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(71) Applicant *(for all designated States except US)*: **VITAE PHARMACEUTICALS, INC.** [US/US]; 502 West Office Center Drive, Fort Washington, PA 19034 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CLAREMON, David, A.** [US/US]; 1508 Aidenn Lair Road, Maple Glen, PA 19002 (US). **ZHUANG, Linghang** [CN/US]; 3135 Fox Drive, Chalfont, PA 18914 (US). **YE, Yuanjie** [CN/US]; 835 Meetinghouse Road, Ambler, PA 19002 (US). **SINGH, Suresh, B.** [US/US]; 4 Adams Road, Kendall Park, NJ 08824 (US). **TICE, Colin, M.** [US/US]; 1325 Pinebrook Court, Ambler, PA 19002 (US). **SIMPSON, Robert, D.** [US/US]; 2001 N. Van Buren Street, Wilmington, DE 19802 (US).

(74) Agents: **DAVIS, Steven, G.** et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA 01742-9133 (US).

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(54) **Title**: INHIBITORS OF 11BETA-HYDROXYSTEROID DEHYDROGENASE 1

(57) **Abstract**: This invention relates to novel compounds of the Formula (I), any of the formulas I_1-I_{26} Ia_{1-3}-Ij_{1-3} or pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, which are useful for the therapeutic treatment of diseases associated with the modulation or inhibition of 11 β-HSD1 in mammals. The invention further relates to pharmaceutical compositions of the novel compounds and methods for their use in the reduction or control of the production of Cortisol in a cell or the inhibition of the conversion of cortisone to Cortisol in a cell.

INHIBITORS OF 11β-HYDROXYSTEROID DEHYDROGENASE 1

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 61/065,890, filed on February 15, 2008, the entire teachings of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), pharmaceutical compositions thereof and methods of using the same.

BACKGROUND OF THE INVENTION

Glucocorticoids, such as cortisol (hydrocortisone), are steroid hormones that regulate fat metabolism, function and distribution, and play a role in carbohydrate, protein and fat metabolism. Glucocorticoids are also known to have physiological effects on development, neurobiology, inflammation, blood pressure, metabolism, and programmed cell death. Cortisol and other corticosteroids bind both the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), which are members of the nuclear hormone receptor superfamily and have been shown to mediate cortisol function in vivo. These receptors directly modulate transcription via DNA-binding zinc finger domains and transcriptional activation domains.

Until recently, the major determinants of glucocorticoid action were attributed to three primary factors: (1) circulating levels of glucocorticoid (driven primarily by the hypothalamic-pituitary-adrenal (HPA) axis); (2) protein binding of glucocorticoids in circulation; and (3) intracellular receptor density inside target tissues. Recently, a fourth determinant of glucocorticoid function has been identified: tissue-specific pre-receptor metabolism by glucocorticoid-activating and -inactivating enzymes. These 11β-hydroxysteroid dehydrogenase (11β-HSD) pre-receptor control enzymes

modulate activation of GR and MR by regulation of glucocorticoid hormones. To date, two distinct isozymes of 11-beta-HSD have been cloned and characterized: 11β-HSD1 (also known as 11-beta-HSD type 1, 11betaHSD1, HSD11B1, HDL, and HSD11L) and 11β-HSD2. 11β-HSD1 is a bi-directional oxidoreductase that regenerates active cortisol from inactive 11-keto forms, whereas 11β-HSD2 is a unidirectional dehydrogenase that inactivates biologically active cortisol by converting it into cortisone.

The two isoforms are expressed in a distinct tissue-specific fashion, consistent with the differences in their physiological roles. 11β-HSD1 is widely distributed in rat and human tissues; expression of the enzyme and corresponding mRNA have been detected in human liver, adipose tissue, lung, testis, bone and ciliary epithelium. In adipose tissue, increased cortisol concentrations stimulate adipocyte differentiation and may play a role in promoting visceral obesity. In the eye, 11β-HSD1 may regulate intraocular pressure and may contribute to glaucoma; some data suggest that inhibition of 11β-HSD1 may cause a drop in intraocular pressure in patients with intraocular hypertension (Kotelevstev et al. (1997), Proc. Natl. Acad. Sci. USA 94(26):14924-9). Although 11β-HSD1 catalyzes both 11-beta-dehydrogenation and the reverse 11-oxoreduction reaction, 11β-HSD1 acts predominantly as a NADPH-dependent oxoreductase in intact cells and tissues, catalyzing the formation of active cortisol from inert cortisone (Low et al. (1994) J. Mol. Endocrin. 13: 167-174). In contradistinction, 11β-HSD2 expression is found mainly in mineralocorticoid target tissues such as kidney (cortex and medulla), placenta, sigmoid and rectal colon, salivary gland and colonic epithelial cell lines. 11β-HSD2 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 shown to protect the MR from glucocorticoid excess (e.g., high levels of receptor-active cortisol) (Blum, et al. (2003) Prog. Nucl. Acid Res. Mol. Biol. 75:173-216).

Mutations in either the 11β-HSD1 or the 11β-HSD2 genes result in human pathology. For example, individuals with mutations in 11β-HSD2 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 (Edwards et al. (1988) Lancet 2: 986-989; Wilson

et al. (1998) Proc. Natl. Acad. Sci. 95: 10200-10205). Similarly, mutations in 11β-HSD1 and in the gene encoding a co-localized NADPH-generating enzyme, hexose 6-phosphate dehydrogenase (H6PD), can result in cortisone reductase deficiency (CRD); 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).

Notably, disruption of homeostasis in the HPA axis by either deficient or excess 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 or receiving glucocorticoid therapy develop reversible visceral fat obesity. 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). Although the role of glucocorticoids in human obesity is not fully characterized, there is mounting evidence that 11β-HSD1 activity plays an important role in obesity and metabolic syndrome (Bujalska et al. (1997) Lancet 349: 1210-1213); (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).

Data from studies in mouse transgenic models supports the hypothesis that adipocyte 11β-HSD1 activity plays a central role in visceral obesity and metabolic syndrome (Alberts et al. (2002) Diabetologia. 45(11): 1526-32). Over-expression in adipose tissue of 11β-HSD1 under the control of the aP2 promoter in transgenic mice produced a phenotype remarkably similar to human metabolic syndrome (Masuzaki et al. (2001) Science 294: 2166-2170; Masuzaki et al. (2003) J. Clinical Invest. 112: 83-90). Moreover, the increased activity of 11β-HSD1 in these mice is very similar to that observed in human obesity (Rask et al. (2001) J. Clin. Endocrinol. Metab. 86: 1418-1421). In addition, data from studies with 11β-HSD1-deficient mice produced by homologous recombination demonstrate that the loss of 11β-HSD1 leads to an increase in insulin sensitivity and glucose tolerance due to a tissue-specific

deficiency in active glucocorticoid levels (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).

The published data supports the hypothesis that increased expression of 11β-HSD1 contributes to increased local conversion of cortisone to cortisol in adipose tissue and hence that 11β-HSD1 plays a role in the pathogenesis of central obesity and the appearance of the metabolic syndrome in humans (Engeli, et al., (2004) Obes. Res. 12: 9-17). Therefore, 11β-HSD1 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). Furthermore, inhibition of 11β-HSD1 activity may prove beneficial in treating numerous glucocorticoid-related disorders. For example, 11β-HSD1 inhibitors could be effective in combating obesity and/or aspects of the metabolic syndrome cluster, including glucose intolerance, insulin resistance, hyperglycemia, hypertension, and/or hyperlipidemia (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). In addition, inhibition of 11β-HSD1 activity may have beneficial effects on the pancreas, including the enhancement of glucose-stimulated insulin release (Billaudel and Sutter (1979) Horm. Metab. Res. 11: 555-560; Ogawa et al. (1992) J. Clin. Invest. 90: 497-504; Davani et al. (2000) J. Biol. Chem. 275: 34841-34844).

Furthermore, given that 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) and dysregulation of the HPA axis resulting in chronic exposure to glucocorticoid excess in certain brain subregions has been theorized to contribute to the decline of cognitive function (McEwen and Sapolsky (1995) Curr. Opin. Neurobiol. 5: 205-216), one might predict that inhibition of 11β-HSD1 could reduce exposure to glucocorticoids in the brain and thereby protect against deleterious glucocorticoid effects on neuronal function, including cognitive impairment, dementia, and/or depression. Notably, it is known that stress and glucocorticoids influence cognitive function (de Quervain et al. (1998) Nature 394: 787-790); and it has been shown that 11β-HSD1, through its control of glucocorticoid action in the brain, may have effects on neurotoxicity (Rajan et al. (1996) Neuroscience 16: 65-70; Seckl (2000) Neuroendocrinol. 18:49-99).

There is also evidence that glucocorticoids and 11β-HSD1 play a role in regulation of in intra-ocular pressure (IOP) (Stokes et al. (2000) Invest. Ophthalmol. Vis. Sci. 41: 1629-1683; Rauz et al. (2001) Invest. Ophthalmol. Vis. Sci. 42: 2037-2042); if left untreated, elevated IOP can lead to partial visual field loss and eventually blindness. Thus, inhibition of 11β-HSD1 in the eye could reduce local glucocorticoid concentrations and IOP, and 11β-HSD1 hence could potentially be used to treat glaucoma and other visual disorders.

Transgenic aP2-11βHSD1 mice exhibit high arterial blood pressure and have increased sensitivity to dietary salt. Moreover, plasma angiotensinogen levels are elevated in the transgenic mice, as are angiotensin II and aldosterone; and treatment of the mice with an angiotensin II antagonist alleviates the hypertension (Masuzaki et al. (2003) J. Clinical Invest. 112: 83-90). This suggests that hypertension may be caused or exacerbated by 11β-HSD1 activity. Thus, 11β-HSD1 inhibitors may be useful for treatment of hypertension and hypertension-related cardiovascular disorders. Inhibition of 11β-HSD1 in mature adipocytes is also expected to attenuate secretion of plasminogen activator inhibitor 1 (PAI-1), which is an independent cardiovascular risk factor (Halleux et al. (1999) J. Clin. Endocrinol. Metabl. 84: 4097-4105).

Glucocorticoids can have adverse effects on skeletal tissues; and prolonged exposure to even moderate glucocorticoid doses can result in osteoporosis (Cannalis (1996) J. Clin. Endocrinol. Metab. 81: 3441-3447). In addition, 11β-HSD1 has been shown to be present in cultures of human primary osteoblasts as well as cells from adult bone (Cooper et al. (2000) Bone 27: 375-381), and the 11β-HSD1 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 11β-HSD1 is predicted to decrease the local glucocorticoid concentration within osteoblasts and osteoclasts, thereby producing beneficial effects in various forms of bone disease, including osteoporosis.

11β-HSD1 inhibitors may also be useful for immunomodulation. Although glucocorticoids are perceived to suppress the immune system, in actuality, there is a complex, dynamic interaction between the HPA axis and the immune system (Rook (1999) Baillier's Clin. Endocrinol. Metabl. 13: 576-581). Glucocorticoids play a role in modulating the balance between cell-mediated and humoral immune response,

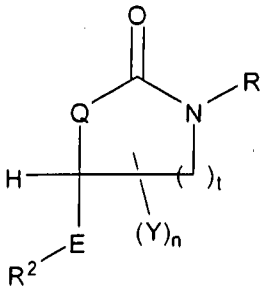
with high glucocorticoid activity normally associated with a humoral response. Inhibition of 11β-HSD1 therefore can be used a means of shifting the immune response towards a cell-mediated response. Certain disease states, such as tuberculosis, leprosy (Hansen's disease) and psoriasis, trigger immune responses that are biased towards a humoral response whereas the more effective immune response may be a cell-mediated response. Hence, 11β-HSD1 inhibitors may be useful for treating such diseases.

It has been reported that glucocorticoids inhibit wound healing, especially in diabetic patients with ulcers (Bitar et al. (1999) J. Surg. Res. 82: 234-243; Bitar et al. (1999) Surgery 125: 594-601; Bitar (2000) Surgery 127: 687-695; Bitar (1998) Am. J. Pathol. 152: 547-554). Patients that exhibit impaired glucose tolerance and/or type 2 diabetes often also have impaired wound healing. Glucocorticoids have been shown to increase the risk of infection and delay wound healing (Anstead (1998) Adv. Wound Care 11:277-285). Moreover, there is a correlation between elevated levels of cortisol in wound fluid and non-healing wounds (EP Patent App. No. 0 902 288). Recent published patent applications have suggested that certain 11β-HSD1 inhibitors may be useful for promoting wound healing (PCT/US2006/043,951).

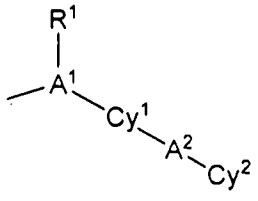
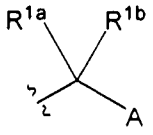
As evidenced herein, there is a continuing need for new and improved drugs that inhibit 11β-HSD1. The novel compounds of the instant invention are effective inhibitors of 11β-HSD1.

SUMMARY OF THE INVENTION

It has now been found that compounds of Formula I or pharmaceutically acceptable salts thereof, are effective inhibitors of 11β-HSD1. Formula I and its constituent members are defined herein as follows:



I

R is  or  ;

R^1 is (a) absent or (b) is selected from $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl or $(C_1\text{-}C_3)$alkoxy$(C_1\text{-}C_3)$alkyl, wherein each is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R^4, R^4O-, $(R^4)_2N$-, R^4O_2C-, R^4S, $R^4S(=O)$-, $R^4S(=O)_2$-, $R^4C(=O)NR^4$-, $(R^4)_2NC(=O)$-, $(R^4)_2NC(=O)O$-, $(R^4)_2NC(=O)NR^4$-, $R^4OC(=O)NR^4$-, $(R^4)_2NC(=NCN)NR^4$-, $(R^4O)_2P(=O)O$-, $(R^4O)_2P(=O)NR^4$-, $R^4OS(=O)_2NR^4$-, $(R^4)_2NS(=O)_2O$-, $(R^4)_2NS(=O)_2NR^4$-, $R^4S(=O)_2NR^4$-, $R^4S(=O)_2NHC(=O)$-, $R^4S(=O)_2NHC(=O)O$-, $R^4S(=O)_2NHC(=O)NR^4$-, $R^4OS(=O)_2NHC(=O)$-, $R^4OS(=O)_2NHC(=O)O$-, $R^4OS(=O)_2NHC(=O)NR^4$-, $(R^4)_2NS(=O)_2NHC(=O)$-, $(R^4)_2NS(=O)_2NHC(=O)O$-, $(R^4)_2NS(=O)_2NHC(=O)NR^4$-, $R^4C(=O)NHS(=O)_2$-, $R^4C(=O)NHS(=O)_2O$-, $R^4C(=O)NHS(=O)_2NR^4$-, $R^4OC(=O)NHS(=O)_2$-, $R^4OC(=O)NHS(=O)_2O$-, $R^4OC(=O)NHS(=O)_2NR^4$-, $(R^4)_2NC(=O)NHS(=O)_2$-, $(R^4)_2NC(=O)NHS(=O)_2O$-, $(R^4)_2NC(=O)NHS(=O)_2NR^4$-, aryl, cycloalkyl, heterocyclyl, heteroaryl, arylamino and heteroarylamino;

A^1 is (a) a bond, or (b) $(C_1\text{-}C_3)$alkylene, CH_2CH_2O, wherein the oxygen is attached to Cy^1, or $CH_2C(=O)$, wherein the carbonyl carbon is attached to Cy^1;

Cy^1 is aryl, heteroaryl, monocyclic cycloalkyl or heterocyclyl, wherein each is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_3\text{-}C_6)$cycloalkyl, $(C_4\text{-}C_7)$cycloalkylalkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, hydroxy$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_6)$cycloalkyl$(C_2\text{-}C_4)$alkynyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_3\text{-}C_6)$cycloalkyl, halo$(C_4\text{-}C_7)$cycloalkylalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkoxy, $(C_4\text{-}C_7)$cycloalkylalkoxy, halo$(C_1\text{-}C_6)$alkoxy, halo$(C_3\text{-}C_6)$cycloalkoxy, halo$(C_4\text{-}C_7)$cycloalkylalkoxy, $(C_1\text{-}C_6)$alkylthio, $(C_3\text{-}C_6)$cycloalkythio, $(C_4\text{-}C_7)$cycloalkylalkylthio, halo$(C_1\text{-}C_6)$alkylthio, halo$(C_3\text{-}C_6)$cycloalkythio, halo$(C_4\text{-}C_7)$cycloalkylalkylthio, $(C_1\text{-}C_6)$alkanesulfinyl, $(C_3\text{-}C_6)$cycloalkanesulfinyl, $(C_4\text{-}C_7)$cycloalkylalkanesulfinyl, halo$(C_1\text{-}C_6)$alkane-sulfinyl, halo$(C_3\text{-}C_6)$cycloalkanesulfinyl, halo$(C_4\text{-}C_7)$cycloalkylalkanesulfinyl, $(C_1\text{-}C_6)$alkanesulfonyl,

(C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cycloalkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl; (C_1-C_6)alkylcarbonyl; (C_3-C_6)cycloalkylcarbonyl, (C_3-C_6)cycloalkylaminocarbonyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminocarbonyl, di(C_3-C_6)cycloalkylaminocarbonyl, (C_3-C_6)cycloalkylaminosulfonyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminosulfonyl, di(C_3-C_6)cycloalkylaminosulfonyl, cyano(C_1-C_6)alkyl, aminocarbonyl(C_1-C_6)alkyl, (C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, di(C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, (C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminocarbonyl(C_1-C_6)alkyl and di(C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl; provided that if (a) t is 2 and Q is O or CH_2 or t is 1 and Q is O, (b) A^1 is CH_2 optionally substituted with R_1 and (c) A^2 is a bond, then Cy^2 is meta or para to the ring atom of Cy^1 that is bonded to A^1 and the aryl, heteroaryl, monocyclic cycloalkyl or heterocyclyl, represented by Cy^1 is not substituted with bromine, iodine, amino, halo(C_1-C_6)alkyl at a ring atom ortho to the carbon atom bounded to A^1;

A^2 is (a) a bond, O, S or NR^4; or (b) (C_1-C_3)alkylene or (C_1-C_2)alkyleneoxy, each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo;

Cy^2 is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-

C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkyl-alkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cyclo-alkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl; (C_1-C_6)alkylcarbonyl; (C_3-C_6)cycloalkylcarbonyl, (C_3-C_6)cycloalkylaminocarbonyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminocarbonyl, di(C_3-C_6)cycloalkylaminocarbonyl, (C_3-C_6)cycloalkylaminosulfonyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminosulfonyl, di(C_3-C_6)cycloalkylaminosulfonyl, cyano(C_1-C_6)alkyl, aminocarbonyl(C_1-C_6)alkyl, (C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, di(C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, (C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminocarbonyl(C_1-C_6)alkyl and di(C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl;

provided that if (a) t is 1; (b) Q is O, (c) A^1 is CH_2 optionally substituted with R^1 and (d) Cy^1 is phenyl then A^2Cy^2 is not NHR^4 or optionally substituted heterocyclyl;

provided that if (a) A^1 is CH_2CH_2O; (b) Cy^1 is phenyl and (c) A^2 is CH_2 then Cy^2 is not heterocyclyl substituted with oxo;

R^{1a} and R^{1b} are each independently selected from (a) hydrogen or (b) (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl or (C_1-C_3)alkoxy(C_1-C_3)alkyl which are optionally substituted with up to three groups independently selected from fluorine, hydroxy, (C_1-C_3)alkoxy and $H_2NC(=O)$;

A is straight or branched (C_1-C_8)alkyl, (C_2-C_8)alkenyl or (C_2-C_8)alkynyl, optionally substituted with up to 4 groups independently selected from fluorine, cyano, oxo, R^4, -OH R^4O-, $(R^4)_2N$-, R^4O_2C-, R^4S, $R^4S(=O)$-, $R^4S(=O)_2$-, $R^4C(=O)NR^4$-, $(R^4)_2NC(=O)$-, $(R^4)_2NC(=O)O$-, $(R^4)_2NC(=O)NR^4$-, $R^4OC(=O)NR^4$-, $(R^4)_2NC(=NCN)NR^4$-, $(R^4O)_2P(=O)O$-, $(R^4O)_2P(=O)NR^4$-, $R^4OS(=O)_2NR^4$-, $(R^4)_2NS(=O)_2O$-, $(R^4)_2NS(=O)_2NR^4$-, $R^4S(=O)_2NR^4$-, $R^4SO_2NR^4$-, $R^4S(=O)_2NHC(=O)$-, $R^4S(=O)_2NHC(=O)O$-, $R^4S(=O)_2NHC(=O)NR^4$-, $R^4OS(=O)_2NHC(=O)$-, $R^4OS(=O)_2NHC(=O)O$-, $R^4OS(=O)_2NHC(=O)NR^4$-, $(R^4)_2NS(=O)_2NHC(=O)$-, $(R^4)_2NS(=O)_2NHC(=O)O$-, $(R^4)_2NS(=O)_2NHC(=O)NR^4$-, $R^4C(=O)NHS(=O)_2$-, $R^4C(=O)NHS(=O)_2O$-, $R^4C(=O)NHS(=O)_2NR^4$-, $R^4OC(=O)NHS(=O)_2$-, $R^4OC(=O)NHS(=O)_2O$-, $R^4OC(=O)NHS(=O)_2NR^4$-, $(R^4)_2NC(=O)NHS(=O)_2$-, $(R^4)_2NC(=O)NHS(=O)_2O$-, $(R^4)_2NC(=O)NHS(=O)_2NR^4$-, heterocyclylamino (wherein the heterocyclyl portion is optionally substituted by alkyl, haloalkyl or oxo); heteroarylamino (wherein the heteroaryl portion is optionally substituted by alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H, $CONH_2$, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); arylamino (wherein the aryl portion is optionally substituted by alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H, $CONH_2$, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); and cycloalkylamino (wherein the cycloalkyl portion is optionally substituted by alkyl, haloalkyl or oxo);

t is 1, 2 or 3;

Y is (C_1-C_6)alkyl or halo(C_1-C_6)alkyl;

n is 0, 1 or 2;

E is (a) a bond or (b) (C_1-C_3)alkylene or (C_1-C_2)alkylenyloxy, wherein the O is attached to R^2, each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo; provided that if Q is NH, then ER^2 is not (C_1-C_6)alkyl or benzyl;

R^2 is (C_1-C_6)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with up to 4 groups independently selected from fluorine,

chlorine, bromine, iodine, nitro, hydroxy, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkylalkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cycloalkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl; (C_1-C_6)alkylcarbonyl; (C_3-C_6)cycloalkylcarbonyl, (C_3-C_6)cycloalkylaminocarbonyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminocarbonyl, di(C_3-C_6)cycloalkylaminocarbonyl, (C_3-C_6)cycloalkylaminosulfonyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminosulfonyl, di(C_3-C_6)cycloalkylaminosulfonyl, cyano(C_1-C_6)alkyl, aminocarbonyl(C_1-C_6)alkyl, (C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, di(C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, (C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminocarbonyl(C_1-C_6)alkyl and di(C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl;

wherein the 1 to 4 substituents for the group represented by R^2 are additionally selected from: amino, cyano, carboxy, (C_1-C_6)alkoxycarbonyl and hydroxy(C_1-C_6)alkyl, when E is bond or (C_1-C_3)alkylene, t is 1 and Q is O or CH_2, provided that ER^2 is not CH_2Cl, CH_2OH, CHO or CH_2Ophenyl;

provided that when (a) t is 2; (b) E is bond and (c) R^2 is phenyl, then R^2 is not substituted with $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkoxy, $(C_4\text{-}C_7)$cycloalkylalkoxy, halo$(C_1\text{-}C_6)$alkoxy, halo$(C_3\text{-}C_6)$cycloalkoxy, halo$(C_4\text{-}C_7)$cycloalkylalkoxy;

provided that when (a) A^1 is bond; (b) R^1 is absent; (c) Cy^1 is phenyl; (d) A^2 is bond (e) Cy^2 is H and (f) E is bond, then R^2 is not unsubstituted phenyl;

provided that when (a) t is 1; (b) Q is NR^5; (c) A^1 is bond; (d) R^1 is absent; (e) Cy^1 is optionally substituted phenyl; (f) A^2 is bond; (g) Cy^2 is H then ER^2 is not unsubstituted (C1-C6) alkyl;

Q is O, NR^5 or CH_2;

each R^4 is independently selected from H, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, di$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl; and

each R^5 is independently H, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, or hydroxy$(C_1\text{-}C_6)$alkyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a pharmaceutical composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) compound of Formulas I, $I_1\text{-}I_{26}$, $Ia_{1\text{-}3}$, $Ib_{1\text{-}3}$, $Ic_{1\text{-}3}$, $Id_{1\text{-}3}$, $Ie_{1\text{-}3}$, $If_{1\text{-}3}$, $Ig_{1\text{-}3}$, $Ih_{1\text{-}3}$, $Ii_{1\text{-}3}$ or $Ij_{1\text{-}3}$ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the invention is a method of inhibiting 11β-HSD1 activity comprising the step of administering to a mammal in need of such treatment an effective amount of a compound of Formulas I, $I_1\text{-}I_{26}$, $Ia_{1\text{-}3}$, $Ib_{1\text{-}3}$, $Ic_{1\text{-}3}$, $Id_{1\text{-}3}$, $Ie_{1\text{-}3}$, $If_{1\text{-}3}$, $Ig_{1\text{-}3}$, $Ih_{1\text{-}3}$, $Ii_{1\text{-}3}$ or $Ij_{1\text{-}3}$ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the invention is a method of treating a subject with a disease associated with the activity or expression of 11β-HSD1, comprising the step of administering to the subject an effective amount of a compound of Formulas I, $I_1\text{-}I_{26}$, $Ia_{1\text{-}3}$, $Ib_{1\text{-}3}$, $Ic_{1\text{-}3}$, $Id_{1\text{-}3}$, $Ie_{1\text{-}3}$, $If_{1\text{-}3}$, $Ig_{1\text{-}3}$, $Ih_{1\text{-}3}$, $Ii_{1\text{-}3}$ or $Ij_{1\text{-}3}$ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the invention is the use of a compound of Formulas I, $I_1\text{-}I_{26}$, $Ia_{1\text{-}3}$, $Ib_{1\text{-}3}$, $Ic_{1\text{-}3}$, $Id_{1\text{-}3}$, $Ie_{1\text{-}3}$, $If_{1\text{-}3}$, $Ig_{1\text{-}3}$, $Ih_{1\text{-}3}$, $Ii_{1\text{-}3}$ or $Ij_{1\text{-}3}$ or a pharmaceutically

acceptable salt, enantiomer or diastereomer thereof for the manufacture of a medicament for inhibiting 11β-HSD1 activity in a mammal in need of such treatment.

Another embodiment of the invention is the use of a compound of I I_1-I_{26} Ia_{1-3}, Ib_{1-3}, Ic_{1-3}, Id_{1-3}, Ie_{1-3}, If_{1-3}, Ig_{1-3}, Ih_{1-3}, Ii_{1-3} or Ij_{1-3} or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for the manufacture of a medicament for treating a subject with a disease associated with the activity or expression of 11β-HSD1.

Another embodiment of the invention is a compound of Formulas I, I_1-I_{26} Ia_{1-3}, Ib_{1-3}, Ic_{1-3}, Id_{1-3}, Ie_{1-3}, If_{1-3}, Ig_{1-3}, Ih_{1-3}, Ii_{1-3} or Ij_{1-3} or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for use in inhibiting 11β-HSD1 activity in a mammal in need of such treatment.

Another embodiment of the invention is a compound of Formulas I, I_1-I_{26} Ia_{1-3}, Ib_{1-3}, Ic_{1-3}, Id_{1-3}, Ie_{1-3}, If_{1-3}, Ig_{1-3}, Ih_{1-3}, Ii_{1-3} or Ij_{1-3} or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for use in for treating a subject with a disease associated with the activity or expression of 11β-HSD1.

The present invention further provides methods of inhibiting 11β-HSD1 by contacting 11β-HSD1 with a compound of Formula I, I_1-I_{26} Ia_{1-3}, Ib_{1-3}, Ic_{1-3}, Id_{1-3}, Ie_{1-3}, If_{1-3}, Ig_{1-3}, Ih_{1-3}, Ii_{1-3} or Ij_{1-3} of the invention.

The present invention further provides methods of inhibiting or reducing the conversion of cortisone to cortisol in a cell using a compound of Formula I, I_1-I_{26} Ia_{1-3}, Ib_{1-3}, Ic_{1-3}, Id_{1-3}, Ie_{1-3}, If_{1-3}, Ig_{1-3}, Ih_{1-3}, Ii_{1-3} or Ij_{1-3} of the invention.

The present invention further provides methods of inhibiting or reducing production of cortisol in a cell using a compound of Formula I, I_1-I_{26} Ia_{1-3}, Ib_{1-3}, Ic_{1-3}, Id_{1-3}, Ie_{1-3}, If_{1-3}, Ig_{1-3}, Ih_{1-3}, Ii_{1-3} or Ij_{1-3} of the invention.

The present invention further provides methods of increasing insulin sensitivity in a subject in need thereof using a compound of Formula I, I_1-I_{26} Ia_{1-3}, Ib_{1-3}, Ic_{1-3}, Id_{1-3}, Ie_{1-3}, If_{1-3}, Ig_{1-3}, Ih_{1-3}, Ii_{1-3} or Ij_{1-3} of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provieds novel compounds that are effective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).

Values and alternative values for the variables in the above-described Structural Formula I are provided herein:

R^1 is (a) absent or (b) is selected from $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl or $(C_1\text{-}C_3)$alkoxy$(C_1\text{-}C_3)$alkyl, wherein each is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R^4, R^4O-, $(R^4)_2N$-, R^4O_2C-, R^4S, $R^4S(=O)$-, $R^4S(=O)_2$-, $R^4C(=O)NR^4$-, $(R^4)_2NC(=O)$-, $(R^4)_2NC(=O)O$-, $(R^4)_2NC(=O)NR^4$-, $R^4OC(=O)NR^4$-, $(R^4)_2NC(=NCN)NR^4$-, $(R^4O)_2P(=O)O$-, $(R^4O)_2P(=O)NR^4$-, $R^4OS(=O)_2NR^4$-, $(R^4)_2NS(=O)_2O$-, $(R^4)_2NS(=O)_2NR^4$-, $R^4S(=O)_2NR^4$-, $R^4S(=O)_2NHC(=O)$-, $R^4S(=O)_2NHC(=O)O$-, $R^4S(=O)_2NHC(=O)NR^4$-, $R^4OS(=O)_2NHC(=O)$-, $R^4OS(=O)_2NHC(=O)O$-, $R^4OS(=O)_2NHC(=O)NR^4$-, $(R^4)_2NS(=O)_2NHC(=O)$-, $(R^4)_2NS(=O)_2NHC(=O)O$-, $(R^4)_2NS(=O)_2NHC(=O)NR^4$-, $R^4C(=O)NHS(=O)_2$-, $R^4C(=O)NHS(=O)_2O$-, $R^4C(=O)NHS(=O)_2NR^4$-, $R^4OC(=O)NHS(=O)_2$-, $R^4OC(=O)NHS(=O)_2O$-, $R^4OC(=O)NHS(=O)_2NR^4$-, $(R^4)_2NC(=O)NHS(=O)_2$-, $(R^4)_2NC(=O)NHS(=O)_2O$-, $(R^4)_2NC(=O)NHS(=O)_2NR^4$-, aryl, cycloalkyl, heterocyclyl, heteroaryl, arylamino and heteroarylamino. In another embodiment, R^1 is $(C_1\text{-}C_6)$alkyl. In another embodiment, R^1 is absent or is optionally substituted methyl or ethyl. Alternatively, R^1 is an optionally substituted methyl or ethyl. In yet another embodiment R^1 is unsubstituted.

A^1 is (a) a bond, or (b) $(C_1\text{-}C_3)$alkylene, CH_2CH_2O, wherein the oxygen is attached to Cy^1, or $CH_2C(=O)$, wherein the carbonyl carbon is attached to Cy^1. In another embodiment, A^1 is $(C_1\text{-}C_3)$alkylene. Alternatively, A^1 is $(C_2\text{-}C_3)$alkylene. In another embodiment, A^1 is a bond. In yet another embodiment A^1 is methylene. Alternatively, A^1 is a bond.

Cy^1 is aryl, heteroaryl, monocyclic cycloalkyl or heterocyclyl, wherein each is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_3\text{-}C_6)$cycloalkyl, $(C_4\text{-}C_7)$cycloalkylalkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, hydroxy$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_6)$cycloalkyl$(C_2\text{-}C_4)$alkynyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_3\text{-}C_6)$cycloalkyl, halo$(C_4\text{-}C_7)$cycloalkylalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkoxy, $(C_4\text{-}C_7)$cycloalkylalkoxy, halo$(C_1\text{-}C_6)$alkoxy, halo$(C_3\text{-}C_6)$cycloalkoxy, halo$(C_4\text{-}C_7)$cycloalkylalkoxy, $(C_1\text{-}C_6)$alkylthio, $(C_3\text{-}C_6)$cycloalkythio, $(C_4\text{-}C_7)$cycloalkylalkylthio, halo$(C_1\text{-}C_6)$alkylthio, halo$(C_3\text{-}C_6)$cycloalkythio, halo$(C_4\text{-}C_7)$cycloalkylalkylthio, $(C_1\text{-}C_6)$alkanesulfinyl, $(C_3\text{-}C_6)$cycloalkanesulfinyl, $(C_4\text{-}C_7)$cycloalkylalkanesulfinyl, halo$(C_1\text{-}C_6)$alkane-sulfinyl, halo$(C_3\text{-}C_6)$cycloalkanesulfinyl, halo$(C_4\text{-}C_7)$cycloalkylalkanesulfinyl, $(C_1\text{-}C_6)$alkanesulfonyl,

(C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cycloalkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl and (C_1-C_6)alkylcarbonyl; provided that if (a) t is 2 and Q is O or CH_2 or t is 1 and Q is O, (b) A^1 is CH_2 optionally substituted with R_1 and (c) A_2 is a bond, then Cy^2 is meta or para to the ring atom of Cy^1 that is bonded to A^1 and the aryl, heteroaryl, monocyclic cycloalkyl or heterocyclyl, represented by Cy^1 is not substituted with bromine, iodine, amino, halo(C_1-C_6)alkyl at a ring atom ortho to the carbon atom bounded to A_1. In another embodiment, Cy^1 is optionally substituted aryl or optionally substituted heteroaryl. In another embodiment, Cy^1 is optionally substituted phenyl, cyclohexyl, pyridyl, N-oxo-pyridyl, thiazolyl or pyrimidinyl optionally substituted with 1 to 4 groups independently selected from halo, methyl, trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy and 2-hydroxy-2-methylpropoxy. In another embodiment, Cy^1 is optionally substituted phenyl or optionally substituted pyridyl. Alternatively, Cy^1 is optionally substituted phenyl. In another embodiment, Cy^1 is phenyl substituted with fluorine, or bromine.

A^2 is (a) a bond, O, S or NR^4; or (b) (C_1-C_3)alkylene or (C_1-C_2)alkyleneoxy, each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo. In another embodiment, A^2 is a bond, O or OCH_2CO. In another embodiment, A^2 is a bond.

Cy^2 is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-

C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkyl-alkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cyclo-alkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl and (C_1-C_6)alkylcarbonyl;provided that if (a) t is 1; (b) Q is O, (c) A^1 is CH_2 optionally substituted with R_1 and (d) Cy^1 is phenyl then A_2Cy^2 is not NHR^4 and Cy^2 is not optionally substituted heterocyclyl. In another embodiment, Cy^2 is optionally substituted aryl or optionally substituted heteroaryl. In another embodiment, Cy^2 is hydrogen, phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl or piperazinyl optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonyl-aminomethyl or tetrazolyl. In yet another embodiment and Cy^2 is optionally substituted phenyl or optionally substituted pyridyl. Alternatively, Cy^2 is optionally substituted phenyl. In another embodiment, Cy^2 is phenyl substituted with 1 to 4

groups independently selected from chlorine or fluorine. Alternatively, Cy^2 is difluorophenyl. In another embodiment, Cy^2 is hydrogen. In another embodiment, Cy^2 is cyclopropyl.

R^{1a} and R^{1b} are each independently selected from (a) hydrogen or (b) (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl or (C_1-C_3)alkoxy(C_1-C_3)alkyl which are optionally substituted with up to three groups independently selected from fluorine, hydroxy, (C_1-C_3)alkoxy and $H_2NC(=O)$. In another embodiment, R^{1a} and R^{1b} are each independently H or (C_1-C_6)alkyl. In yet another embodiment R^{1a} and R^{1b} are each independently H, methyl, or ethyl. In another embodiment, R^{1a} is methyl or ethyl. In yet another embodiment R^{1a} is methyl, In another embodiment, R^{1b} is methyl or hydrogen. Alternatively, R^{1b} is hydrogen.

A is straight or branched (C_1-C_8)alkyl, (C_2-C_8)alkenyl or (C_2-C_8)alkynyl, optionally substituted with up to 4 groups independently selected from fluorine, cyano, oxo, R^4, -OH R^4O-, $(R^4)_2N$-, R^4O_2C-, R^4S, $R^4S(=O)$-, $R^4S(=O)_2$-, $R^4C(=O)NR^4$-, $(R^4)_2NC(=O)$-, $(R^4)_2NC(=O)O$-, $(R^4)_2NC(=O)NR^4$-, $R^4OC(=O)NR^4$-, $(R^4)_2NC(=NCN)NR^4$-, $(R^4O)_2P(=O)O$-, $(R^4O)_2P(=O)NR^4$-, $R^4OS(=O)_2NR^4$-, $(R^4)_2NS(=O)_2O$-, $(R^4)_2NS(=O)_2NR^4$-, $R^4S(=O)_2NR^4$-, $R^4SO_2NR^4$-, $R^4S(=O)_2NHC(=O)$-, $R^4S(=O)_2NHC(=O)O$-, $R^4S(=O)_2NHC(=O)NR^4$-, $R^4OS(=O)_2NHC(=O)$-, $R^4OS(=O)_2NHC(=O)O$-, $R^4OS(=O)_2NHC(=O)NR^4$-, $(R^4)_2NS(=O)_2NHC(=O)$-, $(R^4)_2NS(=O)_2NHC(=O)O$-, $(R^4)_2NS(=O)_2NHC(=O)NR^4$-, $R^4C(=O)NHS(=O)_2$-, $R^4C(=O)NHS(=O)_2O$-, $R^4C(=O)NHS(=O)_2NR^4$-, $R^4OC(=O)NHS(=O)_2$-, $R^4OC(=O)NHS(=O)_2O$-, $R^4OC(=O)NHS(=O)_2NR^4$-, $(R^4)_2NC(=O)NHS(=O)_2$-, $(R^4)_2NC(=O)NHS(=O)_2O$-, $(R^4)_2NC(=O)NHS(=O)_2NR^4$-, heterocyclylamino (wherein the heterocyclyl portion is optionally substituted by alkyl, haloalkyl or oxo); heteroarylamino (wherein the heteroaryl portion is optionally substituted by alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H, $CONH_2$, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); arylamino (wherein the aryl portion is optionally substituted by alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H, $CONH_2$, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); and cycloalkylamino (wherein the cycloalkyl portion is optionally substituted by alkyl, haloalkyl or oxo). In another embodiment, A is hydroxy(C_1-C_6)alkyl or (C_1-C_2) alkoxy(C_1-C_6)alkyl. In another embodiment, , A is (C_1-C_4)alkylcarbonylamino(C_1-C_4)alkyl. In yet another embodiment, A is mono(C_1-

C_2)alkylaminocarbonyl(C_1-C_4)alkyl or di(C_1-C_2)alkylaminocarbonyl(C_1-C_4)alkyl. Alternatively, A is 2-pyrimidinyl-amino(C_1-C_6)alkyl; 2-pyridyl-amino(C_1-C_6)alkyl; mono(C_1-C_2)alkylamino(C_1-C_4)alkyl or di(C_1-C_2)alkylamino(C_1-C_4)alkyl, wherein the pyrimidinyl and pyridyl are each optionally substituted with methyl or ethyl. Alternatively, A is (C_1-C_6)alkyl, optionally substituted with halogen. In another embodiment, A is (C_1-C_4)alkylsulfonyl(C_1-C_4)alkyl. In another embodiment,, A is (C_1-C_4)alkylsulfonylamino(C_1-C_4)alkyl. In another embodiment, A is (C_1-C_4)alkoxyalkylamino(C_1-C_4)alkyl. Alternatively, A is mono(C_1-C_4)alkylaminocarbonyl(C_1-C_4)alkyl or di(C_1-C_4)alkylaminocarbonyl(C_1-C_4)alkyl. Alternatively, A is methyl, ethyl, isopropyl or t-butyl. Alternatively, A is methyl or t-butyl.

t is 1, 2 or 3. Alternatively, t is 1 or 2. Alternatively, t is 1. Alternatively, t is 2.

Y is (C_1-C_6)alkyl or halo(C_1-C_6)alkyl.

n is 0, 1 or 2. Alternatively, n is 0.

E is (a) a bond or (b) (C_1-C_3)alkylene or (C_1-C_2)alkylenyloxy, wherein the O is attached to R^2, each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo. Alternatively, E is a bond or (C_1-C_3)alkylene, optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo. Alternatively, E is a bond or CH_2. Alternatively, E is a bond.

R^2 is (C_1-C_6)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with up to 4 groups independently selected from fluorine, chlorine, bromine, iodine, nitro, hydroxy, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkylalkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cyclo-

alkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkyl-aminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkyl-aminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonyl-amino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl and (C_1-C_6)alkylcarbonyl; wherein the 1 to 4 substituents for the group represented by R^2 are additionally selected from: amino, cyano, carboxy, (C_1-C_6)alkoxycarbonyl and hydroxy(C_1-C_6)alkyl, when E is bond or (C_1-C_3)alkylene, t is 1 and Q is O or CH_2, provided that ER^2 is not CH_2Cl, CH_2OH, CHO or CH_2Ophenyl In another embodiment, R^2 is optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl. In another embodiment, R^2 is phenyl, thienyl or pyridyl each optionally substituted with halo or methyl. In another embodiment, R^2 is optionally substituted phenyl, optionally substituted thienyl or optionally substituted pyridyl. In another embodiment, R^2 is phenyl or pyridyl optionally substituted with one group selected from halo, methyl, methylthio or (4-morpholino)methyl. In yet another embodiment R^2 is optionally substituted phenyl or 4-fluorophenyl. In yet another embodiment R^2 is optionally substituted phenyl. Alternatively, R^2 is fluorophenyl. In another alternative R^2 is not alkyl, pyridinyl, cycloalkyl, cycloalkylalkyl, haloalkyl; unsubstituted phenyl, phenyl substituted with one to three substituents independently selected from fluoro, chloro, bromo, haloalkyl, alkoxy, hydroxy, haloalkyl and haloalkoxy, phenylalkyl or pyridinylalkyl, wherein phenylalkyl and pyridinylalkyl are optionally subtituted with one to three substituents independently selected from alkyl, halogen, haloalkyl and hydroxy, oxetane or oxetane substituted with alkyl, phenylalkoxyalkyl or phenylalkoxyalkyl substituted with one to three substituents independently selected from alkyl and halogen, hydroxyalkyl, pyridinyloxyalkyl or pyridinyloxyalkyl substituted with cyano.

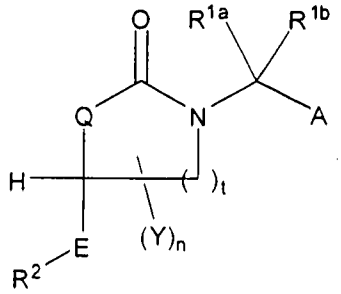
Q is O, NR^5 or CH_2. In another embodiment, Q is CH_2. In another embodiment, Q is O. In yet another embodiment Q is NR^5.

each R^4 is independently selected from H, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, di$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl; and

each R^5 is independently H, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, or hydroxy$(C_1\text{-}C_6)$alkyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

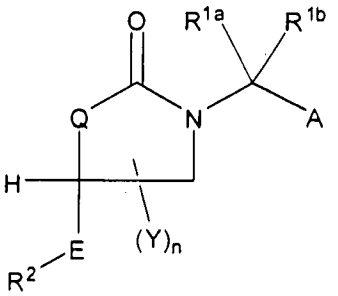
Another embodiment is a compound of Structural Formula I_1:



$\mathbf{I_1}$

and wherein values and alternative values for Q, R^2, E, A, R^{1a}, R^{1b}, Y, n and t are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

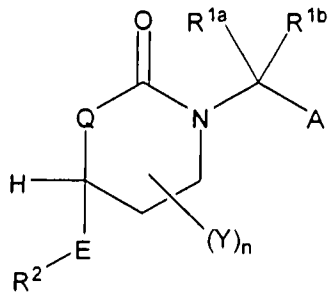
Another embodiment is a compound of Structural Formula I_2:



$\mathbf{I_2}$

and wherein values and alternative values for Q, R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

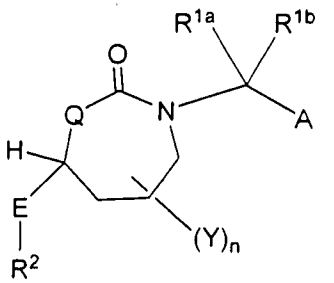
Another embodiment is a compound of Structural Formula I_3:



I_3

and wherein values and alternative values for Q, R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

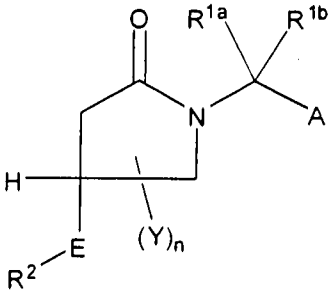
Another embodiment is a compound of Structural Formula I_4:



I_4

and wherein values and alternative values for Q, R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

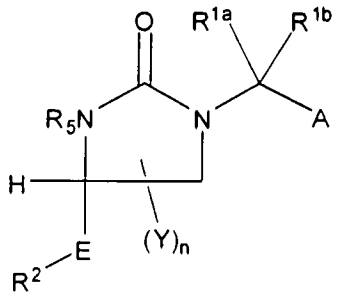
Another embodiment is a compound of Structural Formula I_5:



I_5

and wherein values and alternative values for R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

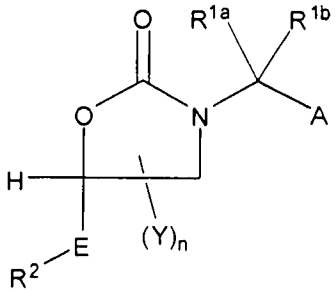
Another embodiment is a compound of Structural Formula I_6:



I_6

and wherein values and alternative values for R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

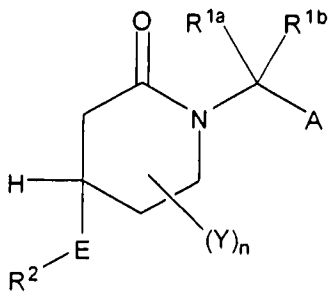
Another embodiment is a compound of Structural Formula I_7:



I_7

and wherein values and alternative values for R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

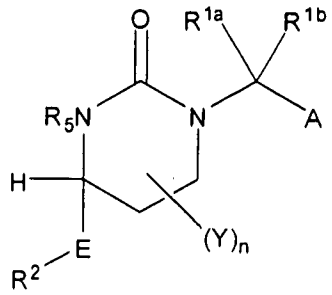
Another embodiment is a compound of Structural Formula I_8:



I_8

and wherein values and alternative values for R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

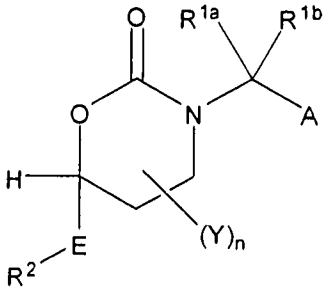
Another embodiment is a compound of Structural Formula I_9:



I_9

and wherein values and alternative values for R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

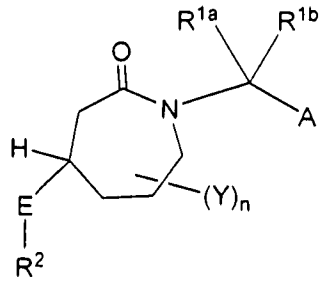
Another embodiment is a compound of Structural Formula I_{10}:



I_{10}

and wherein values and alternative values for R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

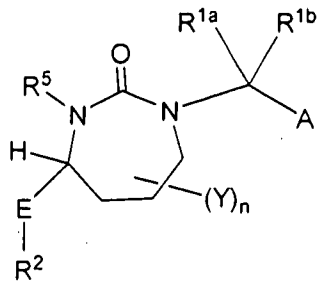
Another embodiment is a compound of Structural Formula I_{11}:



I_{11}

and wherein values and alternative values for R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

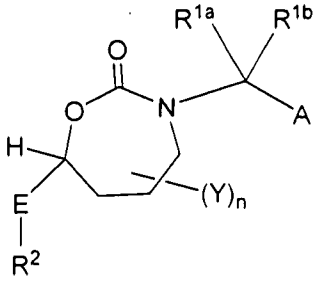
Another embodiment is a compound of Structural Formula I_{12}:



I_{12}

and wherein values and alternative values for R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

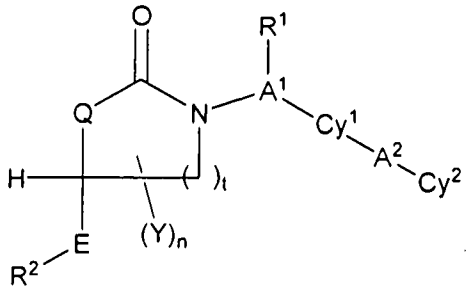
Another embodiment is a compound of Structural Formula I_{13}:



I_{13}

and wherein values and alternative values for R^2, E, A, R^{1a}, R^{1b}, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

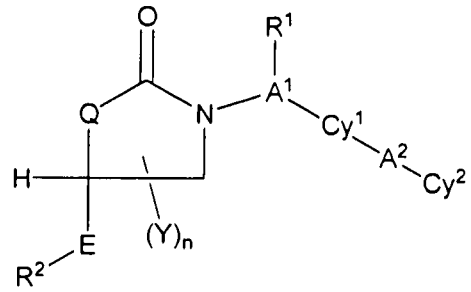
Another embodiment is a compound of Structural Formula I_{14}:



I_{14}

and wherein values and alternative values for Q, R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y, n and t are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

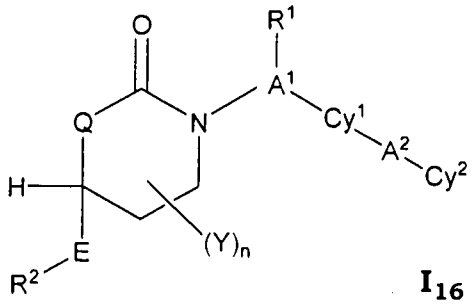
Another embodiment is a compound of Structural Formula I_{15}:



I_{15}

and wherein values and alternative values for Q, R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

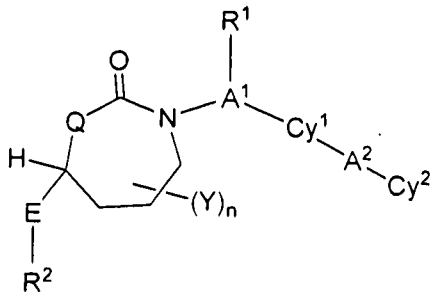
Another embodiment is a compound of Structural Formula I_{16}:



I_{16}

and wherein values and alternative values for Q, R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

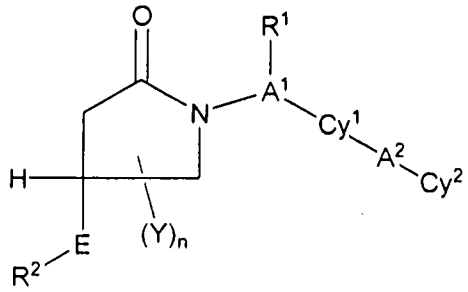
Another embodiment is a compound of Structural Formula I_{17}:



I_{17}

and wherein values and alternative values for Q, R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

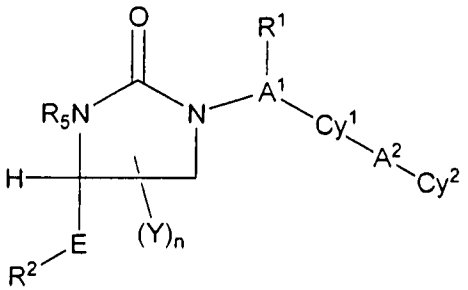
Another embodiment is a compound of Structural Formula I_{18}:



I_{18}

and wherein values and alternative values for R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

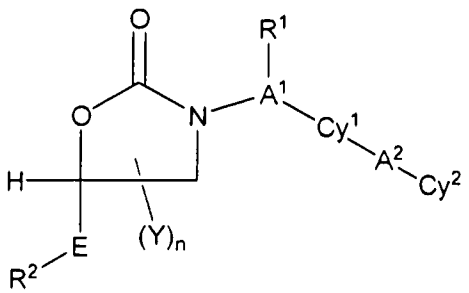
Another embodiment is a compound of Structural Formula I_{19}:



I_{19}

and wherein values and alternative values for R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

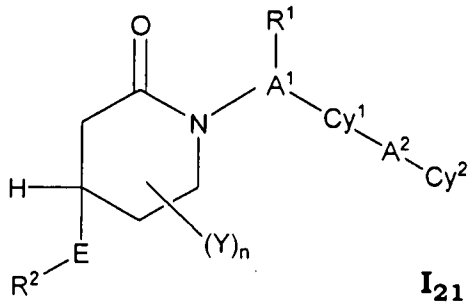
Another embodiment is a compound of Structural Formula I_{20}:



I_{20}

and wherein values and alternative values for R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

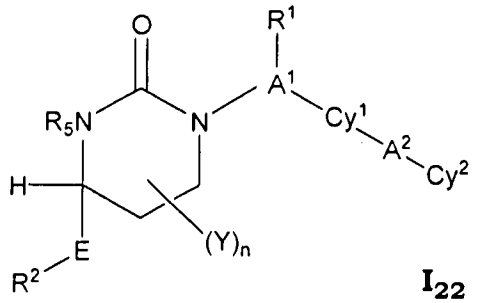
Another embodiment is a compound of Structural Formula I_{21}:



I_{21}

and wherein values and alternative values for R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

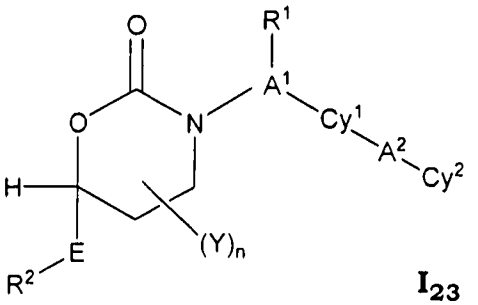
Another embodiment is a compound of Structural Formula I_{22}:



I_{22}

and wherein values and alternative values for R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

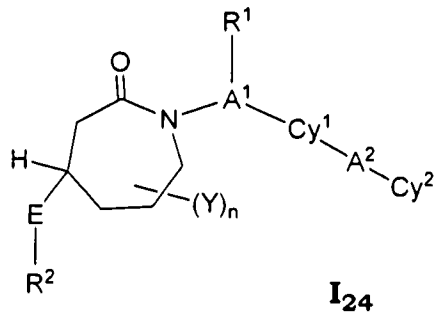
Another embodiment is a compound of Structural Formula I_{23}:



I_{23}

and wherein values and alternative values for R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

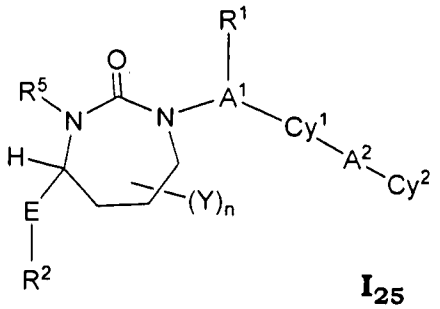
Another embodiment is a compound of Structural Formula I_{24}:



I_{24}

and wherein values and alternative values for R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

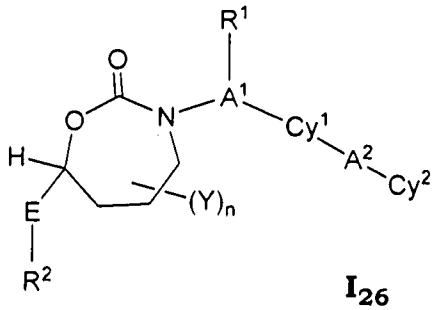
Another embodiment is a compound of Structural Formula I_{25}:



I_{25}

and wherein values and alternative values for R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

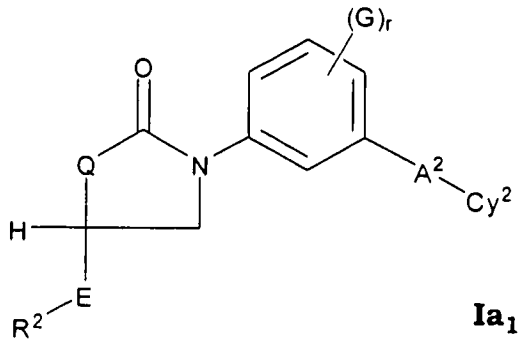
Another embodiment is a compound of Structural Formula I_{26}:



I_{26}

and wherein values and alternative values for R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y and n are as defined for Formula I above or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a compound of Structural Formula Ia_1:



Ia$_1$

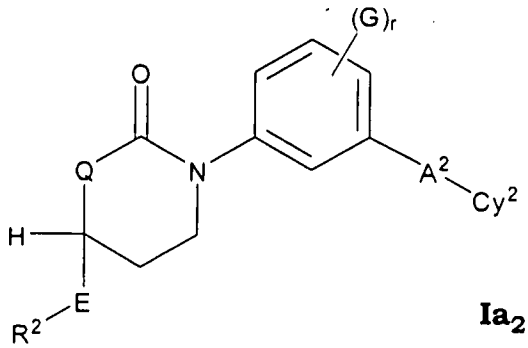
and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above,

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

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkylalkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cyclo-alkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonyl-amino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl,, hydroxy(C_1-C_6)alkoxy, heteroaryl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl or (C_1-C_6)alkylcarbonyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

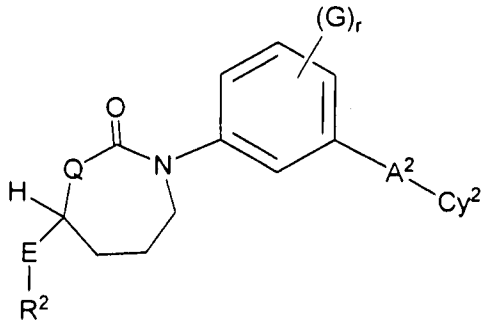
Another embodiment is a compound of Structural Formula Ia_2:



Ia_2

and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above, G and r are as defined for Formula Ia_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

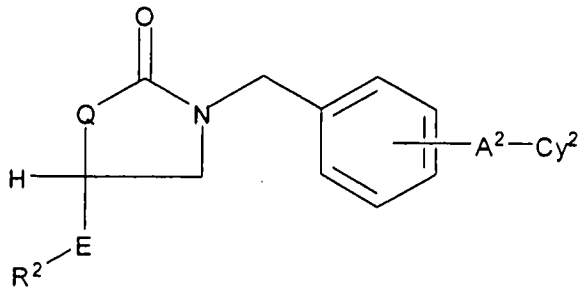
Another embodiment is a compound of Structural Formula Ia_3:



Ia_3

and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above, G and r are as defined for Formula Ia_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

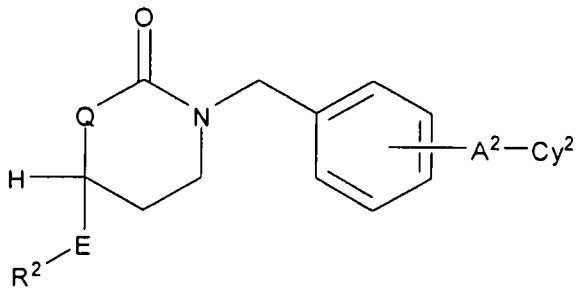
Another embodiment is a compound of Structural Formula Ib_1:



Ib$_1$

and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

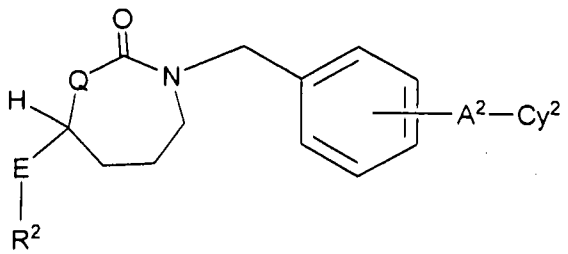
Another embodiment is a compound of Structural Formula Ib$_2$:



Ib$_2$

and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

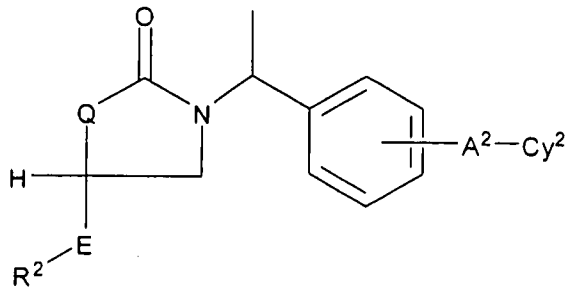
Another embodiment is a compound of Structural Formula Ib$_3$:



Ib$_3$

and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

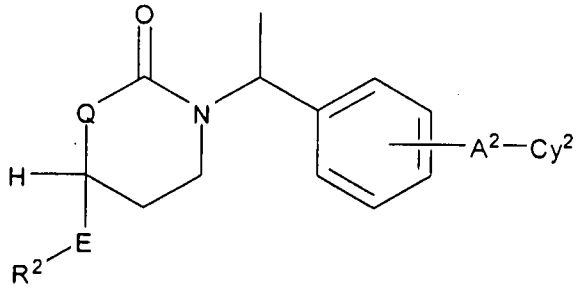
Another embodiment is a compound of Structural Formula Ic_1:



Ic_1

and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

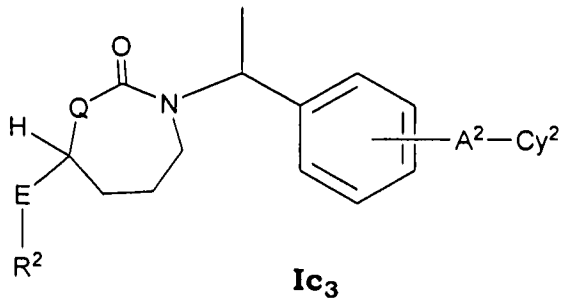
Another embodiment is a compound of Structural Formula Ic_2:



Ic_2

and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

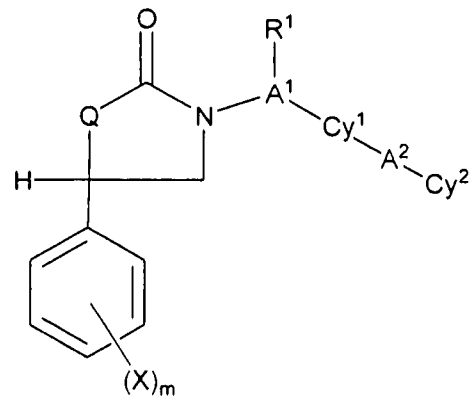
Another embodiment is a compound of Structural Formula Ic_3:



Ic$_3$

and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a compound of Structural Formula Id_1:



Id$_1$

and wherein values and alternative values for Q, R^1, A^1, Cy^1, A^2 and Cy^2 are as defined for Formula I above,

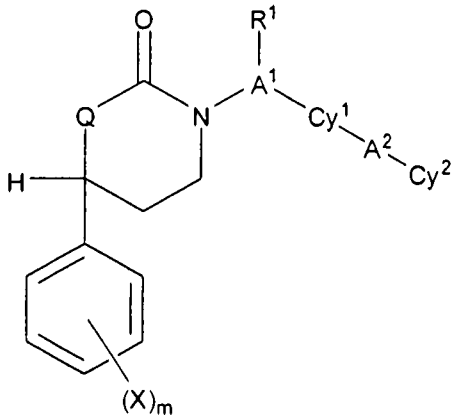
m is 0, 1, 2, 3 or 4 and

X is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkyl-alkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl,

$(C_3$-$C_6)$cycloalkanesulfonyl, $(C_4$-$C_7)$cycloalkylalkanesulfonyl, halo$(C_1$-$C_6)$alkanesulfonyl, halo$(C_3$-$C_6)$cycloalkanesulfonyl, halo$(C_4$-$C_7)$cycloalkylalkanesulfonyl, $(C_1$-$C_6)$alkylamino, di$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1$-$C_6)$alkylaminocarbonyl, di$(C_1$-$C_6)$alkylaminocarbonyl, $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkylaminocarbonyl, heterocyclylcarbonyl, $(C_1$-$C_6)$alkylaminosulfonyl, di$(C_1$-$C_6)$alkylaminosulfonyl, heterocyclsulfonyl, $(C_1$-$C_6)$alkylcarbonylamino, $(C_1$-$C_6)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonylamino, $(C_1$-$C_6)$alkylsulfonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl,, hydroxy$(C_1$-$C_6)$alkoxy, heteroaryl, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, di$(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl amino$(C_2$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxy, di$(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxyl and $(C_1$-$C_6)$alkylcarbonyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

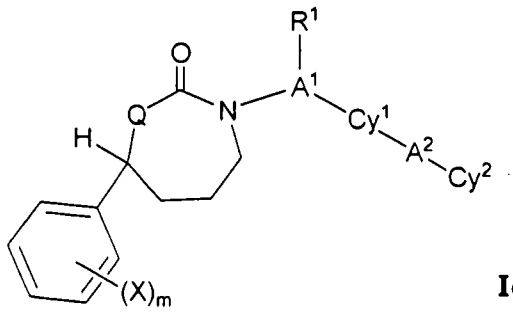
Another embodiment is a compound of Structural Formula Id_2:



Id_2

and wherein values and alternative values for Q, R^1, A^1, Cy^1, A^2 and Cy^2 are as defined for Formula I above, X and m are as defined for Formula Id_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

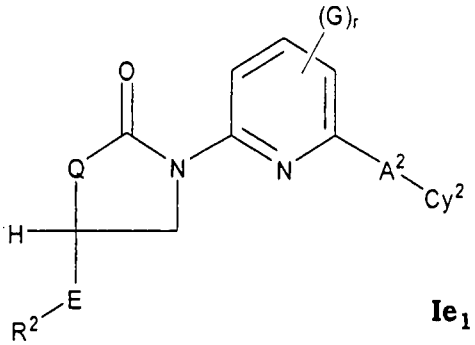
Another embodiment is a compound of Structural Formula Id_3:



Id_3

and wherein values and alternative values for Q, R^1, A^1, Cy^1, A^2 and Cy^2 are as defined for Formula I above, X and m are as defined for Formula Id_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a compound of Structural Formula Ie_1:



Ie_1

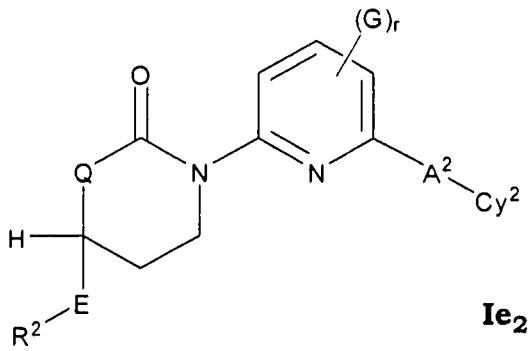
and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above,

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

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, hydroxy$(C_3$-$C_6)$cycloalkyl, $(C_4$-$C_7)$cycloalkylalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_2$-$C_6)$alkenyl, hydroxy$(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_6)$cycloalkyl$(C_2$-$C_4)$alkynyl, halo$(C_1$-$C_6)$alkyl, halo$(C_3$-$C_6)$cycloalkyl, halo$(C_4$-$C_7)$cycloalkylalkyl, $(C_1$-$C_6)$alkoxy, $(C_3$-$C_6)$cycloalkoxy, $(C_4$-$C_7)$cycloalkylalkoxy, halo$(C_1$-$C_6)$alkoxy, halo$(C_3$-$C_6)$cycloalkoxy, halo$(C_4$-$C_7)$cycloalkylalkoxy, $(C_1$-$C_6)$alkylthio, $(C_3$-$C_6)$cycloalkythio, $(C_4$-$C_7)$cycloalkyl-alkylthio, halo$(C_1$-$C_6)$alkylthio, halo$(C_3$-$C_6)$cycloalkythio, halo$(C_4$-$C_7)$cycloalkylalkylthio, $(C_1$-$C_6)$alkanesulfinyl, $(C_3$-$C_6)$cycloalkanesulfinyl, $(C_4$-$C_7)$cycloalkylalkanesulfinyl, halo$(C_1$-$C_6)$alkane-sulfinyl, halo$(C_3$-$C_6)$cycloalkanesulfinyl, halo$(C_4$-$C_7)$cycloalkylalkanesulfinyl, $(C_1$-$C_6)$alkanesulfonyl, $(C_3$-$C_6)$cycloalkanesulfonyl, $(C_4$-$C_7)$cycloalkylalkanesulfonyl, halo$(C_1$-$C_6)$alkanesulfonyl, halo$(C_3$-$C_6)$cycloalkanesulfonyl, halo$(C_4$-$C_7)$cyclo-

alkylalkanesulfonyl, $(C_1$-$C_6)$alkylamino, di$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1$-$C_6)$alkylaminocarbonyl, di$(C_1$-$C_6)$alkylaminocarbonyl, $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkylaminocarbonyl, heterocyclylcarbonyl, $(C_1$-$C_6)$alkylaminosulfonyl, di$(C_1$-$C_6)$alkylaminosulfonyl, heterocyclsulfonyl, $(C_1$-$C_6)$alkylcarbonylamino, $(C_1$-$C_6)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonylamino, $(C_1$-$C_6)$alkylsulfonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl,, hydroxy$(C_1$-$C_6)$alkoxy, heteroaryl, oxo, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, di$(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl amino$(C_2$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxy, di$(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxyl and $(C_1$-$C_6)$alkylcarbonyl, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

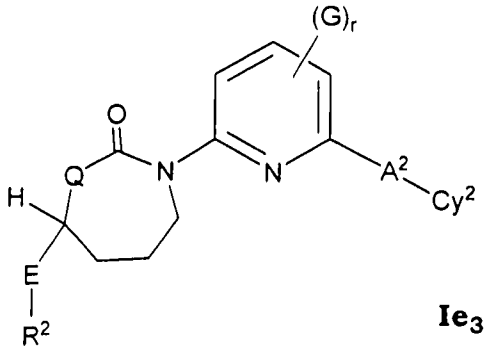
Another embodiment is a compound of Structural Formula Ie_2:



Ie_2

and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above, G and r are as defined for Formula Ie_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

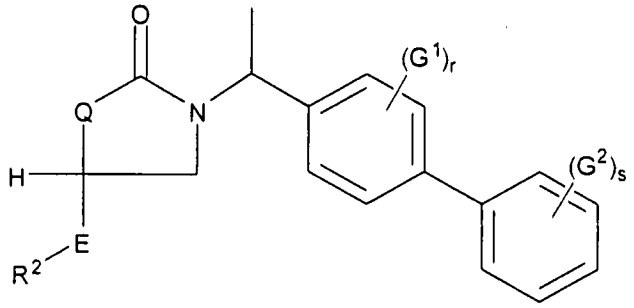
Another embodiment is a compound of Structural Formula Ie_3:



Ie_3

and wherein values and alternative values for Q, R^2, E, A^2 and Cy^2 are as defined for Formula I above, G and r are as defined for Formula Ie_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a compound of Structural Formula If_1:



If_1

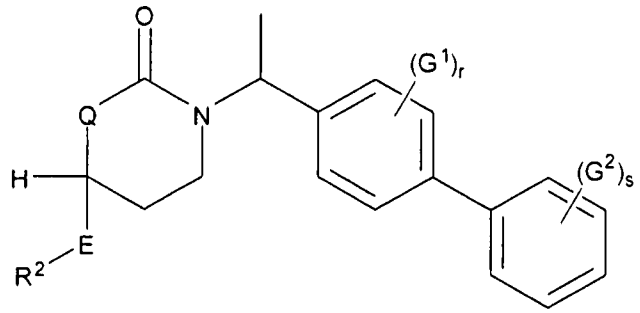
and wherein values and alternative values for Q, R^2 and E are as defined for Formula I above,

r and s are independently 0, 1, 2, 3 or 4 and

G^1 and G^2 are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, hydroxy$(C_3$-$C_6)$cycloalkyl, $(C_4$-$C_7)$cycloalkylalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_2$-$C_6)$alkenyl, hydroxy$(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_6)$cycloalkyl$(C_2$-$C_4)$alkynyl, halo$(C_1$-$C_6)$alkyl, halo$(C_3$-$C_6)$cycloalkyl, halo$(C_4$-$C_7)$cycloalkylalkyl, $(C_1$-$C_6)$alkoxy, $(C_3$-$C_6)$cycloalkoxy, $(C_4$-$C_7)$cycloalkylalkoxy, halo$(C_1$-$C_6)$alkoxy, halo$(C_3$-$C_6)$cycloalkoxy, halo$(C_4$-$C_7)$cycloalkylalkoxy, $(C_1$-$C_6)$alkylthio, $(C_3$-$C_6)$cycloalkythio, $(C_4$-$C_7)$cycloalkylalkylthio, halo$(C_1$-$C_6)$alkylthio, halo$(C_3$-$C_6)$cycloalkythio, halo$(C_4$-$C_7)$cycloalkylalkylthio, $(C_1$-$C_6)$alkanesulfinyl, $(C_3$-$C_6)$cycloalkanesulfinyl, $(C_4$-$C_7)$cycloalkylalkanesulfinyl, halo$(C_1$-$C_6)$alkanesulfinyl, halo$(C_3$-$C_6)$cycloalkanesulfinyl, halo$(C_4$-$C_7)$cycloalkylalkanesulfinyl, $(C_1$-$C_6)$alkanesulfonyl, $(C_3$-$C_6)$cycloalkanesulfonyl, $(C_4$-$C_7)$cycloalkylalkanesulfonyl, halo$(C_1$-$C_6)$alkanesulfonyl, halo$(C_3$-$C_6)$cycloalkanesulfonyl, halo$(C_4$-$C_7)$cycloalkylalkanesulfonyl, $(C_1$-$C_6)$alkylamino, di$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1$-$C_6)$alkylaminocarbonyl, di$(C_1$-$C_6)$alkylaminocarbonyl, $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkylaminocarbonyl, heterocyclylcarbonyl, $(C_1$-$C_6)$alkylaminosulfonyl, di$(C_1$-$C_6)$alkylaminosulfonyl, heterocyclsulfonyl, $(C_1$-$C_6)$alkylcarbonylamino, $(C_1$-$C_6)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonylamino, $(C_1$-

C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl,, hydroxy(C_1-C_6)alkoxy, heteroaryl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl and (C_1-C_6)alkylcarbonyl, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

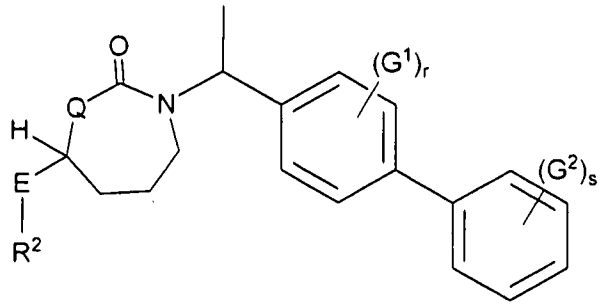
Another embodiment is a compound of Structural Formula If_2:



If_2

and wherein values and alternative values for Q, R^2 and E are as defined for Formula I above, G^1, G^2, r and s are as defined for Formula If_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

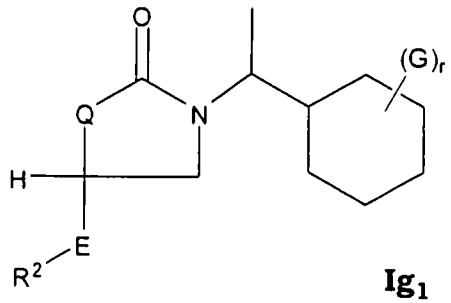
Another embodiment is a compound of Structural Formula If_3:



If_3

and wherein values and alternative values for Q, R^2 and E are as defined for Formula I above, G^1, G^2, r and s are as defined for Formula If_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a compound of Structural Formula Ig_1:



Ig_1

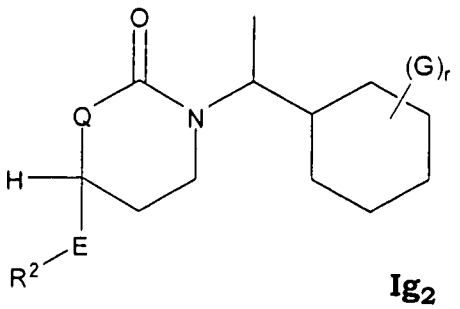
and wherein values and alternative values for Q, R^2 and E are as defined for Formula I above,

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

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_3\text{-}C_6)$cycloalkyl, $(C_4\text{-}C_7)$cycloalkylalkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, hydroxy$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_6)$cycloalkyl$(C_2\text{-}C_4)$alkynyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_3\text{-}C_6)$cycloalkyl, halo$(C_4\text{-}C_7)$cycloalkylalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkoxy, $(C_4\text{-}C_7)$cycloalkylalkoxy, halo$(C_1\text{-}C_6)$alkoxy, halo$(C_3\text{-}C_6)$cycloalkoxy, halo$(C_4\text{-}C_7)$cycloalkylalkoxy, $(C_1\text{-}C_6)$alkylthio, $(C_3\text{-}C_6)$cycloalkythio, $(C_4\text{-}C_7)$cycloalkyl-alkylthio, halo$(C_1\text{-}C_6)$alkylthio, halo$(C_3\text{-}C_6)$cycloalkythio, halo$(C_4\text{-}C_7)$cycloalkylalkylthio, $(C_1\text{-}C_6)$alkanesulfinyl, $(C_3\text{-}C_6)$cycloalkanesulfinyl, $(C_4\text{-}C_7)$cycloalkylalkanesulfinyl, halo$(C_1\text{-}C_6)$alkanesulfinyl, halo$(C_3\text{-}C_6)$cycloalkanesulfinyl, halo$(C_4\text{-}C_7)$cycloalkylalkanesulfinyl, $(C_1\text{-}C_6)$alkanesulfonyl, $(C_3\text{-}C_6)$cycloalkanesulfonyl, $(C_4\text{-}C_7)$cycloalkylalkanesulfonyl, halo$(C_1\text{-}C_6)$alkanesulfonyl, halo$(C_3\text{-}C_6)$cycloalkanesulfonyl, halo$(C_4\text{-}C_7)$cyclo-alkylalkanesulfonyl, $(C_1\text{-}C_6)$alkylamino, di$(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1\text{-}C_6)$alkylaminocarbonyl, di$(C_1\text{-}C_6)$alkylaminocarbonyl, $(C_1\text{-}C_3)$alkoxy$(C_1\text{-}C_3)$alkylaminocarbonyl, heterocyclylcarbonyl, $(C_1\text{-}C_6)$alkylaminosulfonyl, di$(C_1\text{-}C_6)$alkylaminosulfonyl, heterocyclsulfonyl, $(C_1\text{-}C_6)$alkylcarbonylamino, $(C_1\text{-}C_6)$alkylcarbonylamino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonylamino, $(C_1\text{-}C_6)$alkylsulfonylamino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl,, hydroxy$(C_1\text{-}C_6)$alkoxy, heteroaryl, amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, di$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl amino$(C_2\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylamino$(C_2\text{-}C_6)$alkoxy, di$(C_1\text{-}C_6)$alkylamino$(C_2\text{-}$

C_6)alkoxyl and (C_1-C_6)alkylcarbonyl, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

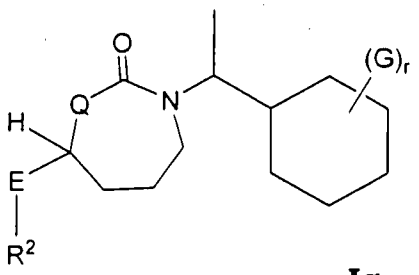
Another embodiment is a compound of Structural Formula Ig_2:



Ig_2

and wherein values and alternative values for Q, R^2 and E are as defined for Formula I above, G and r are as defined for Formula Ig_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

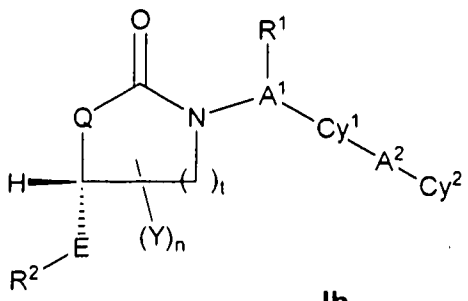
Another embodiment is a compound of Structural Formula Ig_3:



Ig_3

and wherein values and alternative values for Q, R^2 and E are as defined for Formula I above, G and r are as defined for Formula Ig_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

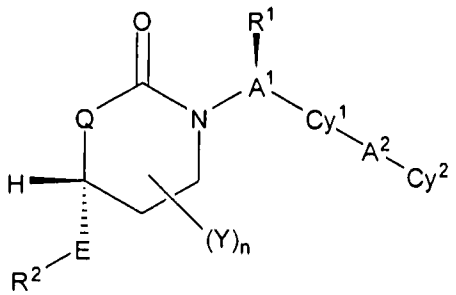
Another embodiment is a compound of Structural Formula Ih_1:



Ih_1

and wherein values and alternative values for Q, R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y , n and t are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

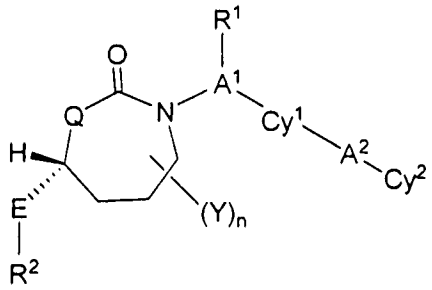
Another embodiment is a compound of Structural Formula Ih_2:



Ih_2

and wherein values and alternative values for Q, R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y , n and t are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

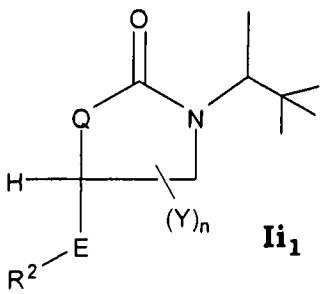
Another embodiment is a compound of Structural Formula Ih_3:



Ih_3

and wherein values and alternative values for Q, R^2, E, A^1, R^1, Cy^1, A^2, Cy^2, Y , n and t are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

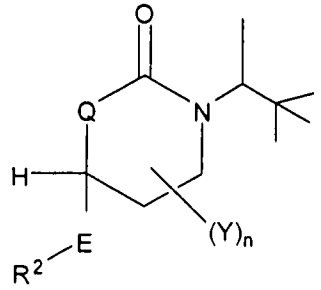
Another embodiment is a compound of Structural Formula Ii_1:



Ii_1

and wherein values and alternative values for Q, R^2, E, Y and n are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

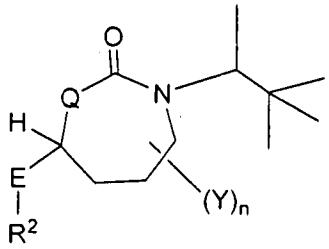
Another embodiment is a compound of Structural Formula Ii_2:



Ii_2

and wherein values and alternative values for Q, R^2, E, Y and n are as defined for Formula I above,or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

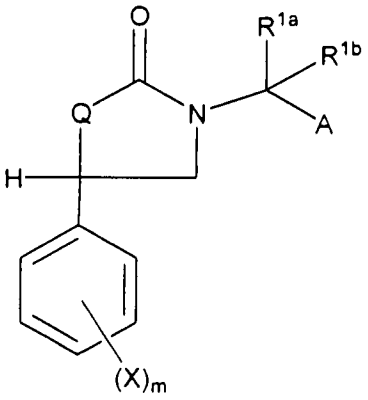
Another embodiment is a compound of Structural Formula Ii_3:



Ii_3

and wherein values and alternative values for Q, R^2, E, Y and n are as defined for Formula I above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

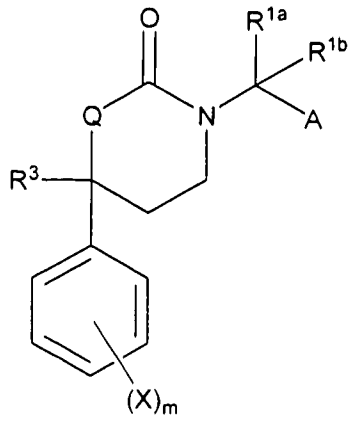
Another embodiment is a compound of Structural Formula Ij_1:



Ij_1

and wherein values and alternative values for Q, R^{1a}, R^{1b} and A are as defined for Formula I above, X and m are as defined for Formula Id_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

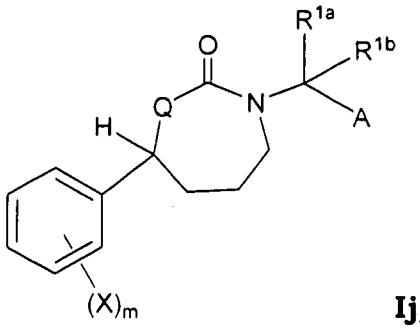
Another embodiment is a compound of Structural Formula Ij_2:



Ij_2

and wherein values and alternative values for Q, R^{1a}, R^{1b} and A are as defined for Formula I above, X and m are as defined for Formula Id_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

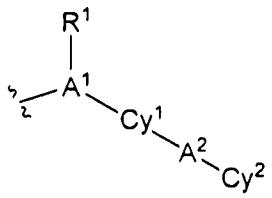
Another embodiment is a compound of Structural Formula Ij_3:



Ij_3

and wherein values and alternative values for Q, R^{1a}, R^{1b} and A are as defined for Formula I above, X and m are as defined for Formula Id_1 above, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In another embodiment of the invention, values for variables in Structural Formula I or any of Structural Formulas I_{14}-I_{26} or Ia_{1-3}-Ih_{1-3} are:

R is  ;

R^1 is absent or is methyl or ethyl;

A^1 is a bond or CH_2;

Cy^1 is phenyl, cyclohexyl, pyridyl, N-oxo-pyridyl, thiazolyl or pyrimidinyl optionally substituted with 1 to 4 groups independently selected from halo, methyl,

trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy and 2-hydroxy-2-methylpropoxy;

A^2 is a bond, O or OCH_2CO;

Cy^2 is (a) hydrogen or (b) phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl or piperazinyl optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonyl-aminomethyl or tetrazolyl;

n is 0;

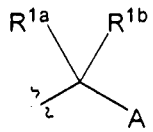
t is 1, 2 or 3;

Q is O, NR^5 or CH_2;

E is a bond or CH_2;

R^2 is phenyl or pyridyl optionally substituted with one group selected from halo, methyl, methylthio or (4-morpholino)methyl.

In another embodiment of the invention, values for variable in the Structural Formula I or any of the formulas I_1-I_{13} or Ij_{1-3} are:



R is ;

R^{1a} is methyl or ethyl;

R^{1b} is methyl or hydrogen;

A is methyl, ethyl, isopropyl or t-butyl;

n is 0;

t is 1, 2 or 3;

Q is O, NR^5 or CH_2;

E is a bond or CH_2; and

R^2 is phenyl, thienyl or pyridyl each optionally substituted with halo or methyl.

DEFINITIONS

The term "alkyl" means a straight or branched hydrocarbon radical having 1-10 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-

butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl and the like.

The term "cycloalkyl" means a monocyclic, bicyclic or tricyclic, saturated hydrocarbon ring having 3-10 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl, spiro [4.4]nonane, adamantyl and the like.

The term "aryl" means an aromatic radical which is a phenyl group, a naphthyl group, an indanyl group or a tetrahydronaphthalene group. An aryl group is optionally substituted with 1-4 substituents. Exemplary substituents include alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H, $CONH_2$, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido.

The term "heteroaryl" means a 5- and 6-membered heteroaromatic radical which may optionally be fused to a saturated or unsaturated ring containing 0-4 heteroatoms selected from N, O, and S and includes, for example, a heteroaromatic radical which is 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3- pyrrolyl, 2-,3-, or 4-pyridyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 3- or 4-pyridazinyl, 1H-indol-6-yl, 1H-indol-5-yl, 1H-benzimidazol-6-yl, 1H-benzimidazol-5-yl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 2-, 3-, 5-, 6-, 7- or 8-quinoxalinyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl, 2-, 4-, or 5-thiazolyl, 2-, 3-, 4-, or 5-pyrazolyl, 2-, 3-, 4-, or 5-imidazolyl. A heteroaryl is optionally substituted. Exemplary substituents include alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H, $CONH_2$, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido, or by oxo to form an N-oxide.

The term "heterocyclyl" means a 4-, 5-, 6- and 7-membered saturated or partially unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O, and S. Exemplary heterocyclyls include pyrrolidine, pyrrolidin-2-one, 1-methylpyrrolidin-2-one, piperidine, piperidin-2-one, 2-pyridone, 4-pyridone, piperazine, 1-(2,2,2-trifluoroethyl)piperazine, piperazin-2-one, 5,6-dihydropyrimidin-4-one, pyrimidin-4-one, tetrahydrofuran, tetrahydropyran, tetrahydrothiophene, tetrahydrothiopyran, isoxazolidine, 1,3-dioxolane, 1,3-dithiolane, 1,3-dioxane, 1,4-dioxane, 1,3-dithiane, 1,4-dithiane, oxazolidin-2-one, imidazolidin-2-one, imidazolidine-2,4-dione, tetrahydropyrimidin-2(1H)-one, morpholine, N-methylmorpholine, morpholin-3-one, 1,3-oxazinan-2-one, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-1,2,5-thiaoxazole 1,1-dioxide, tetrahydro-2H-

1,2-thiazine 1,1-dioxide, hexahydro-1,2,6-thiadiazine 1,1-dioxide, tetrahydro-1,2,5-thiadiazole 1,1-dioxide and isothiazolidine 1,1-dioxide. A heterocyclyl can be optionally substituted with 1-4 susbtituents. Exemplary substituents include alkyl, haloalkyl and oxo.

As used herein the terms "subject" and "patient" may be used interchangeably, and means a mammal in need of treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, pigs, horses, sheep, goats and the like) and laboratory animals (e.g., rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

When a disclosed compound or its pharmaceutically acceptable salt is named or depicted by structure, it is to be understood that solvates or hydrates of the compound or its pharmaceutically acceptable salts are also included. "Solvates" refer to crystalline forms wherein solvent molecules are incorporated into the crystal lattice during crystallization. Solvate may include water or nonaqueous solvents such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and EtOAc. Solvates, wherein water is the solvent molecule incorporated into the crystal lattice, are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water.

Certain of the disclosed comopounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms. The symbol "*" in a structural formula represents the presence of a chiral carbon center. "*R*" and "*S*" represent the configuration of substituents around one or more chiral carbon atoms. Thus, "*R**" and "*S**" denote the relative configurations of substituents around one or more chiral carbon atoms.

"Racemate" or "racemic mixture" means a compound of equimolar quantities of two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light.

"Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon-carbon double bond may be in an E (substituents are on opposite sides of the carbon-carbon double bond) or Z (substituents are oriented on the same side) configuration.

"R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule.

The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. Percent optical purity by weight is the ratio of the weight of the enatiomer over the weight of the enantiomer plus the weight of its optical isomer.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses one enantiomer of compound free from the corresponding optical isomer, a racemic mixture of the compound and mixtures enriched in one enantiomer relative to its corresponding optical isomer.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has at least two chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other

diastereomers, a pair of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diastereomeric pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s).

The compounds of the invention may be present in the form of pharmaceutically acceptable salts. For use in medicines, the salts of the compounds of the invention refer to non-toxic "pharmaceutically acceptable salts." Pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts.

Pharmaceutically acceptable acidic/anionic salts include, the acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, malonate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphospate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, hydrogensulfate, tannate, tartrate, teoclate, tosylate, and triethiodide salts.

Pharmaceutically acceptable basic/cationic salts include, the sodium, potassium, calcium, magnesium, diethanolamine, n-methyl-D-glucamine, L-lysine, L-arginine, ammonium, ethanolamine, piperazine and triethanolamine salts.

The following abbreviations have the indicated meanings:

Abbreviation	Meaning
Boc	*tert*-butoxy carbonyl or *t*-butoxy carbonyl
$(Boc)_2O$	di-*tert*-butyl dicarbonate
Cbz	Benzyloxycarbonyl
CbzCl	Benzyl chloroformate
DAST	diethylaminosulfur trifluoride

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCU	N,N'-dicyclohexylurea
DIAD	diisopropyl azodicarboxylate
DIEA	N,N-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
2,4-DNP	2,4-dinitrophenylhydrazine
DPTBS	Diphenyl-t-butylsilyl
EDC.HCl, EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Equiv	equivalents
EtOAc	ethyl acetate
Fmoc	1-[[(9H-fluoren-9-ylmethoxy)carbonyl]oxy]-
Fmoc-OSu	1-[[(9H-fluoren-9-ylmethoxy)carbonyl]oxy]-2,5-pyrrolidinedione
h, hr	hour(s)
HOBt	1-hydroxybenzotriazole
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
KHMDS	potassium hexamethyldisilazane
LAH or $LiAlH_4$	lithium aluminum hydride
LC-MS	liquid chromatography-mass spectroscopy
LHMDS	lithium hexamethyldisilazane

m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
MsCl	methanesulfonyl chloride
Min	minute
MS	mass spectrum
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaN_3	sodium azide
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
NMM	N-methylmorpholine
NMP	N-methylpyrrolidinone
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
PE	petroleum ether
Quant	quantitative yield
rt	room temperature
Satd	saturated
$SOCl_2$	thionyl chloride
SFC	supercritical fluid chromatography
SPA	scintillation proximity assay
SPE	solid phase extraction
TBAF	tetrabutylammonium fluoride
TBS	t-butyldimethylsilyl
TBDPS	t-butyldiphenylsilyl
TBSCl	t-butyldimethylsilyl chloride
TBDPSCl	t-butyldiphenylsilyl chloride

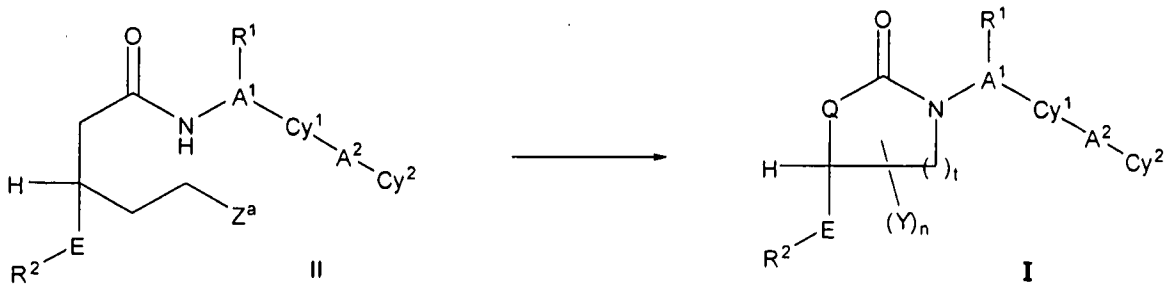
TEA	triethylamine or Et_3N
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Teoc	1-[2-(trimethylsilyl)ethoxycarbonyloxy]-
Teoc-OSu	1-[2-(trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione
TFA	trifluoroacetic acid
Tlc, TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane or trimethylsilyl chloride
t_R	retention time
TsOH	p-toluenesulfonic acid

GENERAL DESCRIPTION OF SYNTHETIC METHODS

Compounds of Formula I can be prepared by several processes. In the discussion below, A, A^1, A^2, Cy^1, Cy^2, E, R^1, R^2, R^5, R^{1a}, R^{1b}, Y, n and t have the meanings indicated above unless otherwise noted. In cases where the synthetic intermediates and final products of Formulas I described below contain potentially reactive functional groups, for example amino, hydroxyl, thiol and carboxylic acid groups, that may interfere with the desired reaction, it may be advantageous to employ protected forms of the intermediate. Methods for the selection, introduction and subsequent removal of protecting groups are well known to those skilled in the art. (T.W. Greene and P. G. M. Wuts "Protective Groups in Organic Synthesis" John Wiley & Sons, Inc., New York 1999). Such protecting group manipulations are assumed in the discussion below and not described explicitly. Generally, reagents in the reaction schemes are used in equimolar amounts; however, in certain cases it may be desirable to use an excess of one reagent to drive a reaction to completion. This is especially the case when the excess reagent can be readily removed by evaporation or extraction. Bases employed to neutralize HCl in reaction mixtures are generally used in slight to substantial excess (1.05 – 5 equivalents).

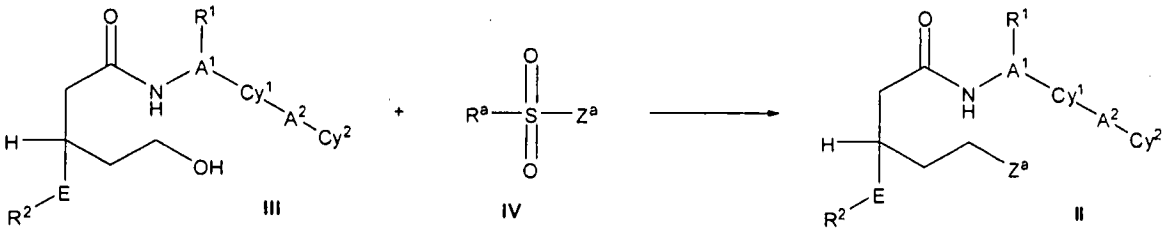
In a first process compounds of Formula I, wherein t is 2, n is 0 and Q is CH_2, are prepared by ring closure of intermediates of Formula II wherein Z^a is a leaving

group such as halide, alkanesulfonate, haloalkanesulfonate or arylsulfonate, using a base such as NaH.



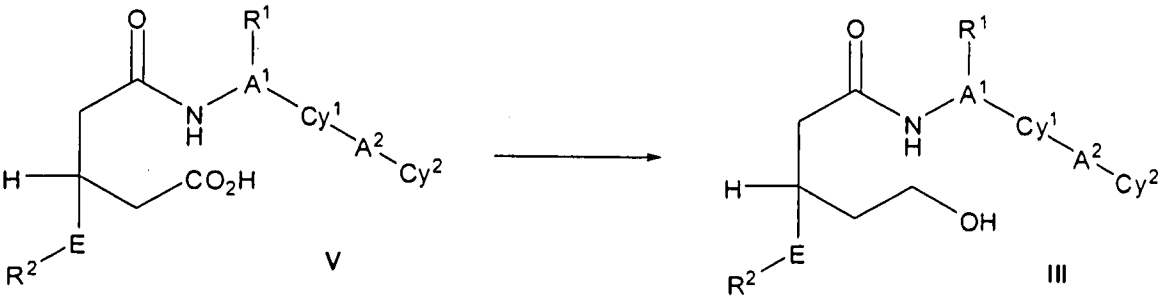
II I

Intermediates of Formula II, wherein Z^a is alkanesulfonate, haloalkanesulfonate or arylsulfonate, can be prepared from alchols of Formula III and sulfonyl chlorides of Formula IV (Z^a = Cl) or sulfonic anhydrides of Formula IV (Z^a = R^aSO_2O-), wherein R^a is alkyl, haloalkyl or aryl.



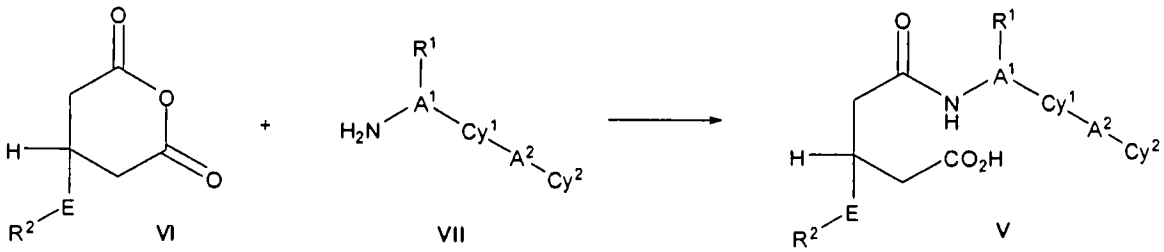
III IV II

Alcohols of Formula III can be prepared by reduction of carboxylic acids of Formula V using, for example, borane in THF.



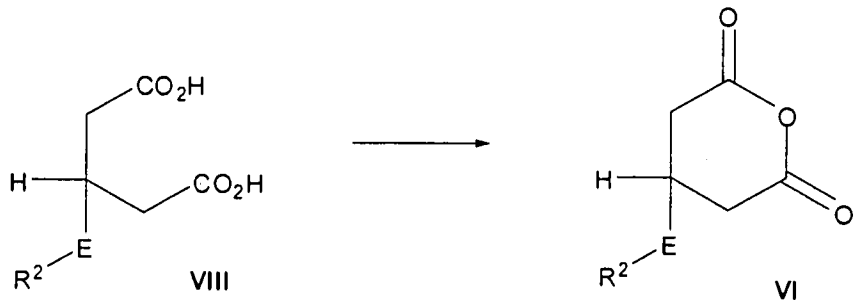
V III

Carboxylic acids of Formula V can be prepared by reaction of cyclic anhydrides of Formula VI with amines of Formula VII.



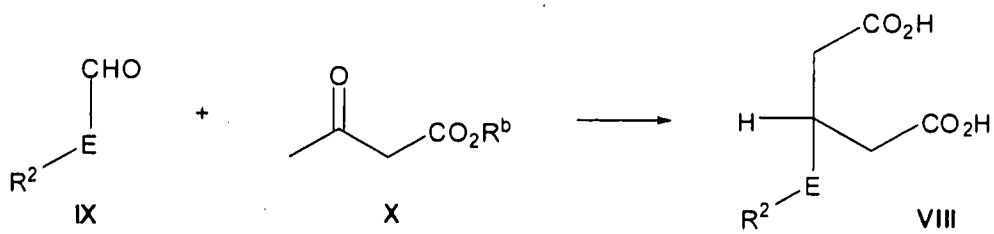
VI VII V

Cyclic anhydrides of Formula VI can be prepared from diacids of Formula VIII by treatment with acetic or trifluoroacetic anhydride.



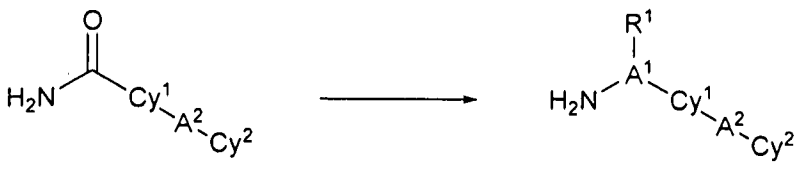
VIII VI

Diacids of Formula VIII can be prepared from aldehydes of Formula IX and β-ketoesters of Formula X, wherein R^b is lower alkyl, by reaction with piperidine under Knoevenagel conditions, followed by treatment with NaOH and with HCl.



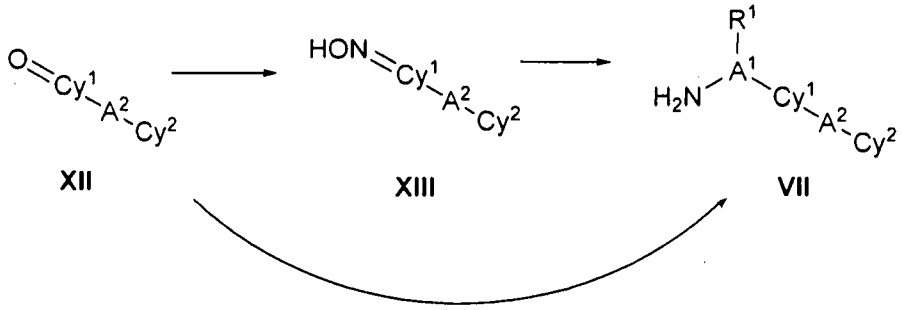
IX X VIII

Amine intermediates of Formula VII, wherein $A^1 = CH_2$ and R^1 is absent, can be prepared by reduction of amides of Formula XI using a hydride reagent such as BH_3.THF solution, $BH_3.Me_2S$ or $LiAlH_4$ in an ethereal solvent such as THF or DME at 20 °C to 100 °C for between 1 h and 48 h:



XI VII

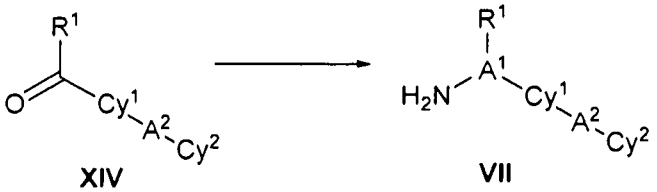
Amine intermediates of Formula VII, wherein A^1 is a bond, R^1 is absent and Cy^1 is not an aromatic or heteroaromatic ring, can be prepared from ketones of formula XII via oximes of Formula XIII or by reductive amination of ketones of Formula XII with ammonia:



XII XIII VII

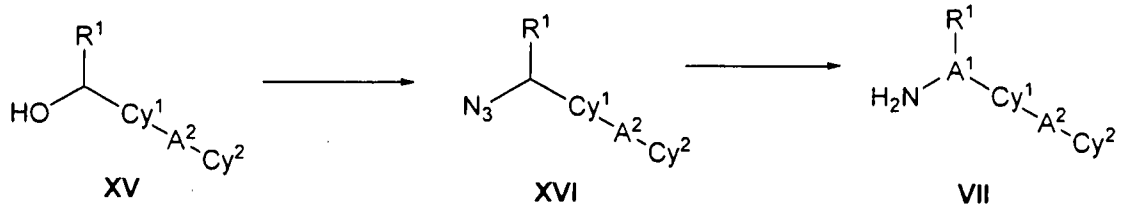
Methods for the conversion of ketones to oximes are described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" pp 1194-1195, 5th Edition, Wiley, New York, NY, 2001. Methods for the reduction of oximes to primary amines are described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" p 1555, 5th Edition, Wiley, New York, NY, 2001. Methods for the reductive amination of ketones are described in Baxter, E. W. and Reitz, A. B. "Organic Reactions" Volume 59, Ed. Overman, L. E., Wiley Interscience, 2002.

Amine intermediates of Formula VII, wherein A^1 is CH, can be prepared from ketones of Formula XIV by reductive amination with ammonia.



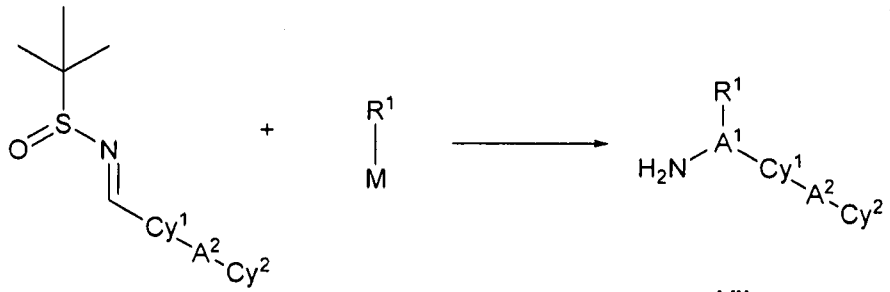
XIV VII

Amine intermediates of Formula VII, wherein A^1 is CH, can be prepared from alcohols of Formula XV via azides of Formula XVI. The conversion of alcohols of Formula XV to azides of Formula XVI can be accomplished with, for example, diphenylphosphoryl azide. Reduction of azides of Formula XVI to amines of Formula VII can be effected, for example, by hydrogenation in the presence of a palladium catalyst or by reaction with triphenylphosphine in wet THF.



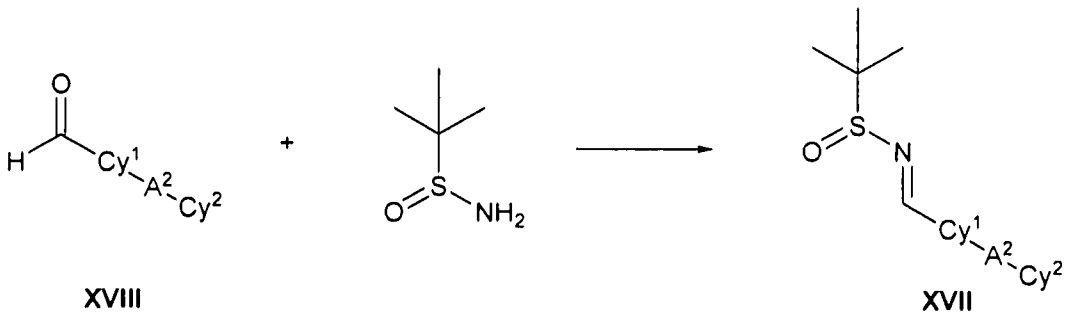
XV XVI VII

Amine intermediates of Formula VII, wherein A^1 is CH, can be prepared by reaction of sulfinyl imine intermediates of Formula XVII with organometallic reagents of Formula XVIII, wherein M is Li, MgCl, MgBr or MgI, followed by treatment with acid to remove the t-butylsulfinyl group.



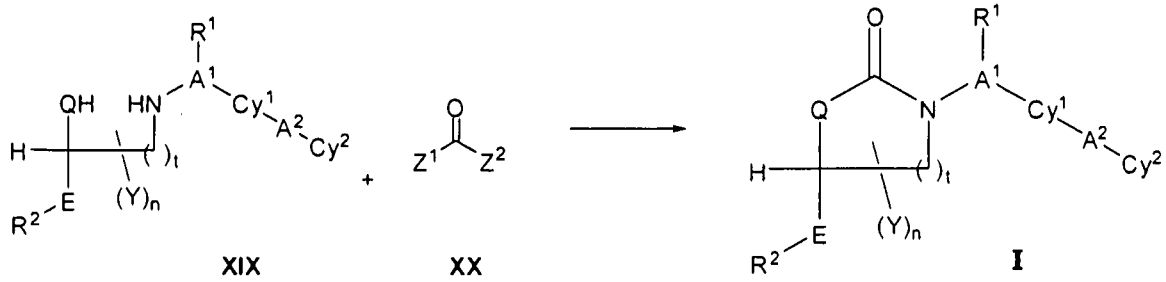
XVII XVIII VII

Sulfinyl imines of Formula XVII can be prepared by treatment of aldehyde intermediates of Formula XVIII with 2-methylpropane-2-sulfinamide.



XVIII XVII

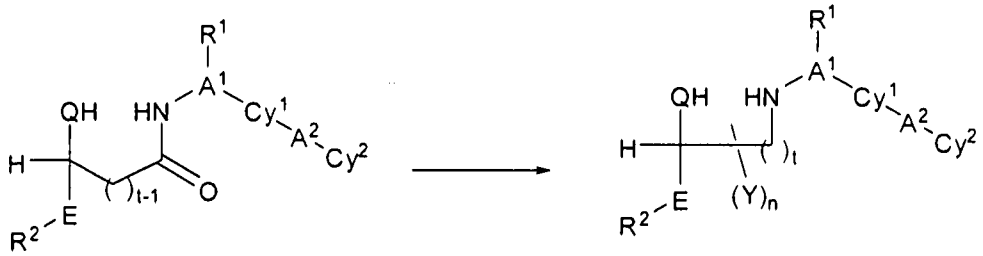
In a second process, compounds of Formula I, wherein Q is O or NR^5, can be prepared by reaction of aminoalcohols or diamines intermediate of Formula XIX with reagents of Formula XX, wherein Z^1 and Z^2 are leaving groups such as chloride, 1-imidazolyl or aryloxide in an inert solvent such as THF, CH_2Cl_2, toluene or MeCN, usually in the presence of an organic or inorganic base such as triethylamine or $NaHCO_3$ respectively, at -10 °C to 120 °C:



XIX XX I

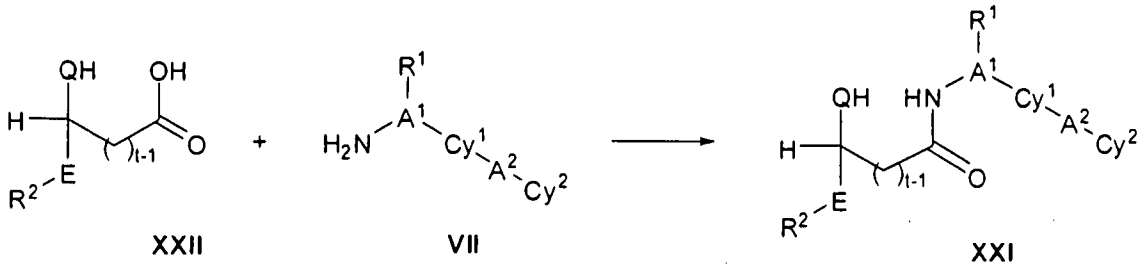
Certain instances of reagent XX are especially convenient because they are commercially available. For example when Z^1 and Z^2 are both chloride, XX is phosgene. When Z^1 and Z^2 are both 1-imidazolyl, XX is carbonyl diimidazole. When Z^1 is chloride and Z^2 is p-nitrophenoxide, XX is p-nitrophenyl chloroformate. When Z^1 and Z^2 are both $OCCl_3$, XX is triphosgene and as little as one third of molar equivalent can be used.

Aminoalcohol and diamine intermediates of Formula XIX, wherein n = 0, can be prepared by reduction of amides of Formula XXI using a hydride reagent such as BH_3.THF solution, $BH_3.Me_2S$ or $LiAlH_4$ in an ethereal solvent such as THF or DME at 20 °C to 100 °C for between 1 h and 48 h:



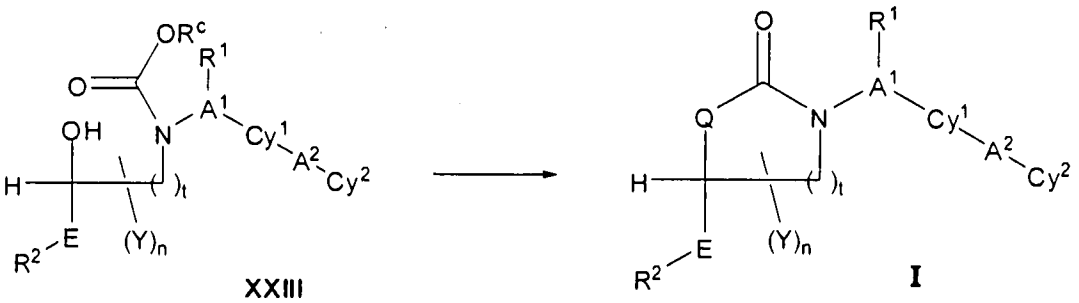
XXI XIX

Intermediates of Formula XXI can be prepared by coupling of α-, β- or γ-hydroxyacids (Q = O) and α-, β- or γ-aminoacids (Q = NR^5) of Formula XXII with amines of Formula VII using standard peptide coupling reagents such as EDC in the presence of HOBt and N,N-diisopropylethylamine in an inert solvent such as CH_2Cl_2 at 0 – 30 °C for between 1 h and 24 h:



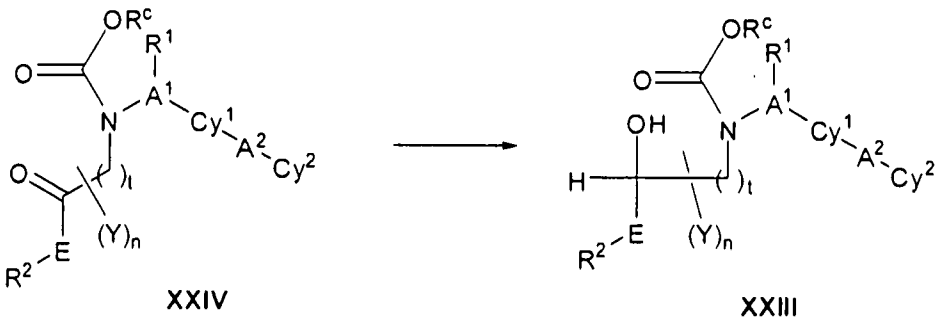
XXII VII XXI

In a third process, compounds of Formula I, wherein Q is O and t is 1 or 2, can be prepared by reaction of hydroxycarbamates of Formula XXIII, wherein R^c is an alkyl or arylalkyl group such as methyl, t-butyl or benzyl, with a strong base such as NaH.



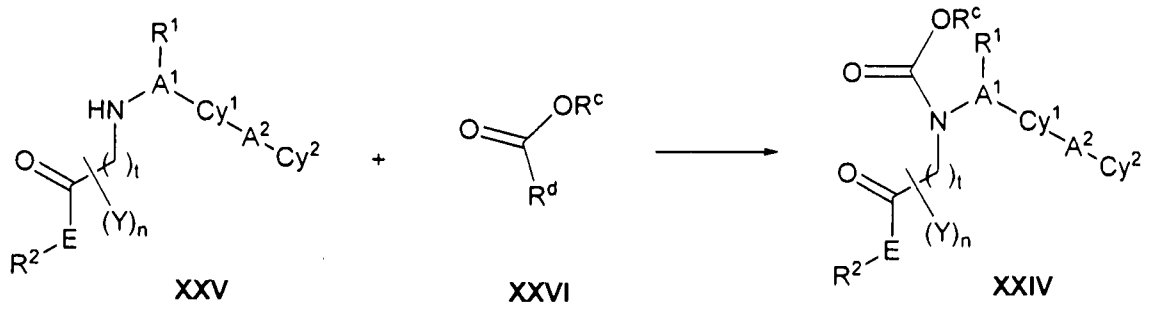
XXIII I

Hydroxycarbamates of Formula XXIII can be prepared by reduction of ketocarbamates of Formula XXIV with, for example, $NaBH_4$ in MeOH.



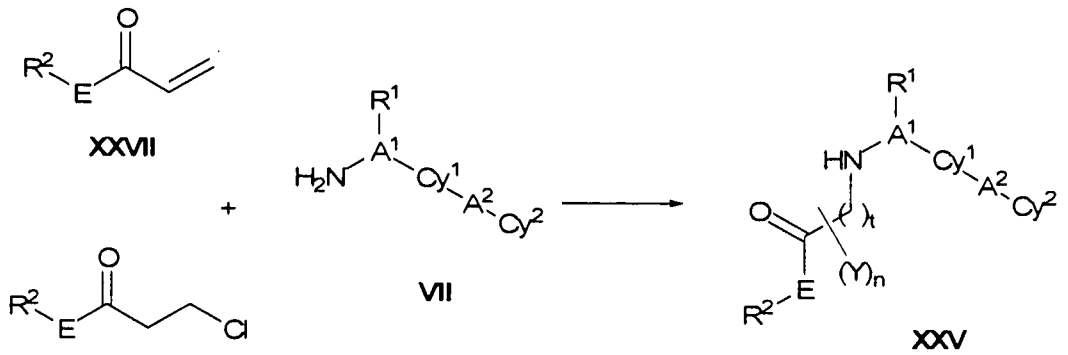
XXIV XXIII

Ketocarbamates of Formula XXIV can be prepared by reaction of β-aminoketones of Formula XXV with reagents of Formula XXVI, wherein R^d is a leaving group such as chloride, succinyloxy, imidazolyl or t-butoxycarboxycarbonyl:



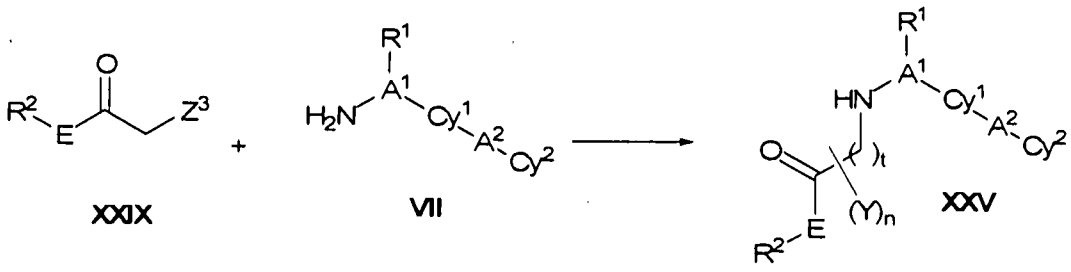
XXV XXVI XXIV

β-Aminoketones of Formula XXV, wherein n = 0 and t is 2, can be prepared by reaction of α,β-unsaturated ketones of Formula XXVII or β-chloroketones of Formula XXVIII with amines of Formula VII:



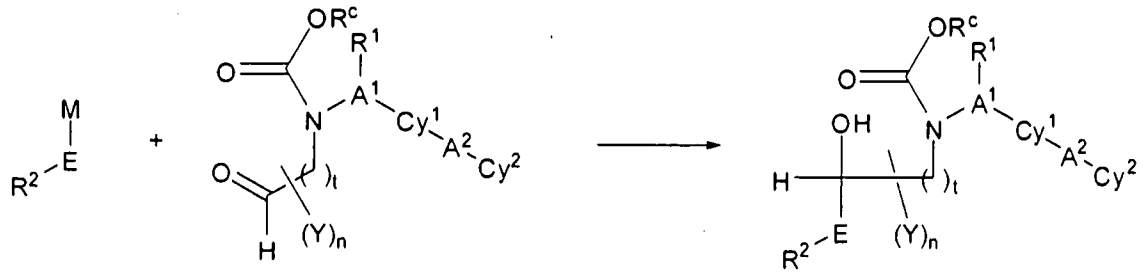
XXVII XXVIII VII XXV

α-Aminoketones of Formula XXV, wherein n = 0 and t is 1, can be prepared by reaction of α-haloketones of Formula XXIX, wherein Z^3 is Br or Cl, with amines of Formula VII:



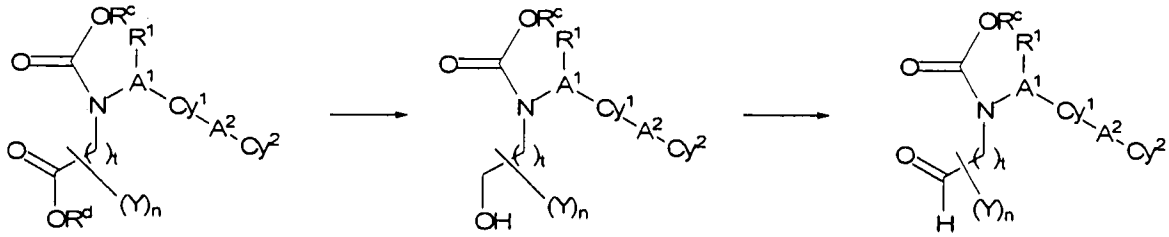
XXIX VII XXV

Hydroxycarbamates of Formula XXIII can also be prepared by addition of organometallic reagents of Formula XXX, wherein M is Li, MgCl, MgBr or MgI, to aldehydes of Formula XXXI.



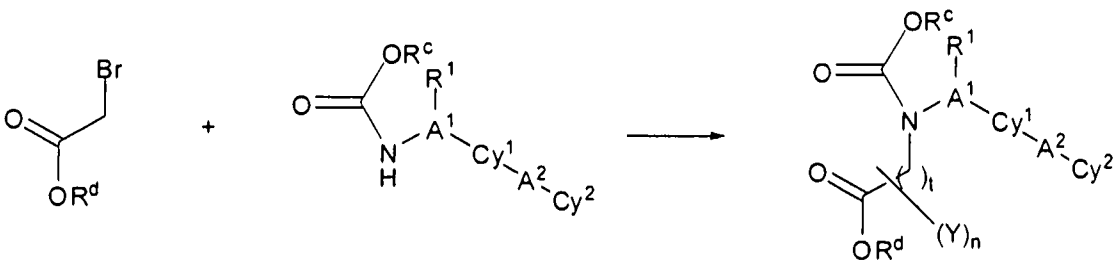
XXX XXXI XXIII

Aldehydes of Formula XXXI can be prepared by oxidation of alcohols of Formula XXXII with, for example, Dess-Martin periodinane. Alcohols of Formula XXXII can be prepared by reduction of esters of Formula XXXIII, wherein R^d Is alkyl or arylalkyl using for example $LiAlH_4$, or by reduction of acids of Formula XXXI, wherein R^d is hydrogen, using for example isobutyl chloroformate and $NaBH_4$.



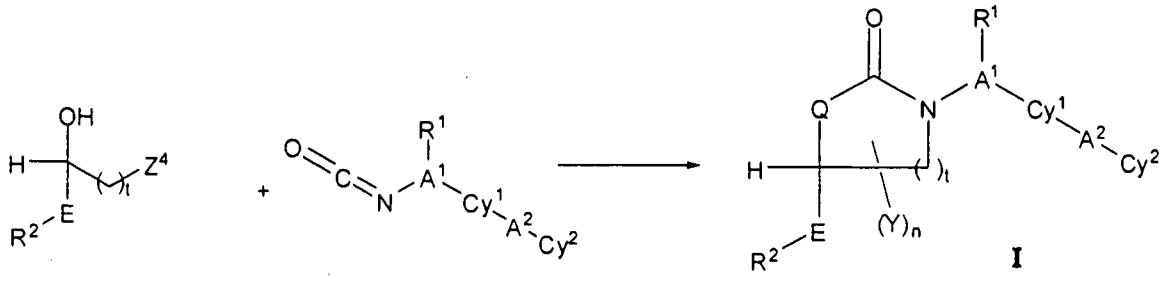
XXXIII XXXII XXIX

Esters of Formula Formula XXXIII, wherein n is 0 and t is 1, can be prepared by alkylation of carbamates of Formula XXXIV with bromoacetic acid esters of Formula XXXV using a base such as NaH.



XXXV XXXIV XXXIII

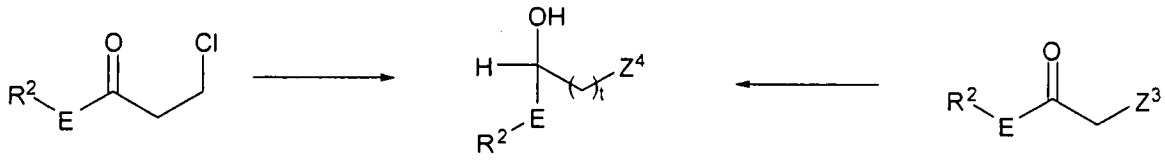
In a fourth process compounds of Formula I, wherein Q is O and t is 1 or 2, can be prepared by reaction of alcohols of Formula XXXVI, wherein Z^4 is halide, alkanesulfonate, haloalkanesulfonate or arylsulfonate, with isocyanates of Formula XXXVII in the presence of a base:



XXXVI XXXVII I

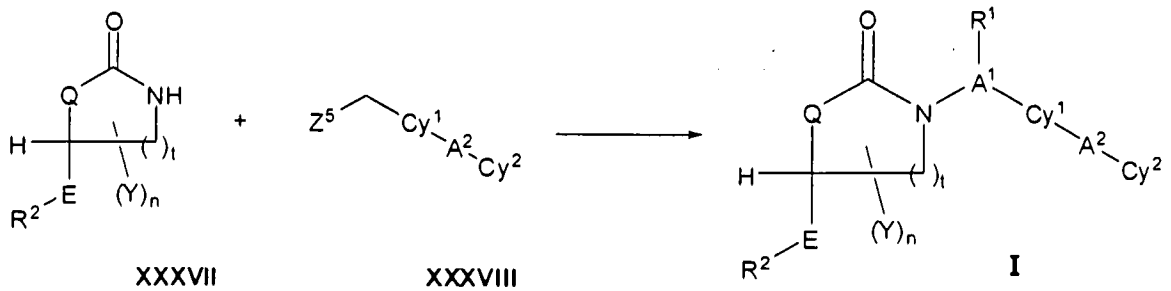
Isocyanates of Formula XXXVII can be prepared from amines of Formula VII by treatment with phosgene, diphosgene or triphosgene.

Alcohols of Formula XXXVI, wherein Z^4 is chloride and t is 2, can be prepared by reduction of β-haloketones of Formula XXVIII with hydride reagents such as $NaBH_4$. Similarly, alcohols of Formula XXXVI, wherein Z^4 is chloride or bromide and t is 1, can be prepared by reduction of α-haloketones of Formula XXIX, wherein Z^3 is chloride or bromide using a hydride reagent such as $NaBH_4$.



XXVIII XXXVI XXIX

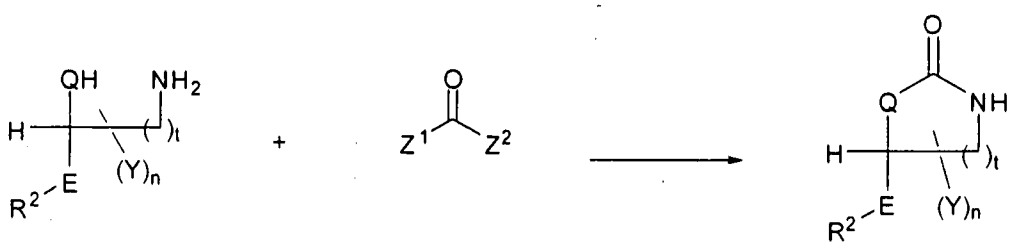
In a fifth process compounds of Formula I, wherein A^1 is CH_2 and R^1 is absent, can be prepared by reaction of compounds of Formula XXXVII, with alkylating agents of Formula XXXVIII, wherein Z^5 is a leaving group such as Br, I, OSO_2Me, OSO_2CF_3 or OSO_2Ph, in the presence of a base such as NaH or K_2CO_3:



XXXVII XXXVIII I

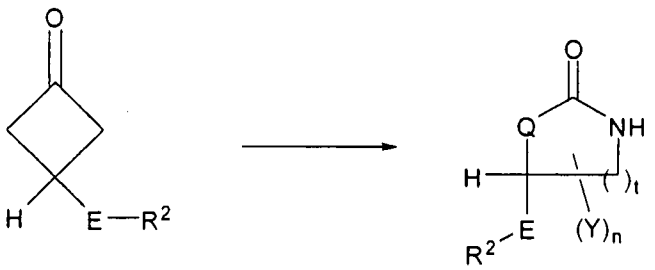
Compounds of Formula XXXVII, wherein Q = O or NR^5, can be prepared by treatment of compounds of Formula XXXIX with various reagents of Formula XX,

wherein Z^1 and Z^2 are leaving groups such as chloride, 1-imidazolyl or aryloxide in an inert solvent such as THF, CH_2Cl_2, toluene or MeCN, usually in the presence of an organic or inorganic base such as triethylamine or $NaHCO_3$ respectively, at -10 °C to 120 °C:



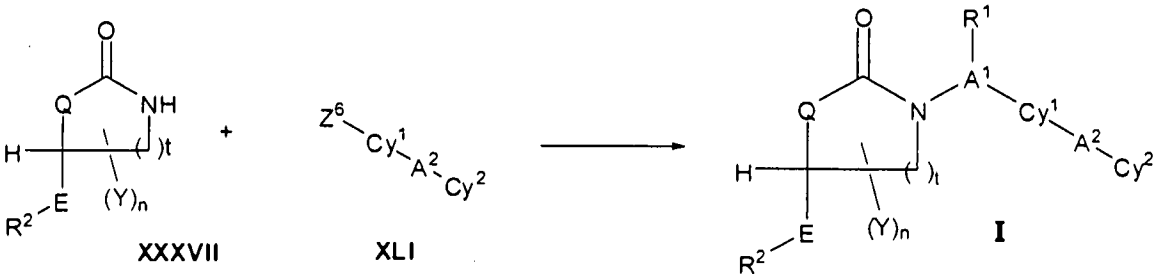
XXXIX XX XXXVII

Compounds of Formula XXXVII, wherein Q is CH_2, can be prepared by ring expansion of ketones of Formula XL with hydrazoic acid under Schmidt reaction conditions.



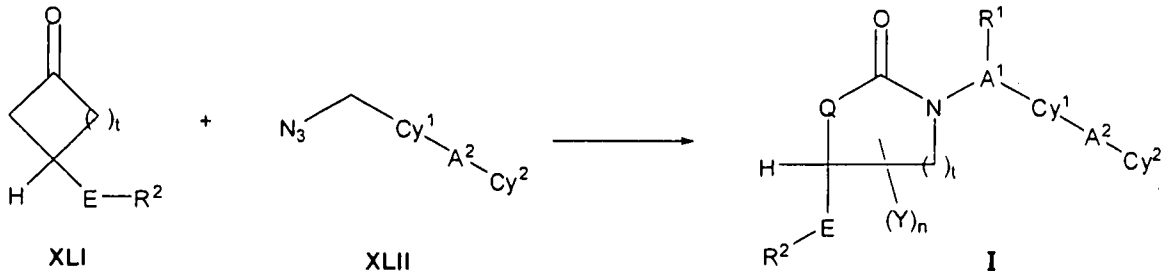
XL XXXVII

In a sixth process compounds of Formula I, wherein A is a bond can be prepared by reaction of compounds of Formula XXXVII, with compounds of Formula XLI, wherein Z^6 is a leaving group such as chloro, bromo, iodo or OSO_2CF_3, in the presence of a base such as K_2CO_3 and a copper or palladium catalyst in an inert solvent such as dioxane, DMF or NMP at elevated temperature:



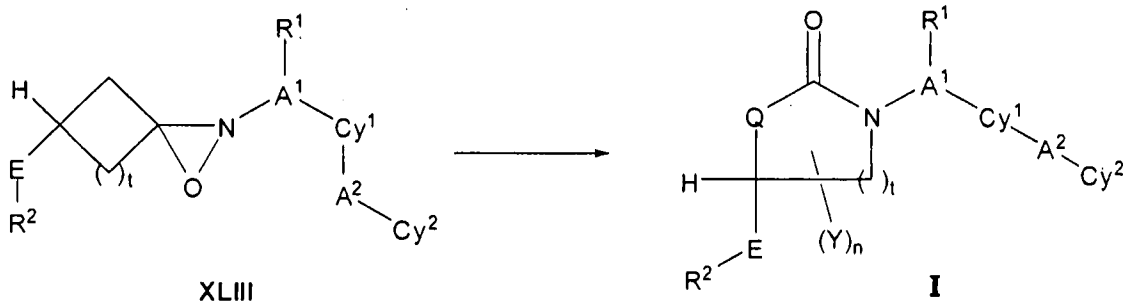
XXXVII XLI I

In a seventh process, compounds of Formula I, wherein Q is CH_2 and A^1 is CH_2 and R^1 is absent, can be prepared by reaction of ketones of Formula XL with azides of Formula XLII in the presence of $TiCl_4$.



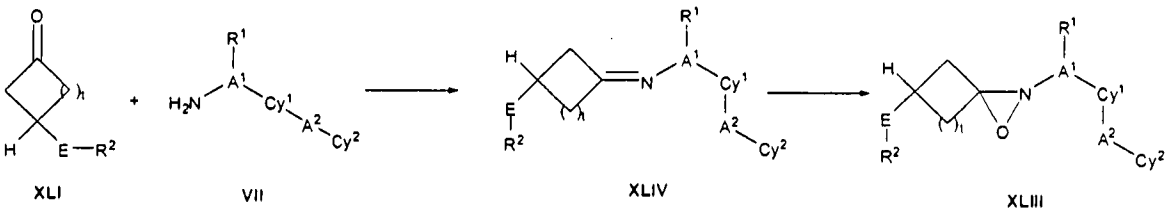
XLI XLII I

In an eighth process, compounds of Formula I, wherein Q is CH_2, are prepared by photolytic rearrangement of oxaziridines of Formula XLIII.



XLIII I

Oxaziridines of Formula XLIII can be prepared from ketones of Formula XL and amines of Formula VII to form imines of Formula XLIV, followed by oxidation with, for example, m-CPBA.



XLI VII XLIV XLIII

In a ninth process, compounds of Formula I can be prepared from other compounds of Formula I. For example:

(1) a compound of Formula I wherein Cy^1 is substituted with bromine or iodine, A^2 is a bond and Cy^2 is hydrogen can be reacted with an optionally substituted aryl or heteroarylboronic acid or ester in the presence of a palladium catalyst to give a compound of Formula I wherein A^2 is a bond and Cy^2 is optionally substituted aryl or heteroaryl.

(2) a compound of Formula I wherein R^1 is ω-hydroxy(C_2-C_6)alkyl can be oxidized to a compound of Formula I wherein R^1 is ω-carboxy(C_1-C_5)alkyl using Jones reagent.

(3) a compound of Formula I wherein R^1 is ω-carboxy(C_1-C_6)alkyl can be coupled with ammonia or a (C_1-C_6)alkylamine using a standard peptide coupling reagent such as EDC to afford a compound of Formula I wherein R^1 is ω-$H_2NC(=O)$(C_1-C_6)alkyl or ω-{(C_1-C_6)alkylNHC(=O)}(C_1-C_6)alkyl .

(4) a compound of Formula I wherein R^1 is ω-hydroxy(C_1-C_6)alkyl can be converted to its methanesulfonate or trifluoromethanesulfonate, treated with sodium azide and reduced to give a compound of Formula I, wherein R^1 is ω-amino(C_1-C_6)alkyl.

(5) a compound of Formula I wherein R^1 is amino(C_1-C_6)alkyl can be reacted with acetic anhydride or acetyl chloride to give a compound of Formula I wherein R^1 is {acetylamino}(C_1-C_6)alkyl.

(6) a compound of Formula I wherein R^1 is amino(C_1-C_6)alkyl can be reacted with methanesulfonyl chloride to give a compound of Formula I wherein R^1 is {methanesulfonylamino}(C_1-C_6)alkyl.

(7) a compound of Formula I, wherein R^1 is (C_2-C_6)alkenyl, is hydroborated to afford a compound of Formula I wherein R^1 is hydroxy(C_2-C_6)alkyl,.

(8) a compound of Formula I, wherein R^1 is (C_2-C_6)alkenyl, can be reacted with osmium tetroxide and N-methylmorpholine-N-oxide to afford a compound of Formula I wherein R^1 is vicinal dihydroxy(C_2-C_6)alkyl,.

(9) a compound of Formula I, wherein R^1 is $H_2C=CH$(C_0-C_4)alkyl-, can be reacted with ozone followed by $NaBH_4$ to give a compound of Formula I wherein R^1 is ω-hydroxy(C_1-C_5)alkyl.

(10) a compound of Formula I wherein R^1 is amino(C_1-C_6)alkyl can be reacted with an (C_1-C_6)alkyl isocyanate to give a compound of Formula I wherein R^1 is (C_1-C_6)alkylaminocarbonylamino(C_1-C_6)alkyl.

(11) a compound of Formula I wherein R^1 is amino(C_1-C_6)alkyl can be reacted with an (C_1-C_6)alkyl chloroformate to give a compound of Formula I wherein R^1 is (C_1-C_6)alkoxycarbonylamino(C_1-C_6)alkyl.

(12) a compound of Formula I wherein R^1 is amino(C_1-C_6)alkyl can be reacted with chlorosulfonyl isocyanate or sulfamide to give a compound of Formula I wherein R^1 is aminosulfonylamino(C_1-C_6)alkyl.

(13) a compound of Formula I wherein R^1 is amino(C_1-C_6)alkyl can be reacted with a (C_1-C_6)alkylsulfamoyl chloride to give a compound of Formula I wherein R^1 is (C_1-C_6)alkylaminosulfonylamino(C_1-C_6)alkyl.

(14) a compound of Formula I wherein R^1 is hydroxy(C_1-C_6)alkyl can be reacted with chlorosulfonyl isocyanate to give a compound of Formula I wherein R^1 is aminosulfonyloxy(C_1-C_6)alkyl.

(15) a compound of Formula I wherein R^1 is hydroxy(C_1-C_6)alkyl can be reacted with p-nitrophenyl chloroformate, pentafluorophenyl chloroformate or carbonyl diimidazole, followed by ammonia, a (C_1-C_6)alkylamine or a di(C_1-C_6)alkylamine to give a compound of Formula I wherein R^1 is aminocarboxy(C_1-C_6)alkyl, (C_1-C_6)alkyl aminocarboxy(C_1-C_6)alkyl or di(C_1-C_6)alkyl aminocarboxy(C_1-C_6)alkyl.

(16) a compound of Formula I wherein R^1 is hydroxy(C_1-C_6)alkyl can be reacted with $POCl_3$ to give a compound of Formula I wherein R^1 is $(HO)_2P(=O)O(C_1$-$C_6)$alkyl.

(17) a compound of Formula I wherein Cy^1 is substituted with bromine or iodine, A^2 is a bond and Cy^2 is hydrogen can be reacted with a cyclic amine in the presence of a palladium catalyst to give a compound of Formula I wherein A^2 is a bond and Cy^2 is a cyclic amino moiety attached through its nitrogen atom.

(18) a compound of Formula I wherein Q is NR^5 and R^5 is H can be reacted with an (C_1-C_6)alkyl halide in the presence of a strong base such as sodium hydride to afford a compound of Formula I wherein Q is NR^5 and R^5 is (C_1-C_6)alkyl.

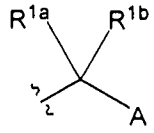
(19) a compound of Formula I wherein R^1 ω-$H_2NCO(C_1$-$C_5)$alkyl can be reacted with TFAA in the presence of pyridine to afford a compound of Formula I wherein R^1 is ω-cyano(C_1-C_5)alkyl.

(20) a compound of Formula I, wherein R^1 is ω-$MeO_2C(C_1$-$C_5)$alkyl can be reacted with at least 2 equivalents of MeMgBr to afford a compound of Formula I, wherein R^1 or $HOC(Me)_2(C_1$-$C_5)$alkyl.

(21) a compound of Formula I wherein R^1 is ω-hydroxy(C_1-C_6)alkyl can be converted to its methanesulfonate or trifluoromethanesulfonate and reacted with

morpholine to give a compound of Formula I, wherein R^1 is ω-(4-morpholino)(C_1-C_6)alkyl.

The synthetic methods described above are generally applicable when R is



PURIFICATION METHODS

Compounds of the invention can be purified by high pressure liquid chromatography (prep HPLC). Unless otherwise specified, prep HPLC refers to preparative reverse phase HPLC on a C-18 column eluted with a water/acetonitrile gradient containing 0.01% TFA run on a Gilson 215 system.

LC-MS METHODS

Method 1 [LC-MS (3 min)]

Column: Chromolith SpeedRod, RP-18e, 50 x 4.6 mm; Mobil phase: A: 0.01%TFA/water, B: 0.01%TFA/CH_3CN; Flow rate: 1 mL/min; Gradient:

Time (min)	A%	B%
0.0	90	10
2.0	10	90
2.4	10	90
2.5	90	10
3.0	90	10

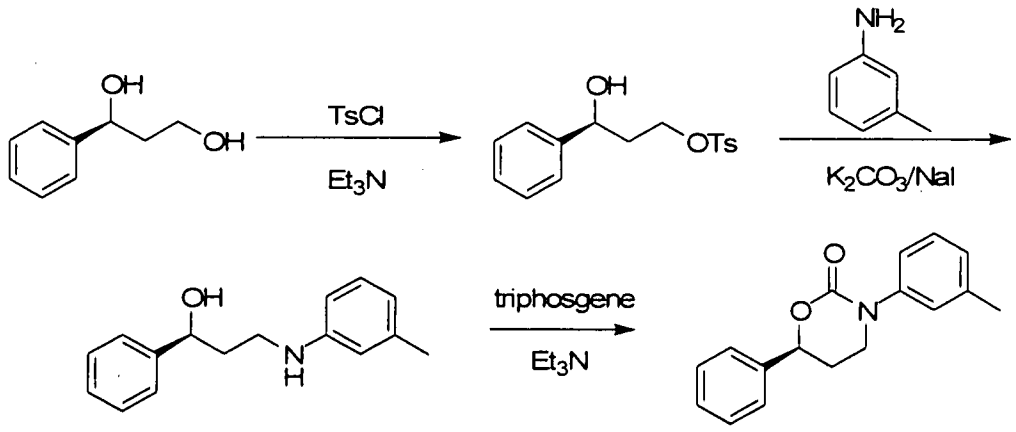
Method 2 (10-80)

Column	YMC-PACK ODS-AQ , 50×2.0mm 5μm
Mobile Phase	A: water (4 L) + TFA (1.5 mL)) B: acetonitrile (4 L) + TFA (0.75 mL))

	TIME(min)	A%	B%
	0	90	10
	2.2	20	80
	2.5	20	80
Flow Rate	1mL/min		
Wavelength	UV 220 nm		
Oven Temp	50 °C		
MS ionization	ESI		

EXAMPLE 1

(S)-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one



Step 1

To a solution of (*S*)-1-phenylpropane-1,3-diol (500 mg, 3.28 mmol) and triethylamine (399 mg, 3.94 mmol) in CH_2Cl_2 (5 mL) was added 4-methylbenzene-1-sulfonyl chloride (626 mg, 3.28 mol) slowly at 0 °C, and the reaction mixture was stirred at rt for 2 h. The reaction solution was dried over Na_2SO_4 and concentrated to give the crude product, which was purified by preparative TLC (3:1 Petroleum ether/EtOAc) to give (*S*)-3-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate (576 mg, 57%). ^1H NMR (400MHz, $CDCl_3$): δ=1.91-2.00 (m, 3H), 2.48 (s, 2H), 4.00 (m, 1H), 4.22 (m, 1H), 4.75 (m, 2H), 7.25-7.30 (m, 7H), 7.75 (d, 2H).

Step 2

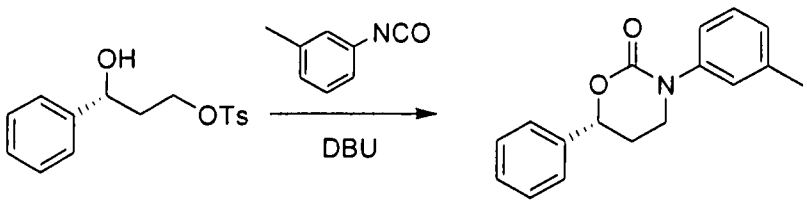
To a solution of the (*S*)-3-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate (100 mg, 0.33 mmol) in anhydrous acetonitrile (2 mL) were added K_2CO_3 (91 mg, 0.66mmol), NaI (12mg, 0.0825 mmol) and m-toluidine (42mg, 0.39mmol). The mixture was refluxed overnight. The mixture was filtered, and the filter cake was washed with EtOAc. The filtrate was concentrated to give the crude product, which was purified by preparative TLC (3:1 Petroleum ether/EtOAc) to give (*S*)-3-(m-tolylamino)-1-phenylpropan-1-ol (45 mg, 57%). ^{1}H NMR (400MHz, $CDCl_3$): δ= 2.05 (m, 2H), 2.25 (s, 3H), 3.25 (m, 2H), 3.40 (s, 2H), 4.90 (m, 1H), 6.50 (m, 4H), 7.05(m, 1H), 7.30 (m, 1H), 7.40 (d, 3H).

Step 3

To a solution of (S)-3-(m-tolylamino)-1-phenylpropan-1-ol (40 mg, 0.17 mmol) in dry CH_2Cl_2 (1 mL) was added triethylamine (50 mg, 0.51 mmol) and bis(trichloromethyl) carbonate (20 mg, 0.067 mmol) at 0 °C, and the reaction mixture was stirred overnight at room temperature. When the reaction was over, the mixture was concentrated to give the crude product, which was purified by preparative TLC (3:1 Petroleum ether/EtOAc) to give (S)-6-phenyl-3-m-tolyl-1,3-oxazinan -2-one (12 mg, 26%). ^{1}H NMR: (400MHz, $CDCl_3$): δ= 2.24-2.37 (m, 5H), 3.52-3.63 (m, 1H), 3.70-3.79 (m, 1H), 5.42 (dd, 1 H), 7.01-7.10 (m, 3H), 7.18-7.23 (m, 2H), 7.32-7.39 (m, 4H).

EXAMPLE 2

(R)-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one

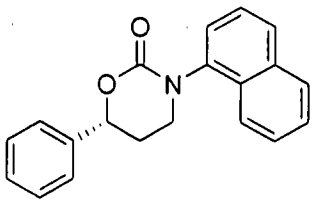


To a solution of (*R*)-3-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate (100 mg, 0.327 mmol) and 1-isocyanato-3-methylbenzene (44 mg, 0.327 mmol) in CH_2Cl_2 (2 mL) was added DBU (149 mg, 0.981 mmol) and the reaction mixture was refluxed

overnight. After the solvent was removed under reduced pressure, the residue was separated by preparative HPLC to give (*R*)-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one (5.34 mg, 6%:). LC-MS (10-80) t_R = 2.439 min, m/z = 268; ^{1}H NMR ($CDCl_3$): 2.30-2.34 (m, 5H), 3.63-3.68 (m, 1H), 3.80-3.86 (m, 1H), 5.49 (dd, 1 H), 7.09-7.45 (m, 9H).

EXAMPLE 3

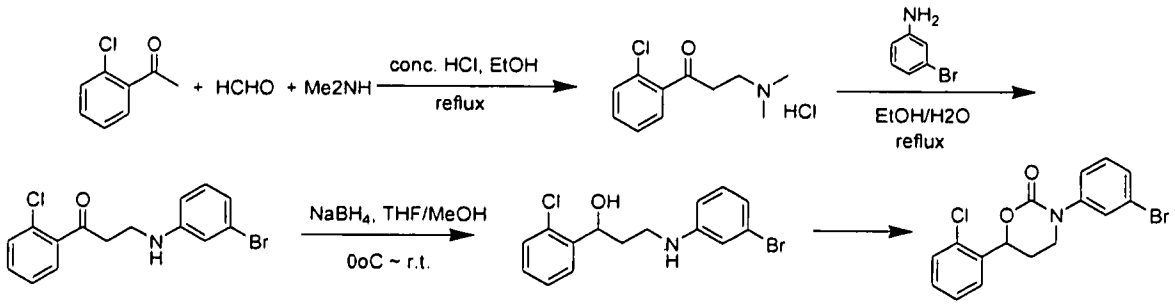
(R)-3-(naphthalen-1-yl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following a procedure analogous to that described in Example 2 using (*R*)-3-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate and 1-isocyanatonaphthalene. LC-MS (10-80) t_R = 2.625 min, m/z = 304; ^{1}H NMR ($CDCl_3$) δ 2.44-2.55 (m, 3H), 3.64-3.69 (m, 1H), 3.84-3.91 (m, 1H), 5.62-5.72 (m, 1 H), 7.38-7.61 (m, 9H), 7.86-7.93 (m, 3H).

EXAMPLE 4

3-(3-bromophenyl)-6-(2-chlorophenyl)-1,3-oxazinan-2-one



Step 1

At 0°C, concentrated HCl was added dropwise to Me_2NH (40% in water, 5.57mL, 1.1 equiv) to acidify the amine. After the addition, 1-(2-chlorophenyl)ethanone (6.18g, 0.04mol) and paraformaldehyde (1.68g, 1.4 equiv) were added. The mixture was dissolved in ethanol (20mL) and heated to reflux for 30 h. LC-MS found the starting material was gone. The reaction mixture was cooled to rt. The volatiles were removed *in vacuo*. EtOAc (30mL) was added and the

suspension was stirred for 15 min. The solid was collected by filtration and washed with EtOAc (2 xX 5 mL). The white solid was dried under vacuum to afford 1-(2-chlorophenyl)-3-(dimethylamino)propan-1-one HCl salt (5.17g, 61% yield). LC-MS (3min) t_R = 0.72 min, m/z 212, 214(M+1).

Step 2

A solution of 1-(2-chlorophenyl)-3-(dimethylamino)propan-1-one HCl salt (5.17g, 20.85mmol) and 3-bromoaniline (2.27mL, 1equiv) in 1:1 ethanol/water (21 mL, 1.0M) was heated at reflux overnight. LC-MS found the starting material was gone. The reaction mixture was cooled to rt. The ethanol was removed *in vacuo*. The residue was partitioned between EtOAc and water. The organic layer was washed with 1% aq HCl (2 x 30 mL), satd aq $NaHCO_3$ solution (20mL), brine (20mL), and dried over Na_2SO_4. After filtration and concentration, the residue (6.08g) was purified by chromatography on a 120-g silica cartridge to afford 3-(3-bromophenylamino)-1-(2-chlorophenyl)propan-1-one (2.75g, 40% yield) as an orange oil. LC-MS (3 min) t_R = 2.03 min, m/z = 340, 341(M+1); ^{1}H NMR ($CDCl_3$) δ 7.47(d, 1H), 7.44-7.38(m, 2H), 7.33(td, 1H), 7.00(m, 1H), 6.84(m, 1H), 6.77(s, 1H), 6.56(m, 1H).

Step 3

A solution of 3-(3-bromophenylamino)-1-(2-chlorophenyl)propan-1-one (50mg, 0.148 mmol) in 4:1 THF/methanol (5 mL) was cooled to 0 °C. $NaBH_4$ (11mg, 2equiv) was added. After 10 min, the mixture was warmed up to rt slowly and stirred for 2 h. The mixture was concentrated, diluted with EtOAc (7 mL), washed with 1% aq HCl (1mL), and dried over Na_2SO_4. Filtration and concentration afforded crude 3-(3-bromophenylamino)-1-(2-chlorophenyl)propan-1-ol which was used without further purification. LC-MS (3 min) t_R = 1.93 min, m/z = 342,343(M+1).

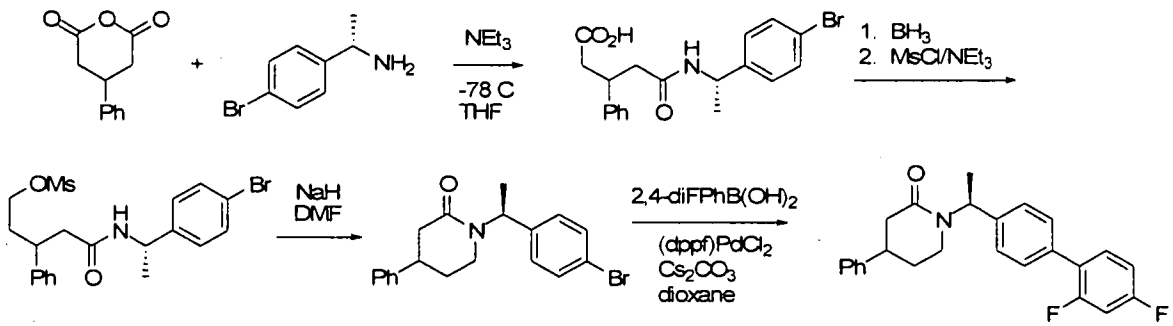
Step 4

Half of the crude 3-(3-bromophenylamino)-1-(2-chlorophenyl)propan-1-ol (0.074 mmol) was mixed with triphosgene (7.5mg, 0.34 equiv), i-Pr_2NEt (26μL, 2equiv), pyridine (30μL, 5 equiv) and acetonitrile (5mL). The mixture was put in the microwave oven for 30 min at 110 °C. LC-MS found the reaction completed. The mixture was concentrated, redissolved in EtOAc (5mL), washed with 1% aq HCl (2 x

2mL), concentrated and purified by preparative HPLC to afford 3-(3-bromo-phenyl)-6-(2-chloro-phenyl)-[1,3]oxazinan-2-one (15.2 mg). LC-MS (3min) t_R = 1.86 min., m/z 368,369(M+1). ^{1}H NMR ($CDCl_3$) δ 7.63(d, 1H), 7.56(s, 1H), 7.43-7.26(m, 6H), 5.83(d, 1H), 3.88(q, 1H), 3.67(m, 1H), 2.55(d, 1H), 2.17(m, 1H).

EXAMPLE 5

1-((1S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-4-phenylpiperidin-2-one



Step 1

3-Phenylglutaric anhydride (1.0 g, 5.26 mmol, 1.0 equiv) was dissolved in toluene (42 mL) and the solution cooled to -78 °C under an N_2 atmosphere. In a separate flask triethylamine (0.75 mL, 542 mg, 5.35 mmol, 1.05 equiv) and (R)-1-(4-bromophenyl)ethanamine (1163 mg, 5.79 mmol, 1.25 equiv) were dissolved in 21 mL of toluene and this solution added drop-wise via syringe over a 0.5 h period and the resulting solution was allowed to stir overnight while warming to rt. After this time 1.0 M aq HCl (~50 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated and the organic layer washed with brine, dried over Na_2SO_4, filtered and evaporated. The resulting 5-((S)-1-(4-bromophenyl)ethylamino)-5-oxo-3-phenylpentanoic acid (1.92g, 93%) was of sufficient purity to use in the next step.

Step 2

5-((S)-1-(4-bromophenyl)ethylamino)-5-oxo-3-phenylpentanoic acid (1.92 g, 4.92 mmol, 1.0 equiv) was dissolved in THF (30 mL) and the resulting solution cooled to 0 °C. Borane (1.0 M in THF, 10.5 mL, 10.5 mmol, 2.1 equiv) was added via syringe. After 0.5 h LC-MS showed formation of the alcohol. The excess borane

was quenched by the drop-wise addition of 1.0 M aq HCl and the mixture was transferred to a separatory funnel. The layers were separated and the organic layer washed with brine, dried over Na_2SO_4, filtered and evaporated. The resulting N-((S)-1-(4-bromophenyl)ethyl)-5-hydroxy-3-phenylpentanamide (~1.9 g, >95% yield) was of sufficient purity to use in the next step.

Step 3

N-((S)-1-(4-bromophenyl)ethyl)-5-hydroxy-3-phenylpentanamide (~1.9 g, 5 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. Methanesulfonyl chloride (1.15 g, 10 mmol, 2.0 equiv) and triethylamine (2.1 g, 20 mmol, 4.0 equiv) were added sequentially and the resulting mixture stirred for 1 h. After this time LC-MS analysis showed consumption of the starting alcohol. The mixture was transferred to a separatory funnel and the organic layer was washed with 0.1 M aq HCl and brine, dried over Na_2SO_4, filtered and evaporated. The mesylate was purified by flash chromatography on silica, eluting with 0-47% EtOAc in hexanes. This provided 5-((S)-1-(4-bromophenyl)ethylamino)-5-oxo-3-phenylpentyl methanesulfonate (834 mg, 37%).

Step 4

Sodium hydride (60% in oil, 294 mg, 7.4 mmol, 4.0 equiv) was slurried in DMF (10 mL) and cooled to 0 °C. 5-((S)-1-(4-bromophenyl)ethylamino)-5-oxo-3-phenylpentyl methanesulfonate (834 mg, 1.8 mmol, 1.0 equiv) was dissolved in DMF (5 mL) and the solution added via syringe to the NaH slurry. The flask was rinsed with DMF and the mixture was stirred for 2 h. After this time the mesylate was consumed. The DMF was removed and the residue was taken up in EtOAc/H_2O. The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. The lactam was purified by flash chromatography to provide 1-((S)-1-(4-bromophenyl)ethyl)-4-phenylpiperidin-2-one (291 mg, 81%).

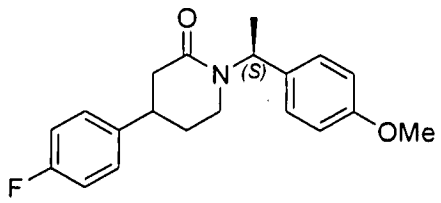
Step 5

1-((S)-1-(4-bromophenyl)ethyl)-4-phenylpiperidin-2-one (291 mg, 0.813 mmol, 1.0 equiv), $PdCl_2$(dppf) (17 mg, 0.020 mmol, 2.5 mol%), Cs_2CO_3 (530 mg, 1.63 mmol. 2.0 equiv), and 2,4-difluorophenylboronic acid (194 mg, 1.72 mmol, 1.5 equiv) were added to a flask which was evacuated and back-filled with nitrogen, This was

repeated twice. Dioxane (20 mL) was added and the red mixture heated to 70 °C under nitrogen for 17 h. After this time LC-MS showed formation of the biaryl. The mixture diluted with EtOAc/H_2O and transferred to a separatory funnel. The organic layer washed with brine, dried over Na_2SO_4, filtered and evaporated. The biaryl was purified by flash chromatography. A small portion was purified by prep HPLC to provide the above biaryl-lactam as a mixture of epimers. LC-MS (3 min): t_R = 2.13 min, m/z = 392. ^{1}H NMR (CD_3OD): δ 7.54-7.42 (m, 5H), 7.32-7.20 (m, 5H), 7.07-7.02 (m, 2H), 6.08 (q, J = 7.0 Hz, 1H), 3.28 (m, 1H), 3.07 (m, 1H), 2.89 (m, 1H), 2.75 (m, 1H), 2.58 (m, 1H), 2.0 (m, 2H), 1.56 (d, J = 7 Hz, 3H) ppm. The methyl group of the minor diastereomer, ~10%, is observed at 1.61 ppm with a similar coupling constant. ^{19}F NMR (CD_3OD): δ -113.8 ("sept"), -115,8 ("q").

EXAMPLE 6

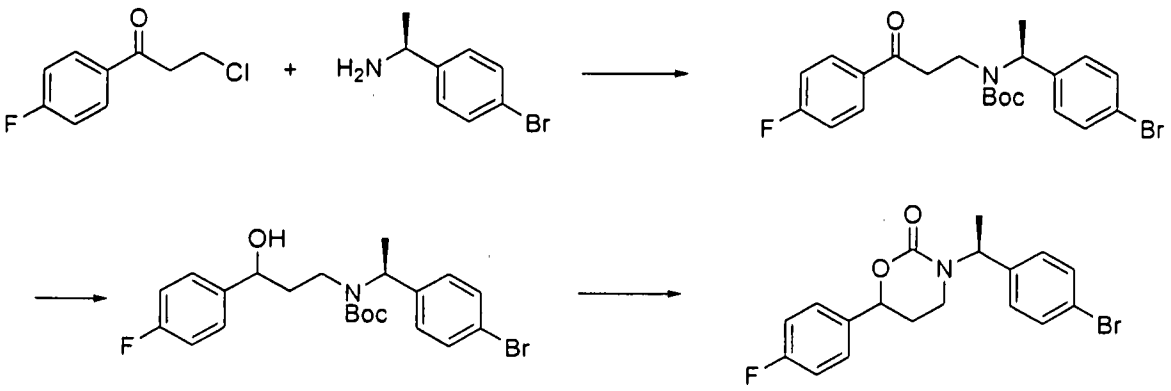
4(-4-fluorophenyl)-1-((1S)-1-(4-methoxylphenyl)ethyl)piperidin-2-one



The title compound was prepared following procedures analogous to those described in Example 5 Step 1-4 using 3-(4-fluorophenylglutaric anhydride and (S)-1-(4-methoxyphenyl)ethanamine in Step 1. LC-MS (3 min): t_R = 1.79 min, m/z = 350. ^{1}H NMR (CD_3OD): 7.25 (m, 4H), 7.01 (m, 2H), 6.90 (m, 2), 5.99 (bt, 1H), 3.76 (s, 3H), 3.1-2.2 (m, 2H), 2.74 (m, 1H), 2.54 (m, 2H), 1.98-1.82 (m, 2H), 1.53 and 1.48 (d, J = 7Hz, 3H). The two diastereomers are observed in ~2:1 ratio. ^{19}F NMR (CD_3OD): δ -119.

EXAMPLE 7

3-((1S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one



Step 1

To a stirred solution of 3-chloro-1-(4-fluorophenyl)propan-1-one (789 mg, 4.23 mmol) and i-Pr_2NEt (0.91 mL, 5.1 mmol) in THF (10 mL) was added (S)-1-(4-bromophenyl)ethanamine (0.68 mL, 4.65 mmol). The mixture was stirred overnight at rt and 10% aq K_2CO_3 (10 mL) and di-tert-butyl dicarbonate (1.38 g, 6.35 mmol) were added. The mixture was stirred overnight at rt and concentrated under reduced pressure. The aqueous residue was extracted with ether (100 mL). The ether extract was washed with 5% aq HCl (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL), and dried over Na_2SO_4. Removal of the solvent left an oil (3.77 g) which was purified by chromatography on a 40-g silica gel cartridge eluted with a 0-60% EtOAc in hexanes gradient to afford (S)-tert-butyl 1-(4-bromophenyl)ethyl(3-(4-fluorophenyl)-3-oxopropyl)carbamate (2.04 g, quant) as a waxy solid. LC-MS (3 min) t_R = 2.35 min, m/z = 474, 472, 452, 450, 352, 350.

Step 2

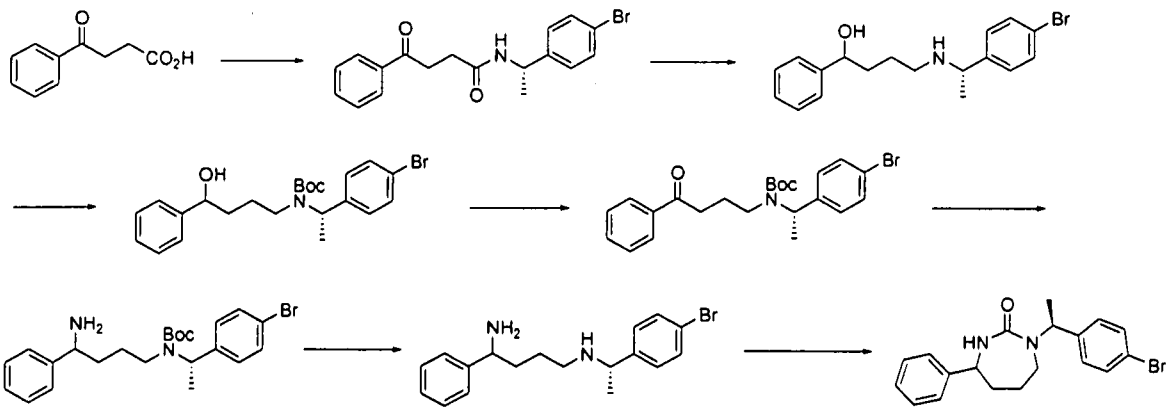
To a stirred solution of (S)-tert-butyl 1-(4-bromophenyl)ethyl(3-(4-fluorophenyl)-3-oxopropyl)carbamate (500 mg, 1.11 mmol) in MeOH (20 mL) was added an $NaBH_4$ caplet (1 g, 26 mmol). The mixture was stirred at rt overnight and concentrated under reduced pressure. The residue was partitioned between EtOAc (80 mL) and water (20 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to leave tert-butyl (S)-1-(4-bromophenyl)ethyl(3-(4-fluorophenyl)-3-hydroxypropyl)carbamate (474 mg, 94%) as an oil. LC-MS (3 min) t_R = 2.33 min, 454. 452, 380, 378.

Step 3

To a stirred solution of tert-butyl (S)-1-(4-bromophenyl)ethyl(3-(4-fluorophenyl)-3-hydroxypropyl)carbamate (474 mg, 1.05 mmol) in dry THF (10 mL) was added 60% NaH in oil (250 mg, 10.4 mmol). The mixture was heated at reflux for 3 h. The mixture was diluted with water (20 mL) and EtOAc (80 mL). The organic layer was separated, washed with 5% aq HCl (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL), and dried over Na_2SO_4. Removal of the solvent left an oil (348 mg). A portion of the crude product was purified by preparative HPLC to afford 3-((1S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one as a 2:1 mixture of diastereomers based on ^1H NMR. LC-MS (3 min) t_R = 1.92 min, m/z = 380, 378. ^1H NMR ($CDCl_3$) δ [selected resonances of major and minor diastereomers] 1.52 (d, major), 1.59 (d, minor), 3.06 (m, major), 3.31 (m, minor), 5.20 (dd, major), 5.25 (dd, minor).

EXAMPLE 8

1-((S)-1-(4-bromophenyl)ethyl)-4-phenyl-1,3-diazepan-2-one



Step 1

To a stirred solution of benzoylpropionic acid (2.00 g, 11.2 mmol), (S)-1-(4-bromophenyl)ethanamine (2.25 g, 11.2 mmol), HOBt (1.72 g, 11.2 mmol) and i-Pr_2NEt (2.2 mL, 12.3 mmol) in CH_2Cl_2 (40 mL) was added EDC.HCl (2.37 g, 12.3 mmol). The mixture was stirred at rt for 4 h and diluted with EtOAc (140 mL) and 5% aq HCl (50 mL). The mixture was filtered and (S)-N-(1-(4-bromophenyl)ethyl)-4-oxo-4-phenylbutanamide (3.80 g, 93%) was collected as a white solid. ^1H NMR (d_6-DMSO) δ 1.28 (d, 3H), 2.50 (m, 2H), 3.19 (m, 2H), 4.82 (m, 1H), 7.23 (d, 2H), 7.47 (4H), 7.59 (m, 1H), 7.92 (d, 2H), 8.38 (d, 1H).

Step 2

A 250-mL RBF equipped with a magnetic stirbar was charged with solid (S)-N-(1-(4-bromophenyl)ethyl)-4-oxo-4-phenylbutanamide (2.85 g, 7.9 mmol) and placed in an ice bath. To the stirred solid was added 1.0 M BH_3 in THF (30 mL, 30 mmol). The ice bath was removed and the mixture was stirred at rt for 2.5 h. The mixture was poured into 5% aq HCl (100 mL) and concentrated under reduced pressure to remove the THF. The aqueous residue was basified to pH 14 by portionwise addition of NaOH pellets. The mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined CH_2Cl_2 extracts were dried over Na_2SO_4. Removal of the solvent afforded crude 4-((S)-1-(4-bromophenyl)ethylamino)-1-phenylbutan-1-ol (2.58 g, 94%) as an oil. LC-MS Method 1 t_R = 1.20 min, m/z = 348, 350.

Step 3

To a stirred solution of crude 4-((S)-1-(4-bromophenyl)ethylamino)-1-phenylbutan-1-ol (2.46 g, 7.1 mmol) in THF (40 mL) was added 10% aq K_2CO_3 (40 mL), followed by di-t-butyl dicarbonate (1.90 g, 8.5 mmol). The mixture was stirred overnight at rt and concentrated to remove THF. The aqueous residue was extracted with EtOAc (2 x 80 mL). The combined EtOAc extracts were washed with brine (40 mL) and dried over $MgSO_4$. Removal of the solvent left tert-butyl (S)-1-(4-bromophenyl)ethyl(4-hydroxy-4-phenylbutyl)carbamate (3.24 g, quant). LC-MS Method 1 t_R = 1.20 min, m/z = 472, 470, 350, 348.

Step 4

To a stirred solution of tert-butyl (S)-1-(4-bromophenyl)ethyl(4-hydroxy-4-phenylbutyl)carbamate (3.24 g, 7.1 mmol) in CH_2Cl_2 (20 mL) at rt was added 15% Dess-Martin periodinane solution in CH_2Cl_2 (23 mL, 10.8 mmol). The mixture was stirred overnight at rt. Satd aq $NaHCO_3$ (50 mL) was added and the mixture was stirred for 10 min. Solid $Na_2S_2O_3$ (5 g) was added and stirring was continued for 1 h. The mixture was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic layer was washed with brine (35 mL) and dried over Na_2SO_4. Removal of the solvent left an amber oil (3.19 g) which was purified by chromatography on a 40-g silica cartridge eluted with a 0-100% EtOAc in hexanes gradient to afford (S)-tert-butyl 1-(4-

bromophenyl)ethyl(4-oxo-4-phenylbutyl)carbamate (2.32 g, 72%) as a yellow oil. LC-MS Method 1 t_R = 2.40 min, m/z = 470, 468, 348, 346.

Step 5

To a stirred solution of (S)-tert-butyl 1-(4-bromophenyl)ethyl(4-oxo-4-phenylbutyl)carbamate (193 mg, 0.43 mmol) and NH_4OAc (670 mg, 8.6 mmol) in MeOH (15 mL) was added $NaCNBH_3$ (270 mg, 4.3 mmol). The mixture was heated at reflux for 22 h and concentrated under reduced pressure. The residue was partitioned between 1 M aq NaOH (25 mL) and CH_2Cl_2 (2 x 50 mL). The combined CH_2Cl_2 layers were washed with brine (15 mL), dried over Na_2SO_4 and concentrated to afford tert-butyl 4-amino-4-phenylbutyl((1S)-1-(4-bromophenyl)ethyl)carbamate (179 mg, 93%) as an oil which was used without further purification. LC-MS Method 1 t_R = 1.57 min, m/z = 449, 447.

Step 6

To a stirred solution of tert-butyl 4-amino-4-phenylbutyl((1S)-1-(4-bromophenyl)ethyl)carbamate (179 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) at rt was added 4 M HCl in dioxane (5 mL). The mixture was stirred for 1 h and concentrated to afford N^1-((1S)-1-(4-bromophenyl)ethyl)-4-phenylbutane-1,4-diamine dihydrochloride (162 mg, 96%). LC-MS Method 1 t_R = 0.92 min, m/z = 349, 347.

Step 7

A stirred solution of N^1-((1S)-1-(4-bromophenyl)ethyl)-4-phenylbutane-1,4-diamine dihydrochloride (19.5 mg, 0.046 mmol) and i-Pr_2NEt (0.10 mL, 0.56 mmol) in CH_2Cl_2 (8 mL) was cooled in an ice bath and solid triphosgene (4.6 mg, 0.015 mmol) was added. The ice bath was allowed to melt and the mixture was stirred overnight at rt. The mixture was diluted with ether (90 mL), washed with 5% aq HCl (20 mL) and satd aq $NaHCO_3$ (20 mL), and dried over $MgSO_4$. Removal of the solvent left a residue (17.5 mg) which was purified by preparative HPLC to afford 1-((S)-1-(4-bromophenyl)ethyl)-4-phenyl-1,3-diazepan-2-one (1.4 mg, 8%). LC-MS (3 min) t_R = 2.05 min, m/z = 375, 373.

BIOLOGICAL TEST EXAMPLE 1

The inhibition of microsomal preparation of 11β-HSD1 by compounds of the invention was measured essentially as previously described (K. Solly, S.S. Mundt, H.J. Zokian, G.J. Ding, A. Hermanowski-Vosatka, B. Strulovici, and W. Zheng, High-Throughput Screening of 11-Beta-Hydroxysteroid Dehydrogenase Type 1 in Scintillation Proximity Assay Format. Assay Drug Dev Technol 3 (2005) 377-384). All reactions were carried out at rt in 96 well clear flexible PET Microbeta plates (PerkinElmer). The assay begins by dispensing 49 µl of substrate solution (50mM HEPES, pH 7.4, 100mM KCl, 5mM NaCl, 2mM $MgCl_2$, 2 mM NADPH and 160 nM [^{3}H]cortisone (1 Ci/mmol)) and mixing in 1 µL of the test compounds in DMSO previously diluted in half-log increments (8 points) starting at 0.1 mM. After a 10 minute pre-incubation, 50 µL of enzyme solution containing microsomes isolated from CHO cells overexpressing human 11β-HSD1 (10-20 µg/ml of total protein) was added, and the plates were incubated for 90 minutes at rt. The reaction was stopped by adding 50 µl of the SPA beads suspension containing10 µM 18β-glycyrrhetinic acid, 5 mg/ml protein A coated YSi SPA beads (GE Healthcare) and 3.3 µg/ml of anti-cortisol antibody (East Coast Biologics) in Superblock buffer (Bio-Rad). The plates were shaken for 120 minutes at rt, and the SPA signal corresponding to [^{3}H]cortisol was measured on a Microbeta plate reader.

BIOLOGICAL TEST EXAMPLE 2

The inhibition of 11β-HSD1 by compounds of this invention was measured in whole cells as follows. Cells for the assay were obtained from two sources: fully differentiated human omental adipocytes from Zen-Bio, Inc.; and human omental pre-adipocytes from Lonza Group Ltd. Pre-differentiated omental adipocytes from Zen-Bio Inc. were purchased in 96-well plates and were used in the assay at least two weeks after differentiation from precursor preadipocytes. Zen-Bio induced differentiation of pre-adipocytes by supplementing medium with adipogenic and lipogenic hormones (human insulin, dexamethasone, isobutylmethylxanthine and PPAR-gamma agonist). The cells were maintained in full adipocyte medium (DMEM/Ham's F-12 (1:1, v/v), HEPES pH 7.4, fetal bovine serum, penicillin, streptomycin and Amphotericin B, supplied by Zen-Bio, Inc.) at 37°C, 5% CO_2.

Pre-adipocytes were purchased from Lonza Group Ltd. and placed in culture in Preadipocyte Growth Medium-2 supplemented with fetal bovine serum, penicillin, and streptomycin (supplied by Lonza) at 37°C, 5% CO_2. Pre-adipocytes were

differentiated by the addition of insulin, dexamethasone, indomethacin and isobutyl-methylxanthine (supplied by Lonza) to the Preadipocyte Growth Medium-2. Cells were exposed to the differentiating factors for 7 days, at which point the cells were differentiated and ready for the assay. One day before running the assay, the differentiated omental adipocytes were transferred into serum- and phenol-red-free medium for overnight incubation. The assay was performed in a total volume of 200 µL. The cells were pre-incubated with serum-free, phenol-red-free medium containing 0.1% (v/v) of DMSO and various concentrations of the test compounds at least 1 h before [^{3}H] cortisone in ethanol (50Ci/mmol, ARC, Inc.) was added to achieve a final concentration of cortisone of 100 nM. The cells were incubated for 3-4 hrs at 37°C, 5% CO_2. Negative controls were incubated without radioactive substrate and received the same amount of [^{3}H] cortisone at the end of the incubation. Formation of [^{3}H] cortisol was monitored by analyzing 25 µL of each supernatant in a scintillation proximity assay (SPA). (Solly, K.; Mundt, S. S.;Zokian, H.J.;Ding, G. J.; Hermanowski-Vosatka, A.; Strulovici, B.; Zheng, W. Assay Drug Dev. Technol. 2005, 3, 377-384). Many compounds of the invention showed significant activity in this assay.

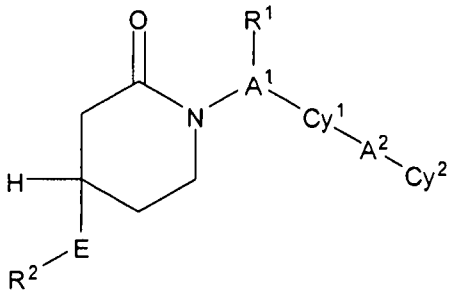
TABLE OF BIOLOGICAL ASSAY RESULTS

Compound	Biological Test Example 1		
	IC_{50} Range[a]	Average % inhibition at 100 nM	Average % inhibition at 111.1 nM
EXAMPLE 1	+	13.7	
EXAMPLE 2	+		27.2
EXAMPLE 3	+		-5.9
EXAMPLE 4	+		22.5
EXAMPLE 5	++	94.5	
EXAMPLE 6	++	89.4	

EXAMPLE 7	++	90.1
EXAMPLE 8	++	100.3

[a] ++ means IC_{50} = <100 nM, + means IC_{50} = 100 – 1000 nM, # means IC_{50} > 100 nM, - means IC_{50} > 1000 nM.

PROPHETIC COMPOUNDS



Compound No	A^1-R^1	Cy^1	A2	Cy^2	E	R^2
1a	CHMe	Ph	bond	H	bond	Ph
2a	CHMe	4-Cl-Ph	bond	H	bond	i-Pr
3a	CHMe	Ph	bond	H	bond	2-Me-Ph
4a	CHMe	Ph	bond	H	bond	4-Me-Ph
5a	CHMe	Ph	bond	H	bond	4-F-Ph
6a	CHMe	c-hex	bond	H	bond	4-F-Ph
7a	CHMe	3-MeO-Ph	bond	H	bond	Ph
8a	CHMe	4-$HOCH_2$-Ph	bond	H	bond	Ph
9a	CHMe	4-MeO-Ph	bond	H	bond	Ph

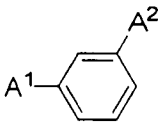
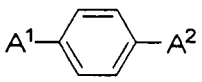
10a	CHMe	4-Me-Ph	bond	H	bond	4-F-Ph
11a	CHMe	4-Cl-Ph	bond	H	bond	Ph
12a	CHMe	3-F-Ph	bond	H	bond	4-F-Ph
13a	CHMe	2-F-Ph	bond	H	bond	4-F-Ph
14a	CHMe	4-F-Ph	bond	H	bond	4-F-Ph
15a	CHMe	4-$HOCH_2CH_2$-Ph	bond	H	bond	Ph
16a	CHMe	4-$MeOCH_2$-Ph	bond	H	bond	Ph
17a	CHMe	4-Br-Ph	bond	H	bond	i-Pr
18a	CHMe	Ph	bond	H	bond	4-MeS-Ph
19a	CHMe	4-$HOCH_2$-Ph	bond	H	bond	4-F-Ph
20a	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph
21a	bond	1,3-C_6H_4	bond	Ph	bond	Ph
22a	bond	3-Br-Ph	bond	H	bond	Ph
23a	CHMe	4-Cl-Ph	bond	H	bond	4-F-Ph
24a	CHMe	1,4-C_6H_4	bond	c-Pr	bond	4-F-Ph
25a	bond	1-(t-BuOC=O)pyrrolidin-3-yl	bond	H	bond	Ph
26a	bond	1,3-C_6H_4	bond	3-F-Ph	bond	Ph
27a	bond	1,3-C_6H_4	bond	4-F-Ph	bond	Ph
28a	bond	1,3-C_6H_4	bond	2-F-Ph	bond	Ph
29a	CHMe	Ph	bond	3-pyrazolyl	bond	Ph
30a	bond	2,6-pyridyl	bond	4-F-Ph	bond	Ph
31a	CHMe	4-$(HOC(Me)_2CH_2$-Ph	bond	H	bond	Ph

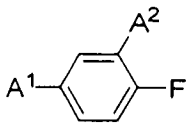
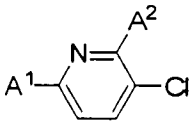
32a	bond	1,3-C_6H_4	bond	2-NC-Ph	bond	Ph
33a	CHMe	4-MeO_2C-Ph	bond	H	bond	4-F-Ph
34a	CHMe	4-$HOC(Me)_2$-Ph	bond	H	bond	4-F-Ph
35a	CHMe	1,4-C_6H_4	bond	4-pyridyl	bond	Ph
36a	CHMe	1,4-C_6H_4	bond	3-pyridyl	bond	Ph
37a	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	i-Pr
38a	bond	1,3-C_6H_4	bond	2-MeO-Ph	bond	Ph
39a	CHMe	4-Br-Ph	bond	H	bond	Ph
40a	CHMe	1,4-C_6H_4	bond	2-thienyl	bond	Ph
41a	bond	1,3-C_6H_4	bond	2-Cl-Ph	bond	Ph
42a	bond	1,3-C_6H_4	bond	3-Cl-Ph	bond	Ph
43a	bond	1,3-C_6H_4	bond	Ph	bond	3-Cl-Ph
44a	CHMe	4-F2HCO-Ph	bond	H	bond	4-F-Ph
45a	bond	1,3-C_6H_4	bond	2,5-diF-Ph	bond	Ph
46a	bond	1,3-C_6H_4	bond	3,5-diF-Ph	bond	Ph
47a	bond	1,3-C_6H_4	bond	2,4-diF-Ph	bond	Ph
48a	bond	1,3-C_6H_4	bond	4-F-Ph	bond	Ph
49a	CHMe	4-Br-Ph	bond	H	bond	2-thienyl
50a	bond	1,3-C6H4	bond	2,4-diF-Ph	bond	2-pyridyl
51a	bond	2,6-pyridyl	bond	4-F-Ph	bond	4-F-Ph
52a	bond	2,6-pyridyl	bond	4-F-Ph	bond	2-F-Ph
53a	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	Ph

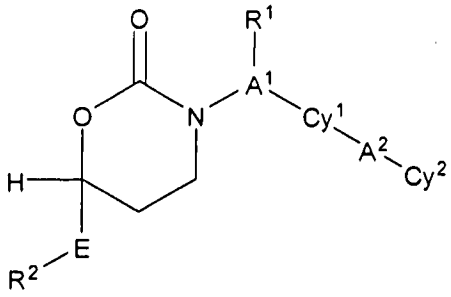
54a	CHMe	3-CF3-Ph	bond	H	bond	4-F-Ph
55a	CHMe	4-CF3-Ph	bond	H	bond	4-F-Ph
56a	CHEt	4-Br-Ph	bond	H	bond	Ph
57a	CHMe	1,4-C_6H_4	bond	2-oxo-5-(1,2-dihydropyridyl)	bond	Ph
58a	CHMe	1,4-C_6H_4	bond	1-oxo-3-pyridyl	bond	Ph
59a	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	Ph
60a	CHMe	1,4-C_6H_4	bond	3-pyridyl	bond	4-F-Ph
61a	CHMe	1,4-C_6H_4	bond	5-F-3-pyridyl	bond	Ph
62a	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph
63a	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	2-thienyl
64a	bond	1,3-C_6H_4	bond	2-Cl-4-F-Ph	bond	Ph
65a	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	Ph
66a	bond	1,3-(4-F)C6H3	bond	4-F-Ph	bond	4-F-Ph
67a	bond	1,3-(4-F)C6H3	bond	4-F-Ph	bond	2-F-Ph
68a	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	4-F-Ph
69a	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	2-F-Ph
70a	CHMe	1,4-C_6H_4	bond	4-morpholinyl	bond	4-F-Ph
71a	CHMe	1,4-C_6H_4	bond	2-MeO-5-pyridyl	bond	Ph
72a	CHMe	1,4-C_6H_4	bond	1-Me-6-oxo-3-(1,6-dihydropyridyl)	bond	Ph
73a	CHEt	1,4-C_6H_4	bond	4-F-Ph	bond	Ph
74a	CHMe	1,4-C_6H_4	bond	2-Me-4-pyridyl	bond	4-F-Ph
75a	CHEt	4-Br-Ph	bond	H	bond	4-F-Ph

76a	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	4-F-Ph
77a	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	Ph
78a	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	3-F-Ph
79a	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	2-F-Ph
80a	CHMe	1,4-C_6H_4	bond	5-F-3-pyridyl	bond	4-F-Ph
81a	CHMe	1,4-C_6H_4	bond	5-Me-1,3,4-thiadiazol-2-yl	bond	4-F-Ph
82a	bond	1,3-C_6H_4	bond	2,6-diCl-Ph	bond	Ph
83a	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	2-thienyl
84a	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	4-F-Ph
85a	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	2-F-Ph
86a	bond	2,6-(5-Cl)-pyridyl	bond	4-F-Ph	bond	2-F-Ph
87a	bond	1,3-(4-F)C_6H_3	bond	2,4-diF-Ph	bond	4-F-Ph
88a	bond	1,3-(4-F)C_6H_3	bond	2,4-diF-Ph	bond	2-F-Ph
89a	CHMe	1,4-C_6H_4	bond	5-MeCO-2-thienyl	bond	Ph
90a	CHMe	1,4-C_6H_4	bond	5-MeO-3-pyridyl	bond	4-F-Ph
91a	CHMe	1,4-C_6H_4	bond	5-(H_2NCHMe)-2-thienyl	bond	Ph
92a	CHEt	1,4-C_6H_4	bond	2,4-diF-Ph	bond	Ph
93a	CHEt	1,4-C_6H_4	bond	4-F-Ph	bond	4-F-Ph
94a	CHMe	1,4-C_6H_4	bond	5-(HOCHMe)-2-thienyl	bond	Ph
95a	CHMe	1,4-C_6H_4	bond	2,4-diMe-5-thiazolyl	bond	4-F-Ph
96a	CHMe	1,4-C_6H_4	bond	5-Cl-3-pyridyl	bond	4-F-Ph
97a	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	4-F-Ph

98a	bond	1,3-(4-F)C_6H_3	bond	2-Cl-4-F-Ph	bond	4-F-Ph
99a	bond	2,6-(5-F)-pyridyl	bond	2,4-diF-Ph	bond	2-F-Ph
100a	CHEt	1,4-C_6H_4	bond	2,4-diF-Ph	bond	4-F-Ph
101a	CHMe	1,4-C_6H_4	bond	3-(CF_3)-1-pyrazolyl	bond	4-F-Ph
102a	CHMe	1,4-C_6H_4	bond	6-CF_3-3-pyridyl	bond	4-F-Ph

[a] Cy^1 = 1,3-C_6H_4 means  Cy^1 = 1,4-C_6H_4 means 

Cy^1 = 1,3-(4-F)C_6H_3 means  Cy^1 = 2,6-(5-Cl)-pyridyl means 



Compound No	A^1-R^1	Cy^1	A2	Cy^2	E	R^2
1b	CHMe	Ph	bond	H	bond	Ph
2b	CHMe	4-Cl-Ph	bond	H	bond	i-Pr
3b	CHMe	Ph	bond	H	bond	2-Me-Ph

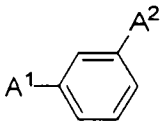
4b	CHMe	Ph	bond	H	bond	4-Me-Ph
5b	CHMe	Ph	bond	H	bond	4-F-Ph
6b	CHMe	c-hex	bond	H	bond	4-F-Ph
7b	CHMe	3-MeO-Ph	bond	H	bond	Ph
8b	CHMe	4-$HOCH_2$-Ph	bond	H	bond	Ph
9b	CHMe	4-MeO-Ph	bond	H	bond	Ph
10b	CHMe	4-Me-Ph	bond	H	bond	4-F-Ph
11b	CHMe	4-Cl-Ph	bond	H	bond	Ph
12b	CHMe	3-F-Ph	bond	H	bond	4-F-Ph
13b	CHMe	2-F-Ph	bond	H	bond	4-F-Ph
14b	CHMe	4-F-Ph	bond	H	bond	4-F-Ph
15b	CHMe	4-$HOCH_2CH_2$-Ph	bond	H	bond	Ph
16b	CHMe	4-$MeOCH_2$-Ph	bond	H	bond	Ph
17b	CHMe	4-Br-Ph	bond	H	bond	i-Pr
18b	CHMe	Ph	bond	H	bond	4-MeS-Ph
19b	CHMe	4-$HOCH_2$-Ph	bond	H	bond	4-F-Ph
20b	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph
21b	bond	1,3-C_6H_4	bond	Ph	bond	Ph
22b	bond	3-Br-Ph	bond	H	bond	Ph
23b	CHMe	4-Cl-Ph	bond	H	bond	4-F-Ph
24b	CHMe	1,4-C_6H_4	bond	c-Pr	bond	4-F-Ph
25b	bond	1-(t-BuOC=O)pyrrolidin-3-yl	bond	H	bond	Ph

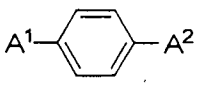
26b	bond	1,3-C_6H_4	bond	3-F-Ph	bond	Ph
27b	bond	1,3-C_6H_4	bond	4-F-Ph	bond	Ph
28b	bond	1,3-C_6H_4	bond	2-F-Ph	bond	Ph
29b	CHMe	Ph	bond	3-pyrazolyl	bond	Ph
30b	bond	2,6-pyridyl	bond	4-F-Ph	bond	Ph
31b	CHMe	4-(HOC(Me)$_2$CH$_2$-Ph	bond	H	bond	Ph
32b	bond	1,3-C_6H_4	bond	2-NC-Ph	bond	Ph
33b	CHMe	4-MeO$_2$C-Ph	bond	H	bond	4-F-Ph
34b	CHMe	4-HOC(Me)$_2$-Ph	bond	H	bond	4-F-Ph
35b	CHMe	1,4-C_6H_4	bond	4-pyridyl	bond	Ph
36b	CHMe	1,4-C_6H_4	bond	3-pyridyl	bond	Ph
37b	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	i-Pr
38b	bond	1,3-C_6H_4	bond	2-MeO-Ph	bond	Ph
39b	CHMe	4-Br-Ph	bond	H	bond	Ph
40b	CHMe	1,4-C_6H_4	bond	2-thienyl	bond	Ph
41b	bond	1,3-C_6H_4	bond	2-Cl-Ph	bond	Ph
42b	bond	1,3-C_6H_4	bond	3-Cl-Ph	bond	Ph
43b	bond	1,3-C_6H_4	bond	Ph	bond	3-Cl-Ph
44b	CHMe	4-F2HCO-Ph	bond	H	bond	4-F-Ph
45b	bond	1,3-C_6H_4	bond	2,5-diF-Ph	bond	Ph
46b	bond	1,3-C_6H_4	bond	3,5-diF-Ph	bond	Ph
47b	bond	1,3-C_6H_4	bond	2,4-diF-Ph	bond	Ph

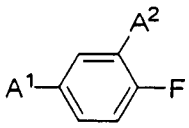
48b	bond	1,3-C_6H_4	bond	4-F-Ph	bond	Ph
49b	CHMe	4-Br-Ph	bond	H	bond	2-thienyl
50b	bond	1,3-C6H4	bond	2,4-diF-Ph	bond	2-pyridyl
51b	bond	2,6-pyridyl	bond	4-F-Ph	bond	4-F-Ph
52b	bond	2,6-pyridyl	bond	4-F-Ph	bond	2-F-Ph
53b	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	Ph
54b	CHMe	3-CF3-Ph	bond	H	bond	4-F-Ph
55b	CHMe	4-CF3-Ph	bond	H	bond	4-F-Ph
56b	CHEt	4-Br-Ph	bond	H	bond	Ph
57b	CHMe	1,4-C_6H_4	bond	2-oxo-5-(1,2-dihydropyridyl)	bond	Ph
58b	CHMe	1,4-C_6H_4	bond	1-oxo-3-pyridyl	bond	Ph
59b	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	Ph
60b	CHMe	1,4-C_6H_4	bond	3-pyridyl	bond	4-F-Ph
61b	CHMe	1,4-C_6H_4	bond	5-F-3-pyridyl	bond	Ph
62b	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph
63b	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	2-thienyl
64b	bond	1,3-C_6H_4	bond	2-Cl-4-F-Ph	bond	Ph
65b	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	Ph
66b	bond	1,3-(4-F)C6H3	bond	4-F-Ph	bond	4-F-Ph
67b	bond	1,3-(4-F)C6H3	bond	4-F-Ph	bond	2-F-Ph
68b	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	4-F-Ph
69b	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	2-F-Ph

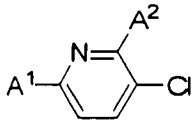
70b	CHMe	1,4-C_6H_4	bond	4-morpholinyl	bond	4-F-Ph
71b	CHMe	1,4-C_6H_4	bond	2-MeO-5-pyridyl	bond	Ph
72b	CHMe	1,4-C_6H_4	bond	1-Me-6-oxo-3-(1,6-dihydropyridyl)	bond	Ph
73b	CHEt	1,4-C_6H_4	bond	4-F-Ph	bond	Ph
74b	CHMe	1,4-C_6H_4	bond	2-Me-4-pyridyl	bond	4-F-Ph
75b	CHEt	4-Br-Ph	bond	H	bond	4-F-Ph
76b	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	4-F-Ph
77b	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	Ph
78b	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	3-F-Ph
79b	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	2-F-Ph
80b	CHMe	1,4-C_6H_4	bond	5-F-3-pyridyl	bond	4-F-Ph
81b	CHMe	1,4-C_6H_4	bond	5-Me-1,3,4-thiadiazol-2-yl	bond	4-F-Ph
82b	bond	1,3-C_6H_4	bond	2,6-diCl-Ph	bond	Ph
83b	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	2-thienyl
84b	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	4-F-Ph
85b	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	2-F-Ph
86b	bond	2,6-(5-Cl)-pyridyl	bond	4-F-Ph	bond	2-F-Ph
87b	bond	1,3-(4-F)C_6H_3	bond	2,4-diF-Ph	bond	4-F-Ph
88b	bond	1,3-(4-F)C_6H_3	bond	2,4-diF-Ph	bond	2-F-Ph
89b	CHMe	1,4-C_6H_4	bond	5-MeCO-2-thienyl	bond	Ph
90b	CHMe	1,4-C_6H_4	bond	5-MeO-3-pyridyl	bond	4-F-Ph
91b	CHMe	1,4-C_6H_4	bond	5-(H_2NCHMe)-2-thienyl	bond	Ph

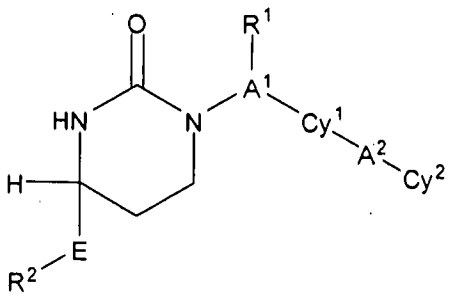
92b	CHEt	1,4-C_6H_4	bond	2,4-diF-Ph	bond	Ph
93b	CHEt	1,4-C_6H_4	bond	4-F-Ph	bond	4-F-Ph
94b	CHMe	1,4-C_6H_4	bond	5-(HOCHMe)-2-thienyl	bond	Ph
95b	CHMe	1,4-C_6H_4	bond	2,4-diMe-5-thiazolyl	bond	4-F-Ph
96b	CHMe	1,4-C_6H_4	bond	5-Cl-3-pyridyl	bond	4-F-Ph
97b	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	4-F-Ph
98b	bond	1,3-(4-F)C_6H_3	bond	2-Cl-4-F-Ph	bond	4-F-Ph
99b	bond	2,6-(5-F)-pyridyl	bond	2,4-diF-Ph	bond	2-F-Ph
100b	CHEt	1,4-C_6H_4	bond	2,4-diF-Ph	bond	4-F-Ph
101b	CHMe	1,4-C_6H_4	bond	3-(CF_3)-1-pyrazolyl	bond	4-F-Ph
102b	CHMe	1,4-C_6H_4	bond	6-CF_3-3-pyridyl	bond	4-F-Ph

[a] Cy^1 = 1,3-C_6H_4 means 

Cy^1 = 1,4-C_6H_4 means 

Cy^1 = 1,3-(4-F)C_6H_3 means 

Cy^1 = 2,6-(5-Cl)-pyridyl means 



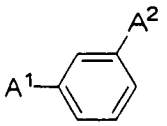
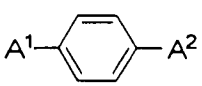
Compound No	A^1-R^1	Cy^1	A2	Cy^2	E	R^2
1c	CHMe	Ph	bond	H	bond	Ph
2c	CHMe	4-Cl-Ph	bond	H	bond	i-Pr
3c	CHMe	Ph	bond	H	bond	2-Me-Ph
4c	CHMe	Ph	bond	H	bond	4-Me-Ph
5c	CHMe	Ph	bond	H	bond	4-F-Ph
6c	CHMe	c-hex	bond	H	bond	4-F-Ph
7c	CHMe	3-MeO-Ph	bond	H	bond	Ph
8c	CHMe	4-$HOCH_2$-Ph	bond	H	bond	Ph
9c	CHMe	4-MeO-Ph	bond	H	bond	Ph
10c	CHMe	4-Me-Ph	bond	H	bond	4-F-Ph
11c	CHMe	4-Cl-Ph	bond	H	bond	Ph
12c	CHMe	3-F-Ph	bond	H	bond	4-F-Ph
13c	CHMe	2-F-Ph	bond	H	bond	4-F-Ph
14c	CHMe	4-F-Ph	bond	H	bond	4-F-Ph
15c	CHMe	4-$HOCH_2CH_2$-Ph	bond	H	bond	Ph
16c	CHMe	4-$MeOCH_2$-Ph	bond	H	bond	Ph

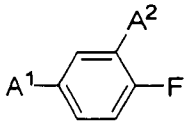
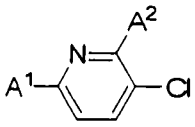
17c	CHMe	4-Br-Ph	bond	H	bond	i-Pr
18c	CHMe	Ph	bond	H	bond	4-MeS-Ph
19c	CHMe	4-$HOCH_2$-Ph	bond	H	bond	4-F-Ph
20c	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph
21c	bond	1,3-C_6H_4	bond	Ph	bond	Ph
22c	bond	3-Br-Ph	bond	H	bond	Ph
23c	CHMe	4-Cl-Ph	bond	H	bond	4-F-Ph
24c	CHMe	1,4-C_6H_4	bond	c-Pr	bond	4-F-Ph
25c	bond	1-(t-BuOC=O)pyrrolidin-3-yl	bond	H	bond	Ph
26c	bond	1,3-C_6H_4	bond	3-F-Ph	bond	Ph
27c	bond	1,3-C_6H_4	bond	4-F-Ph	bond	Ph
28c	bond	1,3-C_6H_4	bond	2-F-Ph	bond	Ph
29c	CHMe	Ph	bond	3-pyrazolyl	bond	Ph
30c	bond	2,6-pyridyl	bond	4-F-Ph	bond	Ph
31c	CHMe	4-$(HOC(Me)_2CH_2$-Ph	bond	H	bond	Ph
32c	bond	1,3-C_6H_4	bond	2-NC-Ph	bond	Ph
33c	CHMe	4-MeO_2C-Ph	bond	H	bond	4-F-Ph
34c	CHMe	4-$HOC(Me)_2$-Ph	bond	H	bond	4-F-Ph
35c	CHMe	1,4-C_6H_4	bond	4-pyridyl	bond	Ph
36c	CHMe	1,4-C_6H_4	bond	3-pyridyl	bond	Ph
37c	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	i-Pr
38c	bond	1,3-C_6H_4	bond	2-MeO-Ph	bond	Ph

39c	CHMe	4-Br-Ph	bond	H	bond	Ph
40c	CHMe	1,4-C_6H_4	bond	2-thienyl	bond	Ph
41c	bond	1,3-C_6H_4	bond	2-Cl-Ph	bond	Ph
42c	bond	1,3-C_6H_4	bond	3-Cl-Ph	bond	Ph
43c	bond	1,3-C_6H_4	bond	Ph	bond	3-Cl-Ph
44c	CHMe	4-F2HCO-Ph	bond	H	bond	4-F-Ph
45c	bond	1,3-C_6H_4	bond	2,5-diF-Ph	bond	Ph
46c	bond	1,3-C_6H_4	bond	3,5-diF-Ph	bond	Ph
47c	bond	1,3-C_6H_4	bond	2,4-diF-Ph	bond	Ph
48c	bond	1,3-C_6H_4	bond	4-F-Ph	bond	Ph
49c	CHMe	4-Br-Ph	bond	H	bond	2-thienyl
50c	bond	1,3-C6H4	bond	2,4-diF-Ph	bond	2-pyridyl
51c	bond	2,6-pyridyl	bond	4-F-Ph	bond	4-F-Ph
52c	bond	2,6-pyridyl	bond	4-F-Ph	bond	2-F-Ph
53c	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	Ph
54c	CHMe	3-CF3-Ph	bond	H	bond	4-F-Ph
55c	CHMe	4-CF3-Ph	bond	H	bond	4-F-Ph
56c	CHEt	4-Br-Ph	bond	H	bond	Ph
57c	CHMe	1,4-C_6H_4	bond	2-oxo-5-(1,2-dihydropyridyl)	bond	Ph
58c	CHMe	1,4-C_6H_4	bond	1-oxo-3-pyridyl	bond	Ph
59c	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	Ph
60c	CHMe	1,4-C_6H_4	bond	3-pyridyl	bond	4-F-Ph

61c	CHMe	1,4-C_6H_4	bond	5-F-3-pyridyl	bond	Ph
62c	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph
63c	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	2-thienyl
64c	bond	1,3-C_6H_4	bond	2-Cl-4-F-Ph	bond	Ph
65c	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	Ph
66c	bond	1,3-(4-F)C6H3	bond	4-F-Ph	bond	4-F-Ph
67c	bond	1,3-(4-F)C6H3	bond	4-F-Ph	bond	2-F-Ph
68c	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	4-F-Ph
69c	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	2-F-Ph
70c	CHMe	1,4-C_6H_4	bond	4-morpholinyl	bond	4-F-Ph
71c	CHMe	1,4-C_6H_4	bond	2-MeO-5-pyridyl	bond	Ph
72c	CHMe	1,4-C_6H_4	bond	1-Me-6-oxo-3-(1,6-dihydropyridyl)	bond	Ph
73c	CHEt	1,4-C_6H_4	bond	4-F-Ph	bond	Ph
74c	CHMe	1,4-C_6H_4	bond	2-Me-4-pyridyl	bond	4-F-Ph
75c	CHEt	4-Br-Ph	bond	H	bond	4-F-Ph
76c	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	4-F-Ph
77c	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	Ph
78c	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	3-F-Ph
79c	CHMe	1,4-C_6H_4	bond	4-F-Ph	bond	2-F-Ph
80c	CHMe	1,4-C_6H_4	bond	5-F-3-pyridyl	bond	4-F-Ph
81c	CHMe	1,4-C_6H_4	bond	5-Me-1,3,4-thiadiazol-2-yl	bond	4-F-Ph
82c	bond	1,3-C_6H_4	bond	2,6-diCl-Ph	bond	Ph

83c	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	2-thienyl
84c	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	4-F-Ph
85c	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	2-F-Ph
86c	bond	2,6-(5-Cl)-pyridyl	bond	4-F-Ph	bond	2-F-Ph
87c	bond	1,3-(4-F)C_6H_3	bond	2,4-diF-Ph	bond	4-F-Ph
88c	bond	1,3-(4-F)C_6H_3	bond	2,4-diF-Ph	bond	2-F-Ph
89c	CHMe	1,4-C_6H_4	bond	5-MeCO-2-thienyl	bond	Ph
90c	CHMe	1,4-C_6H_4	bond	5-MeO-3-pyridyl	bond	4-F-Ph
91c	CHMe	1,4-C_6H_4	bond	5-(H_2NCHMe)-2-thienyl	bond	Ph
92c	CHEt	1,4-C_6H_4	bond	2,4-diF-Ph	bond	Ph
93c	CHEt	1,4-C_6H_4	bond	4-F-Ph	bond	4-F-Ph
94c	CHMe	1,4-C_6H_4	bond	5-(HOCHMe)-2-thienyl	bond	Ph
95c	CHMe	1,4-C_6H_4	bond	2,4-diMe-5-thiazolyl	bond	4-F-Ph
96c	CHMe	1,4-C_6H_4	bond	5-Cl-3-pyridyl	bond	4-F-Ph
97c	CHMe	1,4-C_6H_4	bond	2,4-diF-Ph	bond	4-F-Ph
98c	bond	1,3-(4-F)C_6H_3	bond	2-Cl-4-F-Ph	bond	4-F-Ph
99c	bond	2,6-(5-F)-pyridyl	bond	2,4-diF-Ph	bond	2-F-Ph
100c	CHEt	1,4-C_6H_4	bond	2,4-diF-Ph	bond	4-F-Ph
101c	CHMe	1,4-C_6H_4	bond	3-(CF_3)-1-pyrazolyl	bond	4-F-Ph
102c	CHMe	1,4-C_6H_4	bond	6-CF_3-3-pyridyl	bond	4-F-Ph

[a] Cy^1 = 1,3-C_6H_4 means  Cy^1 = 1,4-C_6H_4 means 

Cy^1 = 1,3-(4-F)C_6H_3 means  Cy^1 = 2,6-(5-Cl)-pyridyl means 

The compounds of the invention are useful for ameliorating or treating disorders or diseases in which decreasing the level of cortisol is effective in treating a disease state. Thus, the compounds of the invention can be used in the treatment or prevention of diabetes mellitus, obesity, symptoms of metabolic syndrome, glucose intolerance, hyperglycemica, hypertension, hyperlipidemia, insulin resistance, cardiovascular disease, dyslipidemia, atherosclerosis, lipodystrophy, osteoporosis, glaucoma, Cushing's syndrome, Addison's Disease, visceral fat obesity associated with glucocorticoid therapy, depression, anxiety, Alzheimer's disease, dementia, cognitive decline (including age-related cognitive decline), polycystic ovarian syndrome, infertility and hypergonadism. In addition, the compounds modulate the function of B and T cells of the immune system and can therefore be used to treat diseases such as tuberculosis, leprosy and psoriasis. They can also be used to promote wound healing, particularly in diabetic patients.

The disclosed compounds can be used alone (i.e. as a monotherapy) or in combination with another therapeutic agent effective for treating any of the above indications. The pharmaceutical compositions can comprise the disclosed compounds alone as the the only pharmaceutically active agent or can comprise one or more additional pharmaceutically active agents.

A pharmaceutical composition of the invention may, alternatively or in addition to a compound of Formula I, I_1-I_{26}, Ia_{1-3}-Ij_{1-3}, comprise a pharmaceutically acceptable salt of a compound of Formula I, I_1-I_{26}, Ia_{1-3}-Ij_{1-3} or a prodrug or pharmaceutically active metabolite of such a compound or salt and one or more pharmaceutically acceptable carriers therefore. Alternatively, a pharmaceutical composition of the invention may comprise a compound of Formula I, I_1-I_{26}, Ia_{1-3}-Ij_{1-3}, or a pharmaceutical salt thereof as the only pharmaceutically active agent in the pharmaceutical composition.

A pharmaceutical composition of the invention may, alternatively or in addition to a compound of Formula I, I_1-I_{26}, Ia_{1-3}-Ij_{1-3}, comprise a pharmaceutically acceptable salt of a compound of Formula I or a prodrug or pharmaceutically active metabolite of such a compound or salt and one or more pharmaceutically acceptable carriers therefore.

The compositions of the invention are 11β-HSD1 inhibitors. Said compositions contain compounds having a mean inhibition constant (IC_{50}) against 11β-HSD1 of below about 1,000 nM; preferably below about 100 nM; more preferably below about 50 nM; even more preferably below about 5 nM; and most preferably below about 1 nM.

The invention includes a therapeutic method for treating or ameliorating an 11β-HSD1 mediated disorder in a subject in need thereof comprising administering to a subject in need thereof an effective amount of a compound of Formula I, I_1-I_{26}, Ia_{1-3}-Ij_{1-3}, or an enantiomer, diastereomer, or pharmaceutically acceptable salt thereof of composition thereof. As used herein, "treating" or "treatment" includes both therpaeutic and prophylactic treatment. Therapeutic treatment includes reducing the symptoms associated with a disease or condition and/or increasing the longevity of a subject with the disease or condition. Prophylactic treatment includes delaying the onset of a disease or condition in a subject at risk of developing the disease or condition or reducing the liklihood that a subject will then develop the disease or condition in a subject that is at risk for developing the disease or condition.

An embodiment of the invention includes administering an 11β-HSD1 inhibiting compound of Formula I, I_1-I_{26}, Ia_{1-3}-Ij_{1-3} or composition thereof in a combination therapy with one or more additional agents for the treatment of diabetes, dyslipidemia, cardiovascular disease, hypertension, obesity, cancer or glaucoma. Agents for the treatment of diabetes include insulins, such as Humulin® (Eli Lilly), Lantus® (Sanofi Aventis), Novolin (Novo Nordisk), and Exubera® (Pfizer); PPAR gamma agonists, such as Avandia® (rosiglitizone maleate, GSK) and Actos® (pioglitazone hydrochloride, Takeda/Eli Lilly); sulfonylureas, such as Amaryl® (glimepiride, Sanofi Aventis), Diabeta® (glyburide, Sanofi Aventis), Micronase®/Glynase® (glyburide, Pfizer), and Glucotrol®/Glucotrol XL® and (glipizide, Pfizer); meglitinides, such as Prandin®/NovoNorm® (repaglinide, Novo Nordisk), Starlix® (nateglinide, Novartis), and Glufast® (mitiglinide, Takeda); biguanides, such as Glucophase®/Glucophase XR® (metformin HCl, Bristol Myers

Squibb) and Glumetza (metformin HCl, Depomed); thiazolidinediones; amylin analogs, GLP-1 analogs; DPP-IV inhibitors; PTB-1B inhibitors; protein kinase inhibitors (including AMP-activated protein kinase inhibitors); glucagon antagonists, glycogen synthase kinase-3 beta inhibitors; glucose-6-phoshatase inhibitors; glycogen phosphorylase inhibitors; sodium glucose co-transporter inhibitors, and alpha-glucosidase inhibitors, such as Precose®/Glucobay®/Prandase®/Glucor® (acarbose, Bayer) and Glyset® (miglitol, Pfizer). Agents for the treatment of dyslipidemia and cardiovascular disease include statins, fibrates, and ezetimbe. Agents for the treatment of hypertension include alpha-blockers, beta-blockers, calcium channel blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, dual ACE and neutral endopeptidase (NEP) inhibitors, angiotensin-receptor blockers (ARBs), aldosterone synthase inhibitor, aldosterone-receptor antagonists, or endothelin receptor antagonist. Agents for the treatment of obesity include orlistat, phentermine, sibutramine and rimonabant.

An embodiment of the invention includes administering an 11β-HSD1 inhibiting compound of Formula I, I_1-I_{26}, Ia_{1-3}-Ij_{1-3} or composition thereof in a combination therapy with one or more other 11β-HSD1 inhibitors (whether such inhibitors are also compounds of Formula I or are compounds of a different class/genus), or with combination products, such as Avandamet® (metformin HCl and rosiglitazone maleate, GSK); Avandaryl® (glimepiride and rosiglitazone maleate, GSK); Metaglip® (glipizide and metformin HCl, Bristol Myers Squibb); and Glucovance® (glyburide and metformin HCl, Bristol Myers Squibb).

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Additionally, the compounds of the present invention can be administered intranasally or transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active ingredient, either compounds or a corresponding pharmaceutically acceptable salt of a compound of the present invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can either be solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets,

suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active ingredient.

In tablets, the active ingredient is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from about one to about seventy percent of the active ingredient. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium caboxymethylcellulose, a low-melting wax, cocoa butter, and the like. Tablets, powders, cachets, lozenges, fast-melt strips, capsules and pills can be used as solid dosage forms containing the active ingredient suitable for oral administration.

For preparing suppositories, a low-melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first-melted and the active ingredient is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, retention enemas, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral administration can be prepared by dissolving the active ingredient in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired. Aqueous suspensions for oral administration can be prepared by dispersing the finely divided active ingredient in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

The pharmaceutical composition is preferably in unit dosage form. In such form, the composition is subdivided into unit doses containing appropriate quantities of the active ingredient. The unit dosage form can be a packaged preparation, the package containing discrete quantities of, for example, tablets, powders, and

capsules in vials or ampules. Also, the unit dosage form can be a tablet, cachet, capsule, or lozenge itself, or it can be the appropriate amount of any of these in packaged form.

The quantity of active ingredient in a unit dose preparation may be varied or adjusted from about 0.1 mg to about 1000.0 mg, preferably from about 0.1 mg to about 100 mg. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill in the art. Also, the pharmaceutical composition may contain, if desired, other compatible therapeutic agents.

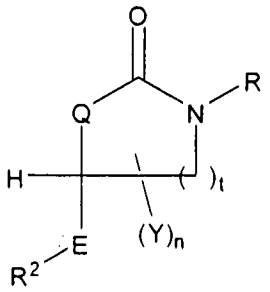
In therapeutic treatment or as a method-of-use as an inhibitor of 11β-HSD1 or an inhibitor in the production of cortisol in the cell, the active ingredient is preferably administered orally in a solid dosage form as disclosed above in an amount of about 0.1 mg to about 100 mg per daily dose where the dose is administered once or more than once daily.

All publications, patents and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually designated as having been incorporated by reference. It is understood that the examples and embodiments described herein are for illustrative purposes only, and it will be appreciated that the invention is susceptible to modification, variation and change without departing from the proper scope or fair meaning of the appended claims.

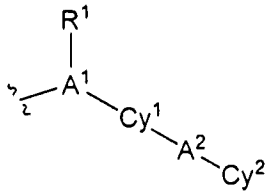
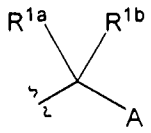
CLAIMS

What is claimed is:

1. A compound of Formula (I)



I ; wherein

R is  or  ;

R^1 is (a) absent or (b) is selected from $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl or $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkyl, wherein each is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R^4, R^4O-, $(R^4)_2N$-, R^4O_2C-, R^4S, $R^4S(=O)$-, $R^4S(=O)_2$-, $R^4C(=O)NR^4$-, $(R^4)_2NC(=O)$-, $(R^4)_2NC(=O)O$-, $(R^4)_2NC(=O)NR^4$-, $R^4OC(=O)NR^4$-, $(R^4)_2NC(=NCN)NR^4$-, $(R^4O)_2P(=O)O$-, $(R^4O)_2P(=O)NR^4$-, $R^4OS(=O)_2NR^4$-, $(R^4)_2NS(=O)_2O$-, $(R^4)_2NS(=O)_2NR^4$-, $R^4S(=O)_2NR^4$-, $R^4S(=O)_2NHC(=O)$-, $R^4S(=O)_2NHC(=O)O$-, $R^4S(=O)_2NHC(=O)NR^4$-, $R^4OS(=O)_2NHC(=O)$-, $R^4OS(=O)_2NHC(=O)O$-, $R^4OS(=O)_2NHC(=O)NR^4$-, $(R^4)_2NS(=O)_2NHC(=O)$-, $(R^4)_2NS(=O)_2NHC(=O)O$-, $(R^4)_2NS(=O)_2NHC(=O)NR^4$-, $R^4C(=O)NHS(=O)_2$-, $R^4C(=O)NHS(=O)_2O$-, $R^4C(=O)NHS(=O)_2NR^4$-, $R^4OC(=O)NHS(=O)_2$-, $R^4OC(=O)NHS(=O)_2O$-, $R^4OC(=O)NHS(=O)_2NR^4$-, $(R^4)_2NC(=O)NHS(=O)_2$-, $(R^4)_2NC(=O)NHS(=O)_2O$-, $(R^4)_2NC(=O)NHS(=O)_2NR^4$-, aryl, cycloalkyl, heterocyclyl, heteroaryl, arylamino and heteroarylamino;

A^1 is (a) a bond, or (b) $(C_1$-$C_3)$alkylene, CH_2CH_2O, wherein the oxygen is attached to Cy^1, or $CH_2C(=O)$, wherein the carbonyl carbon is attached to Cy^1;

Cy^1 is aryl, heteroaryl, monocyclic cycloalkyl or heterocyclyl, wherein each is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, hydroxy$(C_3$-$C_6)$cycloalkyl, $(C_4$-$C_7)$cycloalkylalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_2$-$C_6)$alkenyl, hydroxy$(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_6)$cycloalkyl$(C_2$-$C_4)$alkynyl, halo$(C_1$-$C_6)$alkyl, halo$(C_3$-$C_6)$cycloalkyl, halo$(C_4$-$C_7)$cycloalkylalkyl, $(C_1$-$C_6)$alkoxy, $(C_3$-$C_6)$cycloalkoxy, $(C_4$-$C_7)$cycloalkylalkoxy, halo$(C_1$-$C_6)$alkoxy, halo$(C_3$-$C_6)$cycloalkoxy, halo$(C_4$-$C_7)$cycloalkylalkoxy, $(C_1$-$C_6)$alkylthio, $(C_3$-$C_6)$cycloalkythio, $(C_4$-$C_7)$cycloalkylalkylthio, halo$(C_1$-$C_6)$alkylthio, halo$(C_3$-$C_6)$cycloalkythio, halo$(C_4$-$C_7)$cycloalkylalkylthio, $(C_1$-$C_6)$alkanesulfinyl, $(C_3$-$C_6)$cycloalkanesulfinyl, $(C_4$-$C_7)$cycloalkylalkanesulfinyl, halo$(C_1$-$C_6)$alkane-sulfinyl, halo$(C_3$-$C_6)$cycloalkanesulfinyl, halo$(C_4$-$C_7)$cycloalkylalkanesulfinyl, $(C_1$-$C_6)$alkanesulfonyl, $(C_3$-$C_6)$cycloalkanesulfonyl, $(C_4$-$C_7)$cycloalkylalkanesulfonyl, halo$(C_1$-$C_6)$alkanesulfonyl, halo$(C_3$-$C_6)$cycloalkanesulfonyl, halo$(C_4$-$C_7)$cycloalkylalkanesulfonyl, $(C_1$-$C_6)$alkylamino, di$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1$-$C_6)$alkylaminocarbonyl, di$(C_1$-$C_6)$alkylaminocarbonyl, $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkylaminocarbonyl, heterocyclylcarbonyl, $(C_1$-$C_6)$alkylaminosulfonyl, di$(C_1$-$C_6)$alkylaminosulfonyl, heterocyclsulfonyl, $(C_1$-$C_6)$alkylcarbonylamino, $(C_1$-$C_6)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonylamino, $(C_1$-$C_6)$alkylsulfonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkoxy, heteroaryl, oxo, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, di$(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl amino$(C_2$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxy, di$(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxyl; $(C_1$-$C_6)$alkylcarbonyl; $(C_3$-$C_6)$cycloalkylcarbonyl, $(C_3$-$C_6)$cycloalkylaminocarbonyl, {$(C_3$-$C_6)$cycloalkyl}{$(C_1$-$C_6)$alkyl}aminocarbonyl, di$(C_3$-$C_6)$cycloalkylaminocarbonyl, $(C_3$-$C_6)$cycloalkylaminosulfonyl, {$(C_3$-$C_6)$cycloalkyl}{$(C_1$-$C_6)$alkyl}aminosulfonyl, di$(C_3$-$C_6)$cycloalkylaminosulfonyl, cyano$(C_1$-$C_6)$alkyl, aminocarbonyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylaminocarbonyl$(C_1$-$C_6)$alkyl, di$(C_1$-$C_6)$alkylaminocarbonyl$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkylaminocarbonyl$(C_1$-$C_6)$alkyl, {$(C_3$-$C_6)$cycloalkyl}{$(C_1$-$C_6)$alkyl}aminocarbonyl$(C_1$-$C_6)$alkyl and di$(C_3$-

C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl; provided that if (a) t is 2 and Q is O or CH_2 or t is 1 and Q is O, (b) A^1 is CH_2 optionally substituted with R_1 and (c) A^2 is a bond, then Cy^2 is meta or para to the ring atom of Cy^1 that is bonded to A^1 and the aryl, heteroaryl, monocyclic cycloalkyl or heterocyclyl, represented by Cy^1 is not substituted with bromine, iodine, amino, halo(C_1-C_6)alkyl at a ring atom ortho to the carbon atom bounded to A^1;

A^2 is (a) a bond, O, S or NR^4; or (b) (C_1-C_3)alkylene or (C_1-C_2)alkyleneoxy, each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo;

Cy^2 is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkyl-alkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cyclo-alkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-

C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl; (C_1-C_6)alkylcarbonyl; (C_3-C_6)cycloalkylcarbonyl, (C_3-C_6)cycloalkylaminocarbonyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminocarbonyl, di(C_3-C_6)cycloalkylaminocarbonyl, (C_3-C_6)cycloalkylaminosulfonyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminosulfonyl, di(C_3-C_6)cycloalkylaminosulfonyl, cyano(C_1-C_6)alkyl, aminocarbonyl(C_1-C_6)alkyl, (C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, di(C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, (C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminocarbonyl(C_1-C_6)alkyl and di(C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl;

provided that if (a) t is 1; (b) Q is O, (c) A^1 is CH_2 optionally substituted with R^1 and (d) Cy^1 is phenyl then A^2Cy^2 is not NHR^4 or optionally substituted heterocyclyl;

provided that if (a) A^1 is CH_2CH_2O; (b) Cy^1 is phenyl and (c) A^2 is CH_2 then Cy^2 is not heterocyclyl substituted with oxo;

R^{1a} and R^{1b} are each independently selected from (a) hydrogen or (b) (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl or (C_1-C_3)alkoxy(C_1-C_3)alkyl which are optionally substituted with up to three groups independently selected from fluorine, hydroxy, (C_1-C_3)alkoxy and $H_2NC(=O)$;

A is straight or branched (C_1-C_8)alkyl, (C_2-C_8)alkenyl or (C_2-C_8)alkynyl, optionally substituted with up to 4 groups independently selected from fluorine, cyano, oxo, R^4, -OH R^4O-, $(R^4)_2N$-, R^4O_2C-, R^4S, $R^4S(=O)$-, $R^4S(=O)_2$-, $R^4C(=O)NR^4$-, $(R^4)_2NC(=O)$-, $(R^4)_2NC(=O)O$-, $(R^4)_2NC(=O)NR^4$-, $R^4OC(=O)NR^4$-, $(R^4)_2NC(=NCN)NR^4$-, $(R^4O)_2P(=O)O$-, $(R^4O)_2P(=O)NR^4$-, $R^4OS(=O)_2NR^4$-, $(R^4)_2NS(=O)_2O$-, $(R^4)_2NS(=O)_2NR^4$-, $R^4S(=O)_2NR^4$-, $R^4SO_2NR^4$-, $R^4S(=O)_2NHC(=O)$-, $R^4S(=O)_2NHC(=O)O$-, $R^4S(=O)_2NHC(=O)NR^4$-, $R^4OS(=O)_2NHC(=O)$-, $R^4OS(=O)_2NHC(=O)O$-, $R^4OS(=O)_2NHC(=O)NR^4$-, $(R^4)_2NS(=O)_2NHC(=O)$-, $(R^4)_2NS(=O)_2NHC(=O)O$-, $(R^4)_2NS(=O)_2NHC(=O)NR^4$-, $R^4C(=O)NHS(=O)_2$-, $R^4C(=O)NHS(=O)_2O$-, $R^4C(=O)NHS(=O)_2NR^4$-, $R^4OC(=O)NHS(=O)_2$-, $R^4OC(=O)NHS(=O)_2O$-, $R^4OC(=O)NHS(=O)_2NR^4$-, $(R^4)_2NC(=O)NHS(=O)_2$-, $(R^4)_2NC(=O)NHS(=O)_2O$-, $(R^4)_2NC(=O)NHS(=O)_2NR^4$-, heterocyclylamino (wherein the heterocyclyl portion is optionally substituted by alkyl, haloalkyl or oxo); heteroarylamino (wherein the heteroaryl portion is optionally substituted by alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro,

cyano, CO_2H, $CONH_2$, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); arylamino (wherein the aryl portion is optionally substituted by alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H, $CONH_2$, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); and cycloalkylamino (wherein the cycloalkyl portion is optionally substituted by alkyl, haloalkyl or oxo);

t is 1, 2 or 3;

Y is $(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkyl;

n is 0, 1 or 2;

E is (a) a bond or (b) $(C_1\text{-}C_3)$alkylene or $(C_1\text{-}C_2)$alkylenyloxy, wherein the O is attached to R^2, each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo; provided that if Q is NH, then ER^2 is not $(C_1\text{-}C_6)$alkyl or benzyl;

R^2 is $(C_1\text{-}C_6)$alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with up to 4 groups independently selected from fluorine, chlorine, bromine, iodine, nitro, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_3\text{-}C_6)$cycloalkyl, $(C_4\text{-}C_7)$cycloalkylalkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, hydroxy$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_6)$cycloalkyl$(C_2\text{-}C_4)$alkynyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_3\text{-}C_6)$cycloalkyl, halo$(C_4\text{-}C_7)$cycloalkylalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkoxy, $(C_4\text{-}C_7)$cycloalkylalkoxy, halo$(C_1\text{-}C_6)$alkoxy, halo$(C_3\text{-}C_6)$cycloalkoxy, halo$(C_4\text{-}C_7)$cycloalkylalkoxy, $(C_1\text{-}C_6)$alkylthio, $(C_3\text{-}C_6)$cycloalkythio, $(C_4\text{-}C_7)$cycloalkylalkylthio, halo$(C_1\text{-}C_6)$alkylthio, halo$(C_3\text{-}C_6)$cycloalkythio, halo$(C_4\text{-}C_7)$cycloalkylalkylthio, $(C_1\text{-}C_6)$alkanesulfinyl, $(C_3\text{-}C_6)$cycloalkanesulfinyl, $(C_4\text{-}C_7)$cycloalkylalkanesulfinyl, halo$(C_1\text{-}C_6)$alkane-sulfinyl, halo$(C_3\text{-}C_6)$cycloalkanesulfinyl, halo$(C_4\text{-}C_7)$cycloalkylalkanesulfinyl, $(C_1\text{-}C_6)$alkanesulfonyl, $(C_3\text{-}C_6)$cycloalkanesulfonyl, $(C_4\text{-}C_7)$cycloalkylalkanesulfonyl, halo$(C_1\text{-}C_6)$alkanesulfonyl, halo$(C_3\text{-}C_6)$cycloalkanesulfonyl, halo$(C_4\text{-}C_7)$cycloalkylalkanesulfonyl, $(C_1\text{-}C_6)$alkylamino, di$(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkoxy, H_2NCO, H_2NSO_2, $(C_1\text{-}C_6)$alkylaminocarbonyl, di$(C_1\text{-}C_6)$alkylaminocarbonyl, $(C_1\text{-}C_3)$alkoxy$(C_1\text{-}C_3)$alkylaminocarbonyl, heterocyclylcarbonyl, $(C_1\text{-}C_6)$alkylaminosulfonyl, di$(C_1\text{-}C_6)$alkylaminosulfonyl, heterocyclsulfonyl, $(C_1\text{-}C_6)$alkylcarbonylamino, $(C_1\text{-}C_6)$alkylcarbonylamino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonylamino, $(C_1\text{-}C_6)$alkylsulfonylamino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}$

C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl; (C_1-C_6)alkylcarbonyl; (C_3-C_6)cycloalkylcarbonyl, (C_3-C_6)cycloalkylaminocarbonyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminocarbonyl, di(C_3-C_6)cycloalkylaminocarbonyl, (C_3-C_6)cycloalkylaminosulfonyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminosulfonyl, di(C_3-C_6)cycloalkylaminosulfonyl, cyano(C_1-C_6)alkyl, aminocarbonyl(C_1-C_6)alkyl, (C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, di(C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, (C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl, {(C_3-C_6)cycloalkyl}{(C_1-C_6)alkyl}aminocarbonyl(C_1-C_6)alkyl and di(C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl;

wherein the 1 to 4 substituents for the group represented by R^2 are additionally selected from: amino, cyano, carboxy, (C_1-C_6)alkoxycarbonyl and hydroxy(C_1-C_6)alkyl, when E is bond or (C_1-C_3)alkylene, t is 1 and Q is O or CH_2, provided that ER^2 is not CH_2Cl, CH_2OH, CHO or CH_2Ophenyl;

provided that when (a) t is 2; (b) E is bond and (c) R^2 is phenyl, then R^2 is not substituted with (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy;
provided that when (a) A^1 is bond; (b) R^1 is absent; (c) Cy^1 is phenyl; (d) A^2 is bond (e) Cy^2 is H and (f) E is bond, then R^2 is not unsubstituted phenyl;
provided that when (a) t is 1; (b) Q is NR^5; (c) A^1 is bond; (d) R^1 is absent; (e) Cy^1 is optionally substituted phenyl; (f) A^2 is bond; (g) Cy^2 is H then ER^2 is not unsubstituted (C1-C6) alkyl;

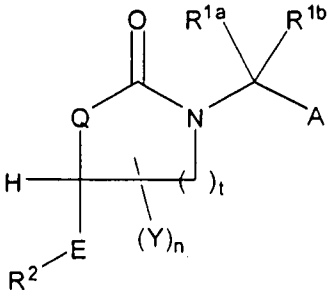
Q is O, NR^5 or CH_2;

each R^4 is independently selected from H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl and (C_1-C_6)alkoxy(C_1-C_6)alkyl; and

each R^5 is independently H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, or hydroxy(C_1-C_6)alkyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

2. The compound of Claim 1, wherein the compound is of Formula (I_1)

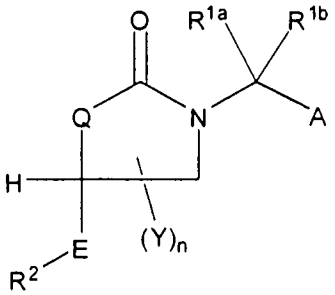


I_1

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

3. The compound of claim 2 wherein the compound is of Formula (I_2)

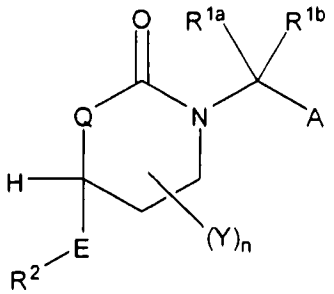


I_2

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

4. The compound of claim 2 wherein the compound is of Formula (I_3)

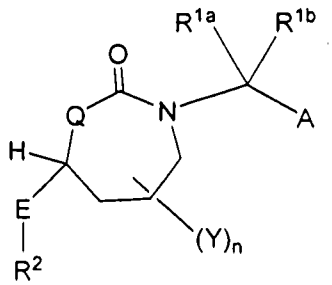


I_3

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

5. The compound of claim 2 wherein the compound is of Formula (I_4)

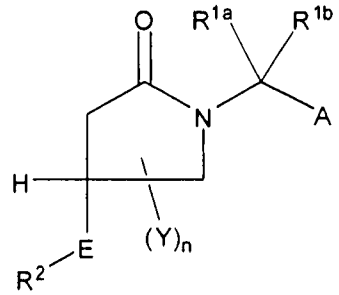


I_4

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

6. The compound of claim 3 wherein the compound is of Formula (I_5)

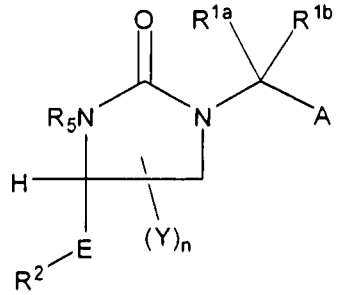


I_5

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

7. The compound of claim 3 wherein the compound is of Formula (I_6)

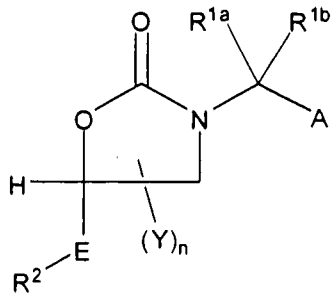


I_6

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

8. The compound of claim 3 wherein the compound is of Formula (I_7)

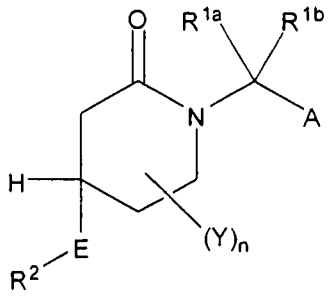


I_7

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

9. The compound of claim 4 wherein the compound is of Formula (I_8)

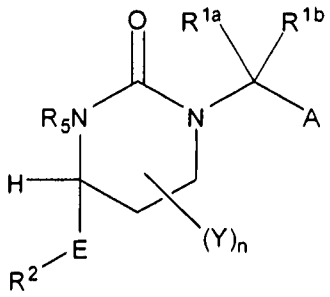


I_8

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

10. The compound of claim 4 wherein the compound is of Formula (I_9)

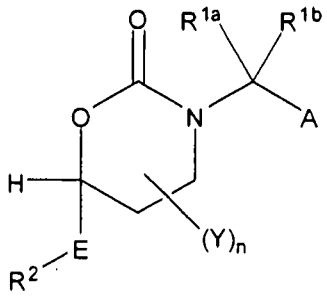


I_9

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

11. The compound of claim 4 wherein the compound is of Formula (I_{10})

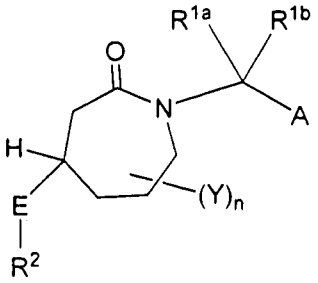


I_{10}

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

12. The compound of claim 5 wherein the compound is of Formula (I_{11})

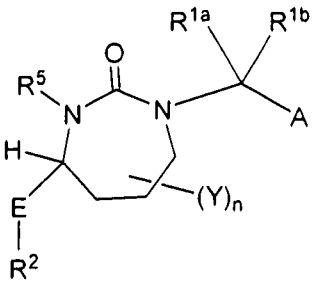


I_{11}

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

13. The compound of claim 5 wherein the compound is of Formula (I_{12})

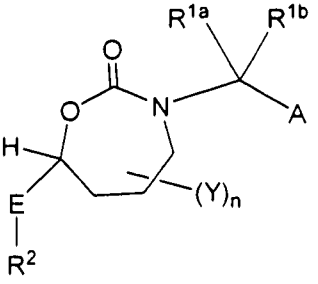


I_{12}

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

14. The compound of claim 5 wherein the compound is of Formula (I_{13})

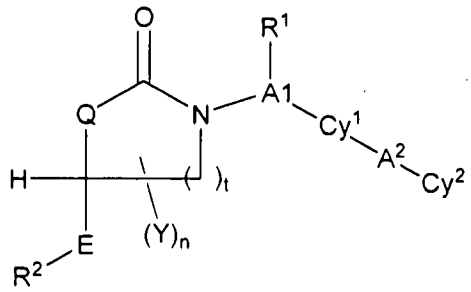


I_{13}

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

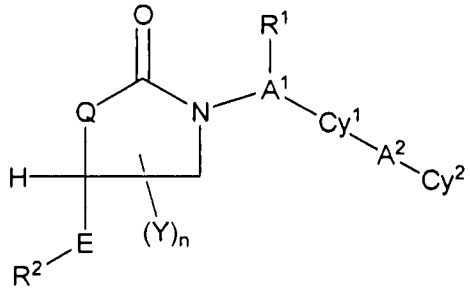
15. The compound of claim 1 wherein the compound is of Formula (I_{14})



I_{14}

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

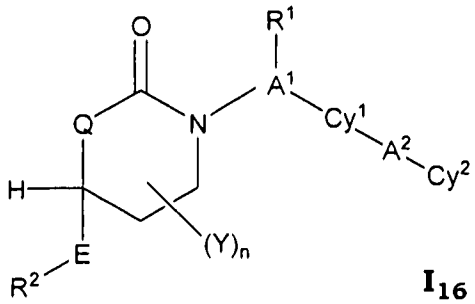
16. The compound of claim 15 wherein the compound is of Formula (I_{15})



I_{15}

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

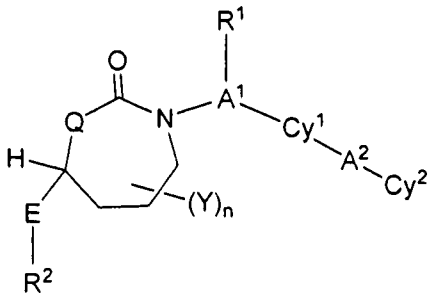
17. The compound of claim 15 wherein the compound is of Formula (I_{16})



I_{16}

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

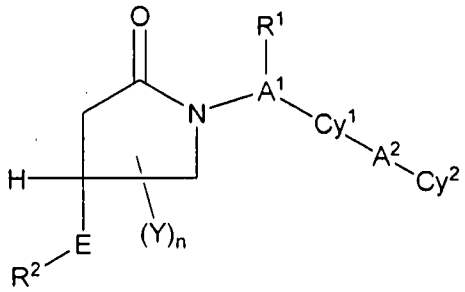
18. The compound of claim 15 wherein the compound is of Formula (I_{17})



I_{17};

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

19. The compound of claim 16 wherein the compound is of Formula (I_{18})

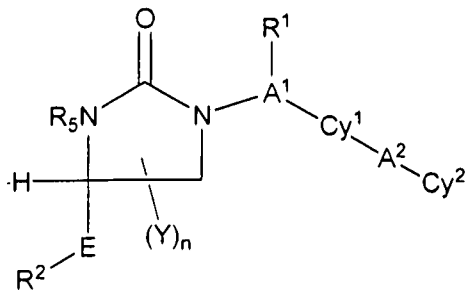


I_{18}

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

20. The compound of claim 16 wherein the compound is of Formula (I_{19})

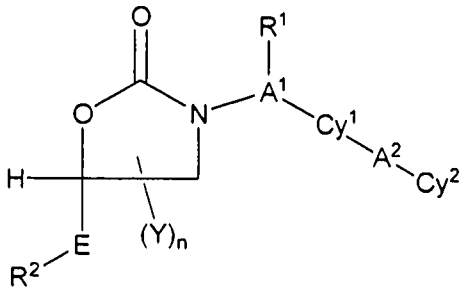


I_{19}

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

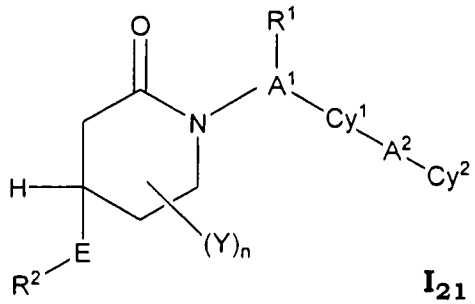
21. The compound of claim 16 wherein the compound is of Formula (I_{20})



I_{20}

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

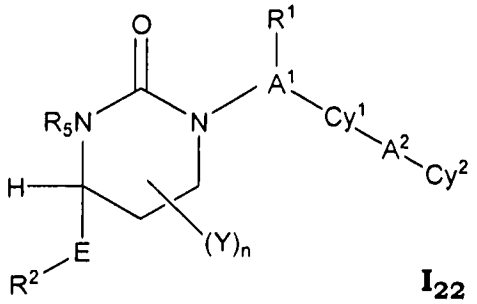
22. The compound of claim 17 wherein the compound is of Formula (I_{21})



I_{21}

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

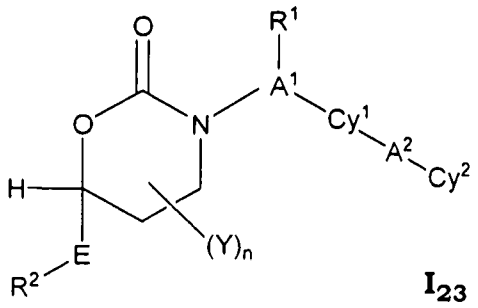
23. The compound of claim 17 wherein the compound is of Formula (I_{22})



I_{22}

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

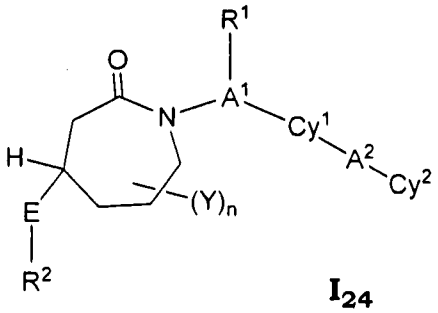
24. The compound of claim 17 wherein the compound is of Formula (I_{23})



I_{23}

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

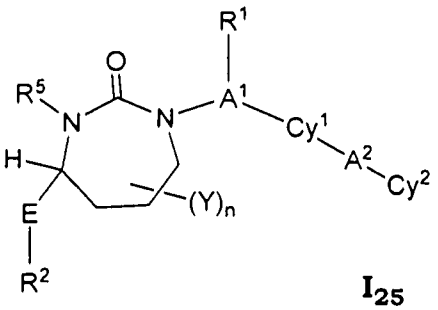
25. The compound of claim 18 wherein the compound is of Formula (I_{24})



I_{24}

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

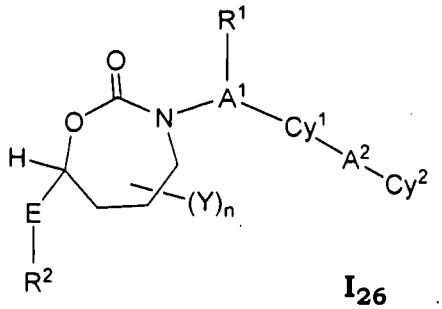
26. The compound of claim 18 wherein the compound is of Formula (I_{25})



I_{25}

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

27. The compound of claim 18 wherein the compound is of Formula (I_{26})



I_{26};

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

28. The compound of any one of claims 1 or 15-27, wherein A^1 is a bond.

29. The compound of any one of claims 1 or 15-27, wherein A^1 is $(C_1\text{-}C_3)$alkylene.

30. The compound of claim 29, wherein A^1 is $(C_2\text{-}C_3)$alkylene.

31. The compound of claim 29, wherein A^1 is methylene.

32. The compound of claim 31, wherein R^1 is $(C_1\text{-}C_6)$alkyl.

33. The compound of claim 32, wherein R^1 is an optionally substituted methyl or ethyl.

34. The compound of claim 33, wherein R^1 is unsubstituted.

35. The compound of any one of claims 1 or 15-27, wherein Cy^1 is optionally substituted aryl or optionally substituted heteroaryl.

36. The compound of any one of claims 1 or 15-27, wherein Cy^1 is optionally substituted phenyl or optionally substituted pyridyl.

37. The compound of claim 36, wherein Cy^1 is optionally substituted phenyl.

38. The compound of claim 37, wherein Cy^1 is substituted with fluorine, or bromine.

39. The compound of claim 37, wherein A^2 is a bond and Cy^2 is hydrogen.

40. The compound of claim 37, wherein A^2 is a bond and Cy^2 is cyclopropyl.

41. The compound of claim 37, wherein A^2 is a bond and Cy^2 is optionally substituted aryl or optionally substituted heteroaryl.

42. The compound of claim 37, wherein A^2 is a bond and Cy^2 is optionally substituted phenyl or optionally substituted pyridyl.

43. The compound of claim 42, wherein Cy^2 is optionally substituted phenyl.

44. The compound of claim 43, wherein Cy^2 is substituted with 1 to 4 groups independently selected from chlorine or fluorine.

45. The compound of claim 43, wherein Cy^2 is difluorophenyl.

46. The compound of any one of claims 1-27 wherein R^2 is optionally substituted aryl, optionally substituted heteroaryl or optionally substituted cycloalkyl.

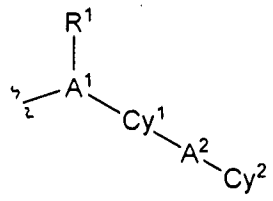
47. The compound of claim 46, wherein R^2 is optionally substituted phenyl, optionally substituted thienyl or optionally substituted pyridyl.

48. The compound of claim 47, wherein R^2 is optionally substituted phenyl.

49. The compound of claim 48, wherein R^2 is fluorophenyl.

50. The compound of any one of claims 1-27, wherein E is a bond.

51. The compound of any one of claims 1 or 15-27, wherein:

R is  ;

R^1 is absent or is methyl or ethyl;

A^1 is a bond or CH_2;

Cy^1 is phenyl, cyclohexyl, pyridyl, N-oxo-pyridyl, thiazolyl or pyrimidinyl optionally substituted with 1 to 4 groups independently selected from halo, methyl, trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy and 2-hydroxy-2-methylpropoxy;

A^2 is a bond, O or OCH_2CO;

Cy^2 is (a) hydrogen or (b) phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl or piperazinyl optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonyl-aminomethyl or tetrazolyl;

n is 0;

E is a bond or CH_2;

R^2 is phenyl or pyridyl optionally substituted with one group selected from halo, methyl, methylthio or (4-morpholino)methyl.

52. The compound of any one of claims 1-14, wherein A is hydroxy(C_1-C_6)alkyl or (C_1-C_2) alkoxy(C_1-C_6)alkyl.

53. The compound of any one of claims 1-14, wherein A is (C_1-C_4)alkylcarbonylamino(C_1-C_4)alkyl.

54. The compound of any one of claims 1-14, wherein A is mono(C_1-C_2)alkylaminocarbonyl(C_1-C_4)alkyl or di(C_1-C_2)alkylaminocarbonyl(C_1-C_4)alkyl.

55. The compound of any one of claims 1-14, wherein A is 2-pyrimidinyl-amino(C_1-C_6)alkyl; 2-pyridyl-amino(C_1-C_6)alkyl; mono(C_1-C_2)alkylamino(C_1-C_4)alkyl or

di(C_1-C_2)alkylamino(C_1-C_4)alkyl, wherein the pyrimidinyl and pyridyl are each optionally substituted with methyl or ethyl.

56. The compound of any one of claims 1-14, wherein A is (C_1-C_6)alkyl, optionally substituted with halogen.

57. The compound of any one of claims 1-14, wherein A is (C_1-C_4)alkylsulfonyl(C_1-C_4)alkyl.

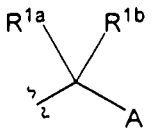
58. The compound of any one of claims 1-14, wherein A is (C_1-C_4)alkylsulfonylamino(C_1-C_4)alkyl.

59. The compound of any one of claims 1-14, wherein A is (C_1-C_4)alkoxyalkylamino(C_1-C_4)alkyl.

60. The compound of any one of claims 1-14, wherein A is mono(C_1-C_4)alkylaminocarbonyl(C_1-C_4)alkyl or di(C_1-C_4)alkylaminocarbonyl(C_1-C_4)alkyl.

61. The compound of any one of claims 1-14, wherein R^{1a} and R^{1b} are H or (C_1-C_6)alkyl.

62. The compound of any one of claims 1-14, wherein



R is ;

R^{1a} is methyl or ethyl;

R^{1b} is methyl or hydrogen;

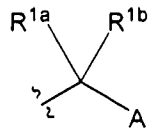
A is methyl, ethyl, isopropyl or t-butyl;

n is 0;

E is a bond or CH_2; and

R^2 is phenyl, thienyl or pyridyl each optionally substituted with halo or methyl.

63. The compound of any one of claims 1-14, wherein



R is ;

R^{1a} is methyl;

R^{1b} is hydrogen or methyl;

A is methyl or t-butyl;

n is 0;

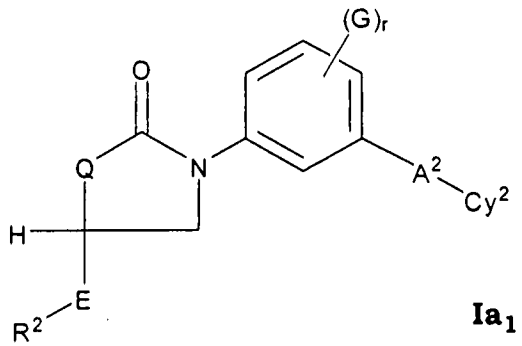
E is a bond; and

R^2 is phenyl or 4-fluorophenyl.

64. The compound of claim 61, wherein R^{1a} and R^{1b} are H, methyl, or ethyl.

65. The compound of claim 64, wherein R^{1a} is Me and R^{1b} is H.

66. The compound of claim 1, 15 or 16 wherein the compound is of Formula (Ia_1)



Ia_1 ; wherein

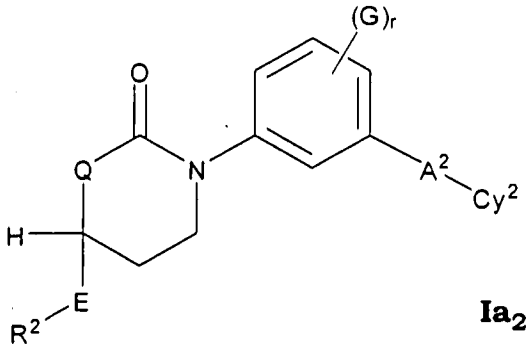
r is 0, 1, 2, 3 or 4; and

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkylalkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-

C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cycloalkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl,, hydroxy(C_1-C_6)alkoxy, heteroaryl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl or (C_1-C_6)alkylcarbonyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

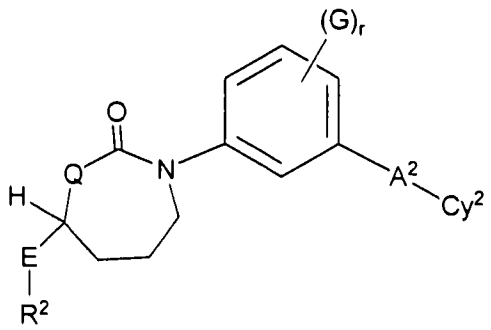
67. The compound of claim 1, 15 and 17 wherein the compound is of Formula (Ia_2)



Ia_2;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

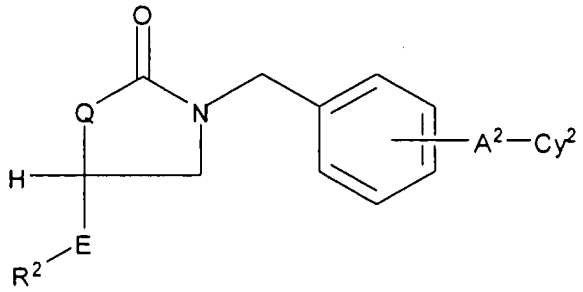
68. The compound of claim 1, 15 and 18 wherein the compound is of Formula (Ia_3)



Ia_3 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

69. The compound of claim 1, 15 or 16 wherein the compound is of Formula (Ib_1)

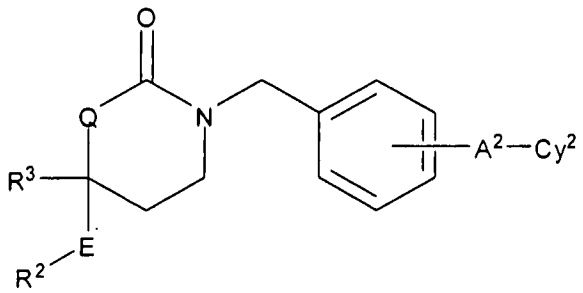


Ib_1

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

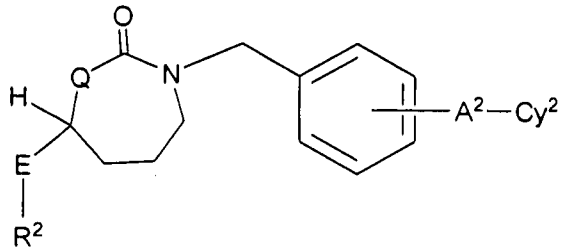
70. The compound of claim 1, 15 and 17 wherein the compound is of Formula (Ib_2)



Ib_2 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

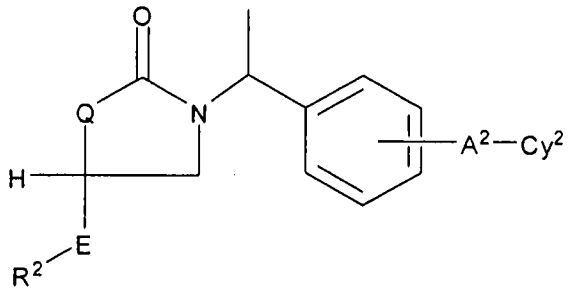
71. The compound of claim 1, 15 and 18 wherein the compound is of Formula (Ib_3)



Ib_3 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

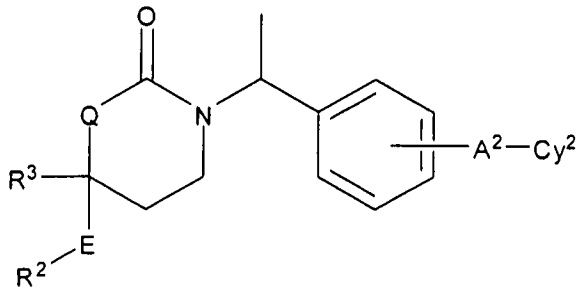
72. The compound of claim 1, 15 or 16 wherein the compound is of Formula (Ic_1)



Ic_1 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

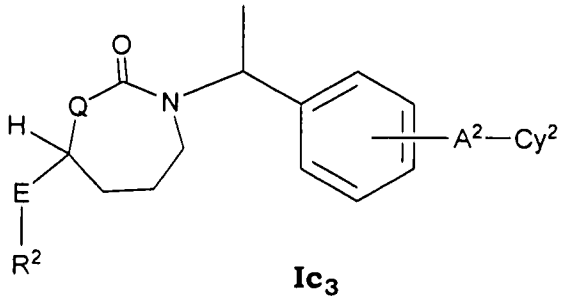
73. The compound of claim 1, 15 and 17 wherein the compound is of Formula (Ic_2)



Ic_2 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

74. The compound of claim 1, 15 and 18 wherein the compound is of Formula (Ic_3)

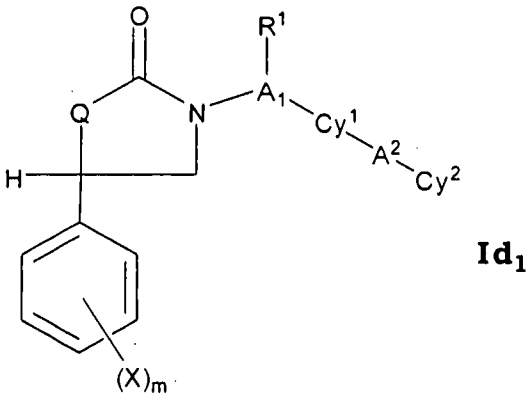


Ic_3

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

75. The compound of claim 1, 15 or 16 wherein the compound is of Formula (Id_1)



Id_1

; wherein

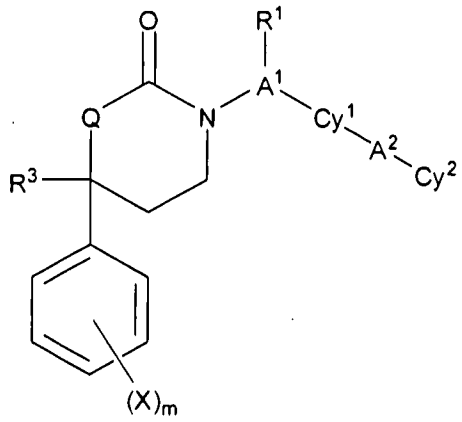
m is 0, 1, 2, 3 or 4;

X is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkyl-alkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl,

$(C_3$-$C_6)$cycloalkanesulfonyl, $(C_4$-$C_7)$cycloalkylalkanesulfonyl, halo$(C_1$-$C_6)$alkanesulfonyl, halo$(C_3$-$C_6)$cycloalkanesulfonyl, halo$(C_4$-$C_7)$cycloalkylalkanesulfonyl, $(C_1$-$C_6)$alkylamino, di$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1$-$C_6)$alkylaminocarbonyl, di$(C_1$-$C_6)$alkylaminocarbonyl, $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkylaminocarbonyl, heterocyclylcarbonyl, $(C_1$-$C_6)$alkylaminosulfonyl, di$(C_1$-$C_6)$alkylaminosulfonyl, heterocyclsulfonyl, $(C_1$-$C_6)$alkylcarbonylamino, $(C_1$-$C_6)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonylamino, $(C_1$-$C_6)$alkylsulfonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl,, hydroxy$(C_1$-$C_6)$alkoxy, heteroaryl, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, di$(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl amino$(C_2$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxy, di$(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxyl and $(C_1$-$C_6)$alkylcarbonyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

76. The compound of claim 1, 15 and 17 wherein the compound is of Formula (Id_2)

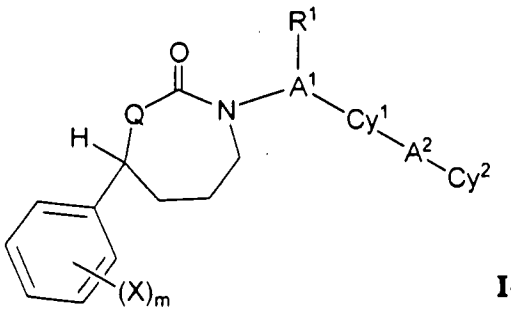


Id_2

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

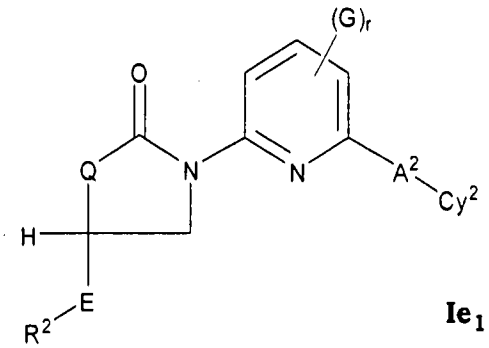
77. The compound of claim 1, 15 and 18 wherein the compound is of Formula (Id_3)



Id$_3$;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

78. The compound of claim 1, 15 or 16 wherein the compound is of Formula (Ie$_1$)



Ie$_1$; wherein

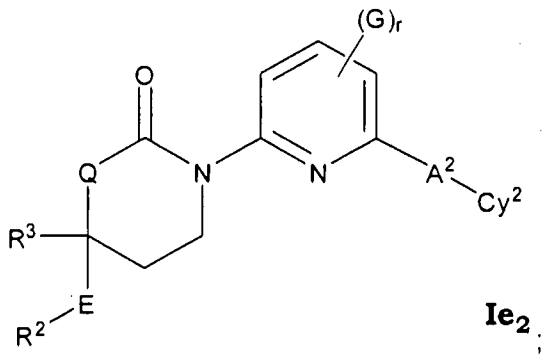
r is 0, 1, 2, 3 or 4;

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkyl-alkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cyclo-alkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-

C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl,, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl and (C_1-C_6)alkylcarbonyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

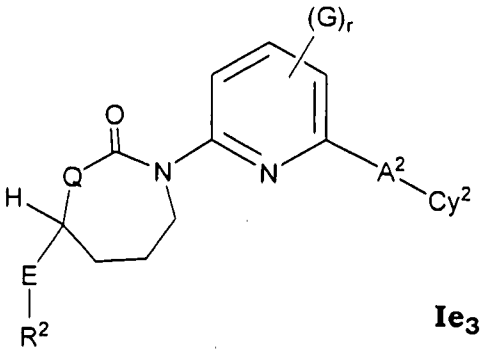
79. The compound of claim 1, 15 and 17 wherein the compound is of Formula (Ie_2)



Ie_2;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

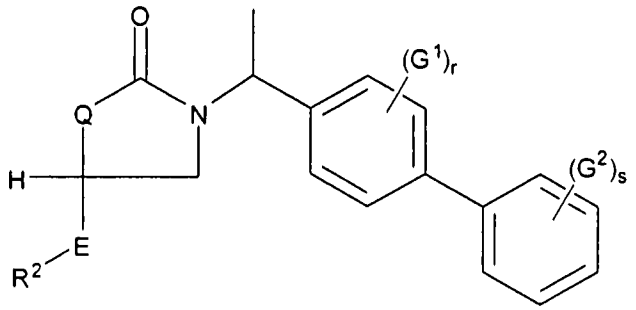
80. The compound of claim 1, 15 and 18 wherein the compound is of Formula (Ie_3)



Ie_3;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

81. The compound of claim 1, 15 or 16 wherein the compound is of Formula (If_1)



If_1

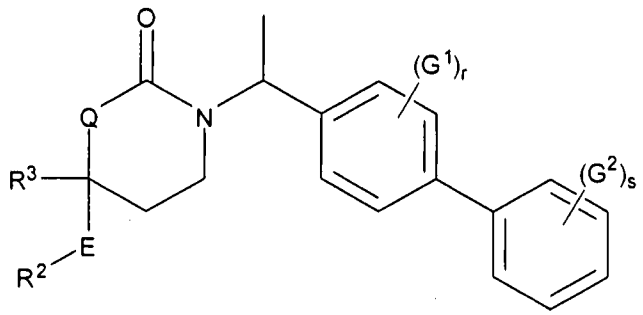
; wherein

r and s are independently 0, 1, 2, 3 or 4; and

G^1 and G^2 are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_3\text{-}C_6)$cycloalkyl, $(C_4\text{-}C_7)$cycloalkylalkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, hydroxy$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_6)$cycloalkyl$(C_2\text{-}C_4)$alkynyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_3\text{-}C_6)$cycloalkyl, halo$(C_4\text{-}C_7)$cycloalkylalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkoxy, $(C_4\text{-}C_7)$cycloalkylalkoxy, halo$(C_1\text{-}C_6)$alkoxy, halo$(C_3\text{-}C_6)$cycloalkoxy, halo$(C_4\text{-}C_7)$cycloalkylalkoxy, $(C_1\text{-}C_6)$alkylthio, $(C_3\text{-}C_6)$cycloalkythio, $(C_4\text{-}C_7)$cycloalkyl-alkylthio, halo$(C_1\text{-}C_6)$alkylthio, halo$(C_3\text{-}C_6)$cycloalkythio, halo$(C_4\text{-}C_7)$cycloalkylalkylthio, $(C_1\text{-}C_6)$alkanesulfinyl, $(C_3\text{-}C_6)$cycloalkanesulfinyl, $(C_4\text{-}C_7)$cycloalkylalkanesulfinyl, halo$(C_1\text{-}C_6)$alkanesulfinyl, halo$(C_3\text{-}C_6)$cycloalkanesulfinyl, halo$(C_4\text{-}C_7)$cycloalkylalkanesulfinyl, $(C_1\text{-}C_6)$alkanesulfonyl, $(C_3\text{-}C_6)$cycloalkanesulfonyl, $(C_4\text{-}C_7)$cycloalkylalkanesulfonyl, halo$(C_1\text{-}C_6)$alkanesulfonyl, halo$(C_3\text{-}C_6)$cycloalkanesulfonyl, halo$(C_4\text{-}C_7)$cyclo-alkylalkanesulfonyl, $(C_1\text{-}C_6)$alkylamino, di$(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1\text{-}C_6)$alkylaminocarbonyl, di$(C_1\text{-}C_6)$alkylaminocarbonyl, $(C_1\text{-}C_3)$alkoxy$(C_1\text{-}C_3)$alkylaminocarbonyl, heterocyclylcarbonyl, $(C_1\text{-}C_6)$alkylaminosulfonyl, di$(C_1\text{-}C_6)$alkylaminosulfonyl, heterocyclsulfonyl, $(C_1\text{-}C_6)$alkylcarbonylamino, $(C_1\text{-}C_6)$alkylcarbonylamino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonylamino, $(C_1\text{-}C_6)$alkylsulfonylamino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxycarbonyl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl,, hydroxy$(C_1\text{-}C_6)$alkoxy, heteroaryl, amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, di$(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl amino$(C_2\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylamino$(C_2\text{-}C_6)$alkoxy, di$(C_1\text{-}C_6)$alkylamino$(C_2\text{-}C_6)$alkoxyl and $(C_1\text{-}C_6)$alkylcarbonyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

82. The compound of claim 1, 15 and 17 wherein the compound is of Formula (If_2)

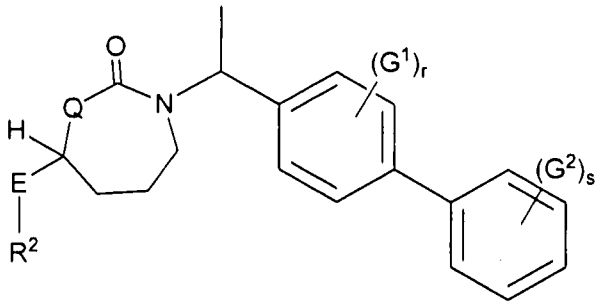


If_2

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

83. The compound of claim 1, 15 and 18 wherein the compound is of Formula (If_3)

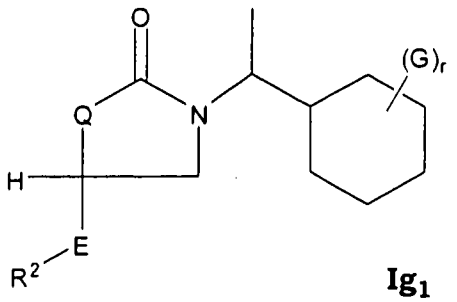


If_3

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

84. The compound of claim 1, 15 or 16 wherein the compound is of Formula (Ig_1)



Ig_1

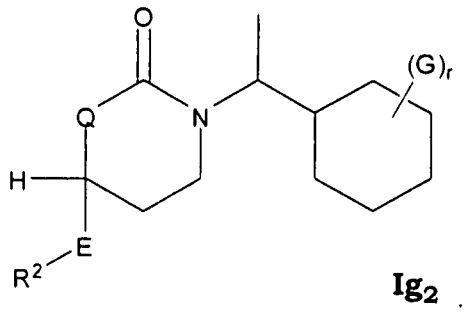
; wherein

r is 0, 1, 2, 3 or 4; and

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkyl-alkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkanesulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cyclo-alkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl,, hydroxy(C_1-C_6)alkoxy, heteroaryl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl and (C_1-C_6)alkylcarbonyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

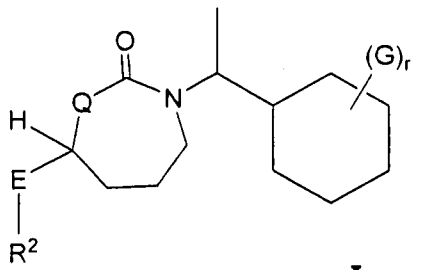
85. The compound of claim 1, 15 and 17 wherein the compound is of Formula (Ig_2)



Ig_2 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

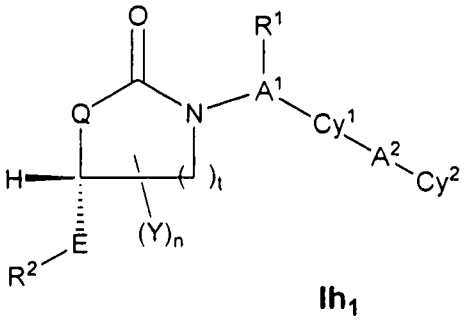
86. The compound of claim 1, 15 and 18 wherein the compound is of Formula (Ig_3)



Ig_3 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

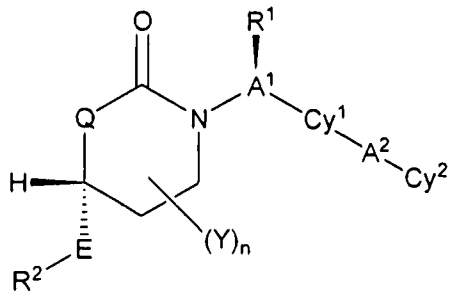
87. The compound of claim 1, 15 or 16 wherein the compound is of Formula (Ih_1)



Ih_1 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

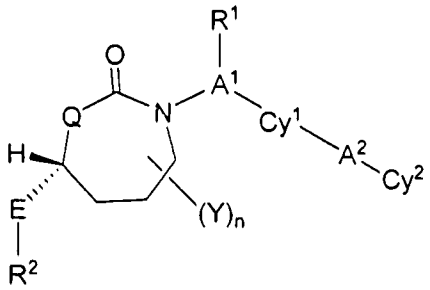
88. The compound of claim 1, 15 and 17 wherein the compound is of Formula (Ih_2)



Ih$_2$

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

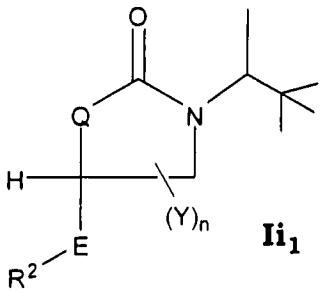
89. The compound of claim 1, 15 and 18 wherein the compound is of Formula (Ih$_3$)



Ih$_3$;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

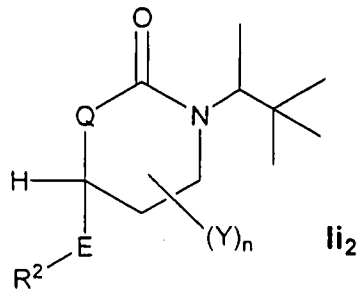
90. The compound of claim 1, 2 or 3 wherein the compound is of Formula (Ii$_1$)



Ii$_1$;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

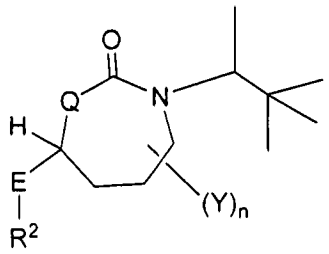
91. The compound of claim 1, 2 or 4 wherein the compound is of Formula (Ii$_2$)



Ii_2 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

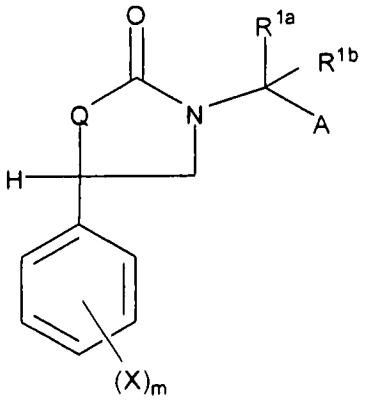
92. The compound of claim 1, 2 or 5 wherein the compound is of Formula (Ii_3)



Ii_3 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

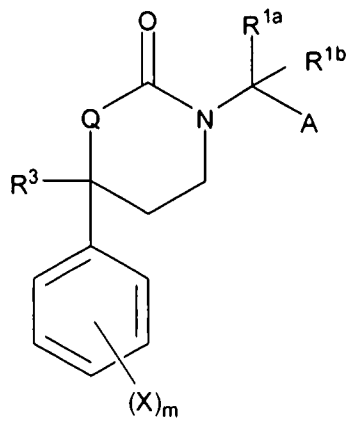
93. The compound of claim 1, 2 or 3 wherein the compound is of Formula (Ij_1)



Ij_1 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

94. The compound of claim 1, 2 or 4 wherein the compound is of Formula (Ij_2)

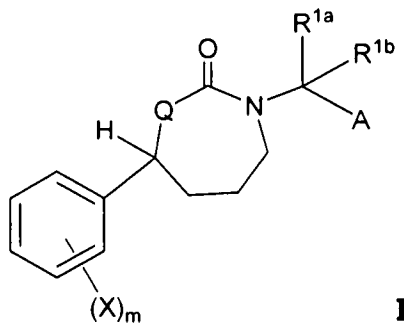


Ij2

;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

95. The compound of claim 1, 2 or 5 wherein the compound is of Formula (Ij_3)



Ij3 ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

96. The compound of any one of claims 1-5, 15-18 or 66-95, wherein Q is CH_2.

97. The compound of any one of claims 1-5, 15-18 or 66-95, wherein Q is O.

98. The compound of any one of claims 1-5, 15-18 or 66-95, wherein Q is NR^5.

99. The compound of claim 1, wherein:

E is a bond or (C_1-C_3)alkylene, optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo; and when Q is NH, ER^2 is not (C_1-C_6)alkyl substituted with halo, hydroxy or phenyl;

Cy^1 is aryl or heteroaryl, optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, cyano, nitro, , hydroxy, carboxy, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, halo$(C_2$-$C_6)$alkenyl, hydroxy$(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, halo$(C_1$-$C_6)$alkylthio, $(C_1$-$C_6)$alkanesulfinyl, halo$(C_1$-$C_6)$alkane-sulfinyl, $(C_1$-$C_6)$alkanesulfonyl, halo$(C_1$-$C_6)$alkanesulfonyl, $(C_1$-$C_6)$alkylamino, di$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1$-$C_6)$alkylaminocarbonyl, di$(C_1$-$C_6)$alkylaminocarbonyl, $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkylaminocarbonyl, $(C_1$-$C_6)$alkylaminosulfonyl, di$(C_1$-$C_6)$alkylaminosulfonyl, $(C_1$-$C_6)$alkylcarbonylamino, $(C_1$-$C_6)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonylamino, $(C_1$-$C_6)$alkylsulfonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkoxy, oxo, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, di$(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl amino$(C_2$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxy, di$(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxyl and $(C_1$-$C_6)$alkylcarbonyl;

Cy^2 is meta or para to the ring atom of Cy^1 that is bonded to A_1;

R^2 is $(C_1$-$C_6)$alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl, each is optionally substituted with up to 4 groups, independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, hydroxy$(C_3$-$C_6)$cycloalkyl, $(C_4$-$C_7)$cycloalkylalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_2$-$C_6)$alkenyl, hydroxy$(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_6)$cycloalkyl$(C_2$-$C_4)$alkynyl, halo$(C_1$-$C_6)$alkyl, halo$(C_3$-$C_6)$cycloalkyl, halo$(C_4$-$C_7)$cycloalkylalkyl, $(C_1$-$C_6)$alkoxy, $(C_3$-$C_6)$cycloalkoxy, $(C_4$-$C_7)$cycloalkylalkoxy, halo$(C_1$-$C_6)$alkoxy, halo$(C_3$-$C_6)$cycloalkoxy, halo$(C_4$-$C_7)$cycloalkylalkoxy, $(C_1$-$C_6)$alkylthio, $(C_3$-$C_6)$cycloalkythio, $(C_4$-$C_7)$cycloalkylalkylthio, halo$(C_1$-$C_6)$alkylthio, halo$(C_3$-$C_6)$cycloalkythio, halo$(C_4$-$C_7)$cycloalkylalkylthio, $(C_1$-$C_6)$alkanesulfinyl, $(C_3$-$C_6)$cycloalkanesulfinyl, $(C_4$-$C_7)$cycloalkylalkanesulfinyl, halo$(C_1$-$C_6)$alkane-sulfinyl, halo$(C_3$-$C_6)$cycloalkanesulfinyl, halo$(C_4$-$C_7)$cycloalkyl-alkanesulfinyl, $(C_1$-$C_6)$alkanesulfonyl, $(C_3$-$C_6)$cycloalkanesulfonyl, $(C_4$-$C_7)$cycloalkyl-alkanesulfonyl, halo$(C_1$-$C_6)$alkanesulfonyl, halo$(C_3$-$C_6)$cycloalkanesulfonyl, halo$(C_4$-$C_7)$cyclo-alkylalkanesulfonyl, $(C_1$-$C_6)$alkylamino, di$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1$-$C_6)$alkylaminocarbonyl, di$(C_1$-$C_6)$alkylaminocarbonyl, $(C_1$-

C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl and (C_1-C_6)alkylcarbonyl, wherein the aryl and heteroaryl represented by R^2 are substituted only meta or para to the ring atom attached to E.

100. A compound selected from the group consisting of:
(S)-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one;
(R)-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one ;
(R)- 3-(naphthalen-1-yl)-6-phenyl-1,3-oxazinan-2-one;
3-(3-Bromo-phenyl)-6-(2-chloro-phenyl)-[1,3]oxazinan-2-one;
1-((1S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-4-phenylpiperidin-2-one;
4(-4-fluorophenyl)-1-((1S)-1-(4-methoxylphenyl)ethyl)piperidin-2-one;
3-((1S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
4-phenyl-1-((1S)-1-phenylethyl)-1,3-diazepan-2-one;
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

101. A method of treating a subject with a disease associated with the activity or expression of 11β-HSD1, comprising the step of administering to the subject an effective amount of the compound of any one of claims 1-100.

102. A method of inhibiting 11β-HSD1 activity comprising the step of administering to a subject in need of such treatment an effective amount of a compound of claims 1-100.

103. A method of claim 101, wherein the disease associated with the activity or expression of 11β-HSD1, is diabetes mellitus, obesity, symptoms of metabolic syndrome, glucose intolerance, hyperglycemica, hypertension, hyperlipidemia, insulin resistance, cardiovascular disease, dyslipidemia, atherosclerosis, lipodystrophy,

osteoporosis, glaucoma, Cushing's syndrome, Addison's Disease, visceral fat obesity associated with glucocorticoid therapy, depression, anxiety, Alzheimer's disease, dementia, cognitive decline (including age-related cognitive decline), polycystic ovarian syndrome, infertility, hypergonadism, tuberculosis, leprosy or psoriasis.

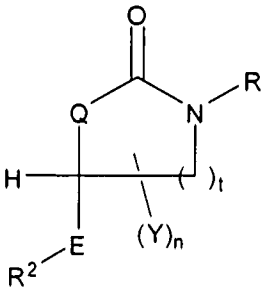
104. A method of claim 101, wherein the disease associated with the activity or expression of 11β-HSD1, is diabetes, cardiovascular disease, anxiety or depression, glaucoma or osteoporosis.

105. A method of claim 102, wherein the subject is in need for treatment for diabetes mellitus, obesity, symptoms of metabolic syndrome, glucose intolerance, hyperglycemica, hypertension, hyperlipidemia, insulin resistance, cardiovascular disease, dyslipidemia, atherosclerosis, lipodystrophy, osteoporosis, glaucoma, Cushing's syndrome, Addison's Disease, visceral fat obesity associated with glucocorticoid therapy, depression, anxiety, Alzheimer's disease, dementia, cognitive decline (including age-related cognitive decline), polycystic ovarian syndrome, infertility, hypergonadism, tuberculosis, leprosy or psoriasis.

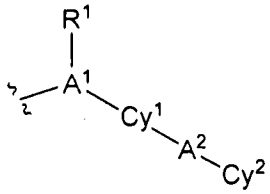
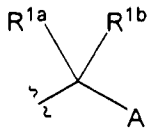
106. A method of claim 102, wherein the subject is in need for treatment for diabetes, cardiovascular disease, anxiety or depression, glaucoma or osteoporosis.

107. A pharmaceutical composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) the compound in any one of claims 1-100; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

108. A method of treating a subject with diabetes, anxiety or depression, glaucoma or osteoporosis, comprising the step of administering to a subject in need of such treatment an effective amount of a compound represented by Structural Formula I:



I ; wherein

R is  or  ;

R^1 is (a) absent or (b) is selected from $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl or $(C_1\text{-}C_3)$alkoxy$(C_1\text{-}C_3)$alkyl, wherein each is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R^4, R^4O-, $(R^4)_2N$-, R^4O_2C-, R^4S, $R^4S(=O)$-, $R^4S(=O)_2$-, $R^4C(=O)NR^4$-, $(R^4)_2NC(=O)$-, $(R^4)_2NC(=O)O$-, $(R^4)_2NC(=O)NR^4$-, $R^4OC(=O)NR^4$-, $(R^4)_2NC(=NCN)NR^4$-, $(R^4O)_2P(=O)O$-, $(R^4O)_2P(=O)NR^4$-, $R^4OS(=O)_2NR^4$-, $(R^4)_2NS(=O)_2O$-, $(R^4)_2NS(=O)_2NR^4$-, $R^4S(=O)_2NR^4$-, $R^4S(=O)_2NHC(=O)$-, $R^4S(=O)_2NHC(=O)O$-, $R^4S(=O)_2NHC(=O)NR^4$-, $R^4OS(=O)_2NHC(=O)$-, $R^4OS(=O)_2NHC(=O)O$-, $R^4OS(=O)_2NHC(=O)NR^4$-, $(R^4)_2NS(=O)_2NHC(=O)$-, $(R^4)_2NS(=O)_2NHC(=O)O$-, $(R^4)_2NS(=O)_2NHC(=O)NR^4$-, $R^4C(=O)NHS(=O)_2$-, $R^4C(=O)NHS(=O)_2O$-, $R^4C(=O)NHS(=O)_2NR^4$-, $R^4OC(=O)NHS(=O)_2$-, $R^4OC(=O)NHS(=O)_2O$-, $R^4OC(=O)NHS(=O)_2NR^4$-, $(R^4)_2NC(=O)NHS(=O)_2$-, $(R^4)_2NC(=O)NHS(=O)_2O$-, $(R^4)_2NC(=O)NHS(=O)_2NR^4$-, aryl, cycloalkyl, heterocyclyl, heteroaryl, arylamino and heteroarylamino;

A^1 is (a) a bond, or (b) $(C_1\text{-}C_3)$alkylene, CH_2CH_2O, wherein the oxygen is attached to Cy^1, or $CH_2C(=O)$, wherein the carbonyl carbon is attached to Cy^1;

Cy^1 is aryl or heteroaryl, wherein each is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_3\text{-}C_6)$cycloalkyl, $(C_4\text{-}C_7)$cycloalkylalkyl, $(C_2\text{-}C_6)$alkenyl, halo$(C_2\text{-}C_6)$alkenyl, hydroxy$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_6)$cycloalkyl$(C_2\text{-}C_4)$alkynyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_3\text{-}C_6)$cycloalkyl, halo$(C_4\text{-}C_7)$cycloalkylalkyl, $(C_1\text{-}$

C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkylalkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cyclo-alkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxy and (C_1-C_6)alkylcarbonyl;

A^2 is (a) a bond, O or S; or (b) (C_2-C_3)alkylene or (C_1-C_2)alkyleneoxy, each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo;

Cy^2 is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkyl-alkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-

C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cycloalkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, heteroaryl, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxy and (C_1-C_6)alkylcarbonyl;

R^{1a} and R^{1b} are each independently selected from (a) hydrogen or (b) (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl or (C_1-C_3)alkoxy(C_1-C_3)alkyl which are optionally substituted with up to three groups independently selected from fluorine, hydroxy, (C_1-C_3)alkoxy and $H_2NC(=O)$;

A is straight or branched (C_1-C_8)alkyl, (C_2-C_8)alkenyl or (C_2-C_8)alkynyl, optionally substituted with up to 4 groups independently selected from fluorine, cyano, oxo, R^4, -OH R^4O-, $(R^4)_2N$-, R^4O_2C-, R^4S, $R^4S(=O)$-, $R^4S(=O)_2$-, $R^4C(=O)NR^4$-, $(R^4)_2NC(=O)$-, $(R^4)_2NC(=O)O$-, $(R^4)_2NC(=O)NR^4$-, $R^4OC(=O)NR^4$-, $(R^4)_2NC(=NCN)NR^4$-, $(R^4O)_2P(=O)O$-, $(R^4O)_2P(=O)NR^4$-, $R^4OS(=O)_2NR^4$-, $(R^4)_2NS(=O)_2O$-, $(R^4)_2NS(=O)_2NR^4$-, $R^4S(=O)_2NR^4$-, $R^4SO_2NR^4$-, $R^4S(=O)_2NHC(=O)$-, $R^4S(=O)_2NHC(=O)O$-, $R^4S(=O)_2NHC(=O)NR^4$-, $R^4OS(=O)_2NHC(=O)$-, $R^4OS(=O)_2NHC(=O)O$-, $R^4OS(=O)_2NHC(=O)NR^4$-, $(R^4)_2NS(=O)_2NHC(=O)$-, $(R^4)_2NS(=O)_2NHC(=O)O$-, $(R^4)_2NS(=O)_2NHC(=O)NR^4$-, $R^4C(=O)NHS(=O)_2$-, $R^4C(=O)NHS(=O)_2O$-, $R^4C(=O)NHS(=O)_2NR^4$-, $R^4OC(=O)NHS(=O)_2$-, $R^4OC(=O)NHS(=O)_2O$-, $R^4OC(=O)NHS(=O)_2NR^4$-, $(R^4)_2NC(=O)NHS(=O)_2$-, $(R^4)_2NC(=O)NHS(=O)_2O$-, $(R^4)_2NC(=O)NHS(=O)_2NR^4$-, heterocyclylamino (wherein the heterocyclyl portion is optionally substituted by alkyl, haloalkyl or oxo); heteroarylamino (wherein the heteroaryl portion is optionally substituted by alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H, $CONH_2$, N-monoalkyl-substituted amido, N,N-dialkyl-substituted

amido, or oxo); arylamino (wherein the aryl portion is optionally substituted by alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H, $CONH_2$, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); and cycloalkylamino (wherein the cycloalkyl portion is optionally substituted by alkyl, haloalkyl or oxo);

Q is O, NR^5 or CH_2;

Y is $(C_1$-$C_6)$alkyl or halo$(C_1$-$C_6)$alkyl;

n is 0, 1 or 2;

t is 1, 2 or 3;

E is (a) a bond or (b) $(C_1$-$C_3)$alkylene or $(C_1$-$C_2)$alkylenyloxy, wherein the O is attached to R^2, each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo; when Q is NH, then ER^2 is not $(C_1$-$C_6)$alkyl optionally substituted with halo, hydroxy or phenyl (alternatively , ER^2 is not $(C_1$-$C_6)$alkyl optionally substituted with halo, hydroxy and ER^2 is not benzyl);

R^2 is $(C_1$-$C_6)$alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with up to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, hydroxy$(C_3$-$C_6)$cycloalkyl, $(C_4$-$C_7)$cycloalkylalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_2$-$C_6)$alkenyl, hydroxy$(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_6)$cycloalkyl$(C_2$-$C_4)$alkynyl, halo$(C_1$-$C_6)$alkyl, halo$(C_3$-$C_6)$cycloalkyl, halo$(C_4$-$C_7)$cycloalkylalkyl, $(C_1$-$C_6)$alkoxy, $(C_3$-$C_6)$cycloalkoxy, $(C_4$-$C_7)$cycloalkylalkoxy, halo$(C_1$-$C_6)$alkoxy, halo$(C_3$-$C_6)$cycloalkoxy, halo$(C_4$-$C_7)$cycloalkylalkoxy, $(C_1$-$C_6)$alkylthio, $(C_3$-$C_6)$cycloalkythio, $(C_4$-$C_7)$cycloalkyl-alkylthio, halo$(C_1$-$C_6)$alkylthio, halo$(C_3$-$C_6)$cycloalkythio, halo$(C_4$-$C_7)$cycloalkylalkylthio, $(C_1$-$C_6)$alkanesulfinyl, $(C_3$-$C_6)$cycloalkanesulfinyl, $(C_4$-$C_7)$cycloalkylalkanesulfinyl, halo$(C_1$-$C_6)$alkane-sulfinyl, halo$(C_3$-$C_6)$cycloalkanesulfinyl, halo$(C_4$-$C_7)$cycloalkylalkanesulfinyl, $(C_1$-$C_6)$alkanesulfonyl, $(C_3$-$C_6)$cycloalkanesulfonyl, $(C_4$-$C_7)$cycloalkylalkanesulfonyl, halo$(C_1$-$C_6)$alkanesulfonyl, halo$(C_3$-$C_6)$cycloalkanesulfonyl, halo$(C_4$-$C_7)$cyclo-alkylalkanesulfonyl, $(C_1$-$C_6)$alkylamino, di$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1$-$C_6)$alkylaminocarbonyl, di$(C_1$-$C_6)$alkylaminocarbonyl, $(C_1$-

C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkoxy, oxo, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxy and (C_1-C_6)alkylcarbonyl;

R^4 is independently selected from H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl and (C_1-C_6)alkoxy(C_1-C_6)alkyl;

R^5 is H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

109. A method of claim 108 wherein the compound is represented by any one of the structural formulas I_1-I_{26}, or Ia_{1-3}-Ij_{1-3}, wherein

r and s are independently 0, 1, 2, 3 or 4;

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkylalkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cyclo-alkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl,

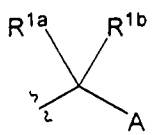
di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl,, hydroxy(C_1-C_6)alkoxy, heteroaryl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl or (C_1-C_6)alkylcarbonyl;

m is 0, 1, 2, 3 or 4;

X is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkythio, (C_4-C_7)cycloalkylalkylthio, halo(C_1-C_6)alkylthio, halo(C_3-C_6)cycloalkythio, halo(C_4-C_7)cycloalkylalkylthio, (C_1-C_6)alkanesulfinyl, (C_3-C_6)cycloalkanesulfinyl, (C_4-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkane-sulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cycloalkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO, H_2NSO_2, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclsulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-C_6)alkylcarbonylamino(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonylamino, (C_1-C_6)alkylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy(C_1-C_6)alkyl,, hydroxy(C_1-C_6)alkoxy, heteroaryl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl amino(C_2-C_6)alkoxy, (C_1-C_6)alkylamino(C_2-C_6)alkoxy, di(C_1-C_6)alkylamino(C_2-C_6)alkoxyl and (C_1-C_6)alkylcarbonyl;

G^1 and G^2 are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, hydroxy$(C_3$-$C_6)$cycloalkyl, $(C_4$-$C_7)$cycloalkylalkyl, $(C_2$-$C_6)$alkenyl, halo$(C_2$-$C_6)$alkenyl, hydroxy$(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_3$-$C_6)$cycloalkyl$(C_2$-$C_4)$alkynyl, halo$(C_1$-$C_6)$alkyl, halo$(C_3$-$C_6)$cycloalkyl, halo$(C_4$-$C_7)$cycloalkylalkyl, $(C_1$-$C_6)$alkoxy, $(C_3$-$C_6)$cycloalkoxy, $(C_4$-$C_7)$cycloalkylalkoxy, halo$(C_1$-$C_6)$alkoxy, halo$(C_3$-$C_6)$cycloalkoxy, halo$(C_4$-$C_7)$cycloalkylalkoxy, $(C_1$-$C_6)$alkylthio, $(C_3$-$C_6)$cycloalkythio, $(C_4$-$C_7)$cycloalkylalkylthio, halo$(C_1$-$C_6)$alkylthio, halo$(C_3$-$C_6)$cycloalkythio, halo$(C_4$-$C_7)$cycloalkylalkylthio, $(C_1$-$C_6)$alkanesulfinyl, $(C_3$-$C_6)$cycloalkanesulfinyl, $(C_4$-$C_7)$cycloalkylalkanesulfinyl, halo$(C_1$-$C_6)$alkanesulfinyl, halo$(C_3$-$C_6)$cycloalkanesulfinyl, halo$(C_4$-$C_7)$cycloalkylalkanesulfinyl, $(C_1$-$C_6)$alkanesulfonyl, $(C_3$-$C_6)$cycloalkanesulfonyl, $(C_4$-$C_7)$cycloalkylalkanesulfonyl, halo$(C_1$-$C_6)$alkanesulfonyl, halo$(C_3$-$C_6)$cycloalkanesulfonyl, halo$(C_4$-$C_7)$cycloalkylalkanesulfonyl, $(C_1$-$C_6)$alkylamino, di$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxycarbonyl, H_2NCO, H_2NSO_2, $(C_1$-$C_6)$alkylaminocarbonyl, di$(C_1$-$C_6)$alkylaminocarbonyl, $(C_1$-$C_3)$alkoxy$(C_1$-$C_3)$alkylaminocarbonyl, heterocyclylcarbonyl, $(C_1$-$C_6)$alkylaminosulfonyl, di$(C_1$-$C_6)$alkylaminosulfonyl, heterocyclsulfonyl, $(C_1$-$C_6)$alkylcarbonylamino, $(C_1$-$C_6)$alkylcarbonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonylamino, $(C_1$-$C_6)$alkylsulfonylamino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxycarbonyl$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl,, hydroxy$(C_1$-$C_6)$alkoxy, heteroaryl, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, di$(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl amino$(C_2$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxy, di$(C_1$-$C_6)$alkylamino$(C_2$-$C_6)$alkoxyl and $(C_1$-$C_6)$alkylcarbonyl, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof, and the rest of variables are as defined in claim 108.

110. A method of claim 108 or 109 wherein the compound is represented by any one of the structural formulas I_1-I_{13} or $Ij_{1\text{-}3}$ wherein

R is 

;

R^{1a} is methyl or ethyl;

R^{1b} is methyl or hydrogen;

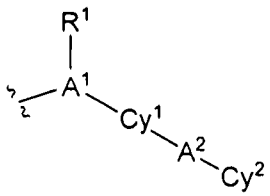
A is methyl, ethyl, isopropyl or t-butyl;

n is 0;

E is a bond or CH_2; and

R^2 is phenyl, thienyl or pyridyl each optionally substituted with halo or methyl, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

111. A method of claim 108 or 109 wherein the compound is represented by any one of the structural formulas I_{14}-I_{26}, or Ia_{1-3}-Ih_{1-3}, wherein

R is  ;

R^1 is absent or is methyl or ethyl;

A^1 is a bond or CH_2;

Cy^1 is phenyl, cyclohexyl, pyridyl, N-oxo-pyridyl, thiazolyl or pyrimidinyl optionally substituted with 1 to 4 groups independently selected from halo, methyl, trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy and 2-hydroxy-2-methylpropoxy;

A^2 is a bond, O or OCH_2CO;

Cy^2 is (a) hydrogen or (b) phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl or piperazinyl optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonyl-aminomethyl or tetrazolyl;

n is 0;

E is a bond or CH_2;

R^2 is phenyl or pyridyl optionally substituted with one group selected from halo, methyl, methylthio or (4-morpholino)methyl; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.