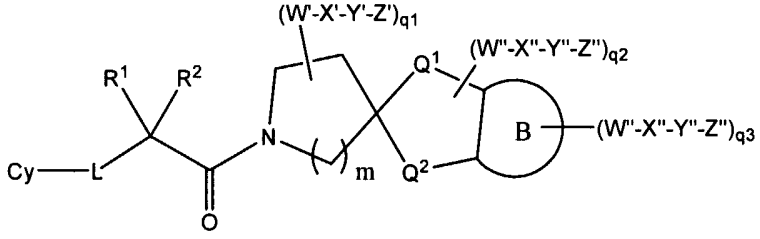
q1 is 0, 1 or 2;

q2 is 0, 1 or 2; and

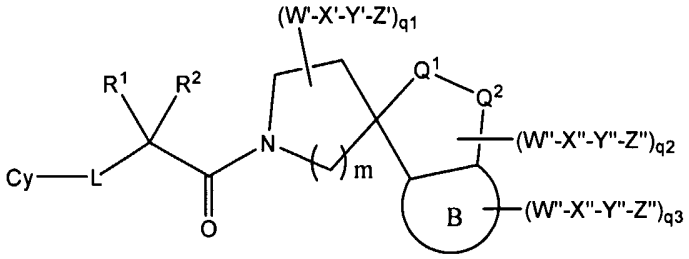
the sum of q1 and q2 is 0, 1, 2, or 3.

23. The compound of claim 22 wherein ring A is bicyclic.

24. The compound of claim 14 having Formula IIf or IIg:



IIf



IIg

wherein:

Q^1 is O, S, NH, CH_2, CO, CS, SO, SO_2, OCH_2, SCH_2, $NHCH_2$, CH_2CH_2, $COCH_2$, CONH, COO, $SOCH_2$, SONH, SO_2CH_2, or SO_2NH;

Q^2 is O, S, NH, CH_2, CO, CS, SO, SO_2, OCH_2, SCH_2, $NHCH_2$, CH_2CH_2, $COCH_2$, CONH, COO, $SOCH_2$, SONH, SO_2CH_2, or SO_2NH;

ring B is a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group;

q1 is 0, 1 or 2;

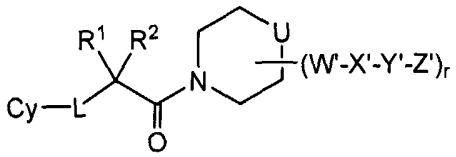
q2 is 0, 1 or 2;

q3 is 0, 1, or 2; and

the sum of q1, q2 and q3 is 0, 1, 2 or 3.

25. The compound of claim 24 wherein Q^1 and Q^2 are each, independently, CH_2, O or CO.

26. A compound of Formula III:



III

or pharmaceutically acceptable salt or prodrug thereof, wherein:

Cy is aryl, heteroaryl, cycloalkyl or heterocycloalkyl, each optionally substituted by 1, 2, 3, 4 or 5 –W-X-Y-Z;

L is CH_2, O or S;

U is NH, CH_2 or O;

R^1 and R^2 together with the C atom to which they are attached form cyclopropyl or cyclobutyl, each optionally substituted by 1, 2 or 3 R^5;

R^5 is halo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl, said C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl is optionally substituted by one or more halo, OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or aryl;

W, W' and W'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, O, S, NR^e, CO, COO, $CONR^e$, SO, SO_2, $SONR^e$, or NR^eCONR^f, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl are each optionally substituted by 1, 2 or 3 halo, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

X, X' and X'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, cycloalkyl, heteroaryl or heterocycloalkyl is optionally substituted by one or more halo, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

Y, Y' and Y'' are each, independently, absent, C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl, O, S, NR^e, CO, COO, $CONR^e$, SO, SO_2, $SONR^e$, or NR^eCONR^f, wherein said C_{1-6} alkylenyl, C_{2-6} alkenylenyl, C_{2-6} alkynylenyl are each optionally substituted by 1, 2 or 3 halo, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino;

Z, Z' and Z'' are each, independently, absent, H, halo, CN, NO_2, OH, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino or C_{2-8} dialkylamino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl is optionally substituted by 1, 2 or 3 halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO_2, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, or $S(O)_2NR^cR^d$;

wherein two –W-X-Y-Z together with the atom to which they are both attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W-X-Y-Z together with the C atom to which they are both attached optionally form a carbonyl;

wherein two –W-X-Y-Z together with two adjacent atoms to which they are attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W-X-Y-Z together with two adjacent atoms to which they are attached optionally form a 5- or fused membered aryl or fused 5- or 6- membered heteroaryl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

wherein two –W'-X'-Y'-Z' together with the atom to which they are both attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W'-X'-Y'-Z' together with the C atom to which they are both attached optionally form a carbonyl;

wherein two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a 3-20 membered cycloalkyl group or 3-20 membered heterocycloalkyl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

or wherein two –W'-X'-Y'-Z' together with two adjacent atoms to which they are attached optionally form a fused 5- or 6- membered aryl or fused 5- or 6- membered heteroaryl group, each optionally substituted by 1, 2 or 3 –W''-X''-Y''-Z'';

wherein –W-X-Y-Z is other than H;

wherein –W'-X'-Y'-Z' is other than H;

wherein –W''-X''-Y''-Z'' is other than H;

R^a is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl;

R^b is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl;

R^c and R^d are each, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, arylalkyl, or cycloalkylalkyl;

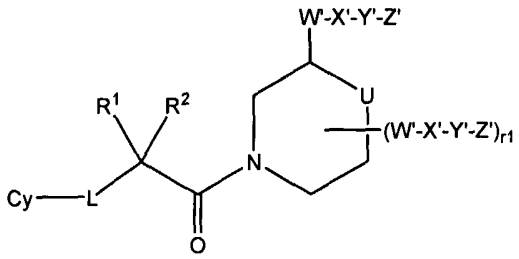
or R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group;

R^e and R^f are each, independently, H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, arylalkyl, or cycloalkylalkyl;

or R^e and R^f together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocycloalkyl group; and

r is 0, 1, 2, 3 or 4.

27. The compound of claim 26 having Formula IIIa:



IIIa

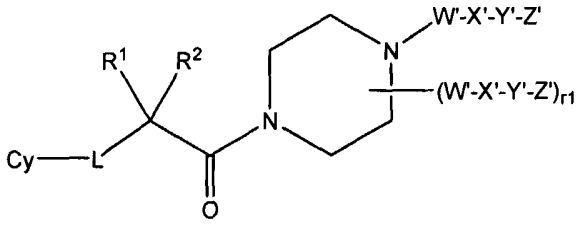
wherein:

U is O or NH; and

r1 is 0, 1, 2 or 3.

28. The compound of claim 27 wherein U is NH.

29. The compound of claim 26 having Formula IIIb:



IIIb

wherein:

r1 is 1, 2 or 3.

30. A compound of claim 1 selected from:

((1S)-2-{[1-(phenylthio)cyclopropyl]carbonyl}-1,2,3,4-tetrahydroisoquinolin-1-yl)methanol;

2-{[1-(phenylthio)cyclopropyl]carbonyl}-1,2,3,4-tetrahydroisoquinoline;

6-{[1-(phenylthio)cyclopropyl]carbonyl}-4,5,6,7-tetrahydrothieno[2,3-c]pyridine;

3-phenyl-1-{[1-(phenylthio)cyclopropyl]carbonyl}piperidine;

1'-{[1-(phenylthio)cyclopropyl]carbonyl}-1,3-dihydrospiro[indene-2,4'-piperidine];

2-methyl-1-phenyl-4-{[1-(phenylthio)cyclopropyl]carbonyl}piperazine;

2-{[1-(phenylthio)cyclopropyl]carbonyl}-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]isoindole;

3-(3-fluorophenyl)-1-{[1-(phenylthio)cyclopropyl]carbonyl}pyrrolidine;

1'-{[1-(phenylthio)cyclopropyl]carbonyl}-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one;

((3S)-2-{[1-(Phenylthio)cyclopropyl]carbonyl}-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol;

2-(4-(Hydroxymethyl)-1-{[1-(phenylthio)cyclopropyl]carbonyl}pyrrolidin-3-yl)phenol;

2-{[1-(Phenylthio)cyclopropyl]carbonyl}-1,2,3,3a,4,9b-hexahydrochromeno[3,4-c]pyrrole;

1'-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one;

1-{[1-(Cyclohexylsulfonyl)cyclopropyl]carbonyl}pyrrolidine;

4-(1-{[1-(Cyclohexylsulfonyl)cyclopropyl]carbonyl}pyrrolidin-3-yl)pyridine;

4-[1-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)pyrrolidin-3-yl]pyridine;

1-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)-3-(3-fluorophenyl)pyrrolidine;

3-(4-Chlorophenyl)-1-({1-[(4-chlorophenyl)thio]cyclopropyl}carbonyl)pyrrolidine;

2-[1-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)pyrrolidin-3-yl]pyridine;

1'-({1-[(3,5-Dichlorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one;

1'-({1-[(3-Chloro-4-fluorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one;

1'-({1-[(2,6-Dichlorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one;

1'-({1-[(4-Fluorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one;

1'-({1-[(4'-Fluorobiphenyl-4-yl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one;

1'-({1-[(3,4-Dichlorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one;

1'-[(1-{[3-(Trifluoromethyl)phenyl]thio}cyclopropyl)carbonyl]-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one;

1'-[(1-{[4-(Trifluoromethoxy)phenyl]thio}cyclopropyl)carbonyl]-3H-spiro[2-benzofuran-1,3'-pyrrolidin]-3-one;

1'-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidine];

1'-({1-[(4'-Fluorobiphenyl-4-yl)thio]cyclopropyl}carbonyl)-3H-spiro[2-benzofuran-1,3'-pyrrolidine];

1-{[1-(Cyclohexylsulfonyl)cyclopropyl]carbonyl}-3-phenylpiperazine;

1-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)-3-phenylpiperazine;

6-{[1-(Phenylthio)cyclopropyl]carbonyl}-3a,4,5,6,7,7a-hexahydrothieno[2,3-c]pyridine;

(4aR,8aS)-2-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)decahydroisoquinoline; and

1-({1-[(4-Chlorophenyl)thio]cyclopropyl}carbonyl)decahydroquinoline, or pharmaceutically acceptable salt thereof.

31. A composition comprising a compound of claim 1, 14, 26, or 30 and a pharmaceutically acceptable carrier.

32. A method of modulating 11βHSD1 or MR comprising contacting said 11βHSD1 or MR with a compound of claim 1, 14, 26, or 30.

33. The method of claim 32 wherein said modulating is inhibiting.

34. A method of treating a disease in a patient, wherein said disease is associated with expression or activity of 11βHSD1 or MR, comprising administering to said patient a therapeutically effective amount of a compound of claim 1, 14, 26, or 30.

35. The method of claim 34 wherein said disease is obesity, diabetes, glucose intolerance, hyperglycemia, hyperlipidemia, lipodystrophy, cognitive impairment, dementia, glaucoma, hypertension, cardiovascular disorders, osteoporosis, hypertension, a cardiovascular, renal or inflammatory disease, heart failure, atherosclerosis, arteriosclerosis, coronary artery disease, thrombosis, angina, peripheral vascular disease, vascular wall damage, stroke, dyslipidemia, hyperlipoproteinaemia, diabetic dyslipidemia, mixed dyslipidemia, hypercholesterolemia, hypertriglyceridemia, type 1 diabetes, type 2 diabetes, obesity, metabolic syndrome, insulin resistance or general aldosterone-related target organ damage.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/22412

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 213/00, 215/00, 217/00; A61K 31/47
US CL : 514/231.2, 252.10, 278, 307, 311, 317; 540/106; 544/358; 546/15. 139, 152, 187
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/231.2, 252.10, 278, 307, 311, 317; 540/106; 544/358; 546/15. 139, 152, 187

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/053915 A2 (SCHERING -PLOUGH CORPORATION) 03 July 2003 (03.07.2003), see entire document.	1-35

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

* Special categories of cited documents:

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"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 2005 (28.08.2005)	02 NOV 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Zinna Northington Davis Telephone No. 571-272-1600

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