



(86) Date de dépôt PCT/PCT Filing Date: 2009/03/18
(87) Date publication PCT/PCT Publication Date: 2009/09/24
(85) Entrée phase nationale/National Entry: 2010/09/10
(86) N° demande PCT/PCT Application No.: US 2009/001712
(87) N° publication PCT/PCT Publication No.: 2009/117109
(30) Priorité/Priority: 2008/03/18 (US61/037,646)

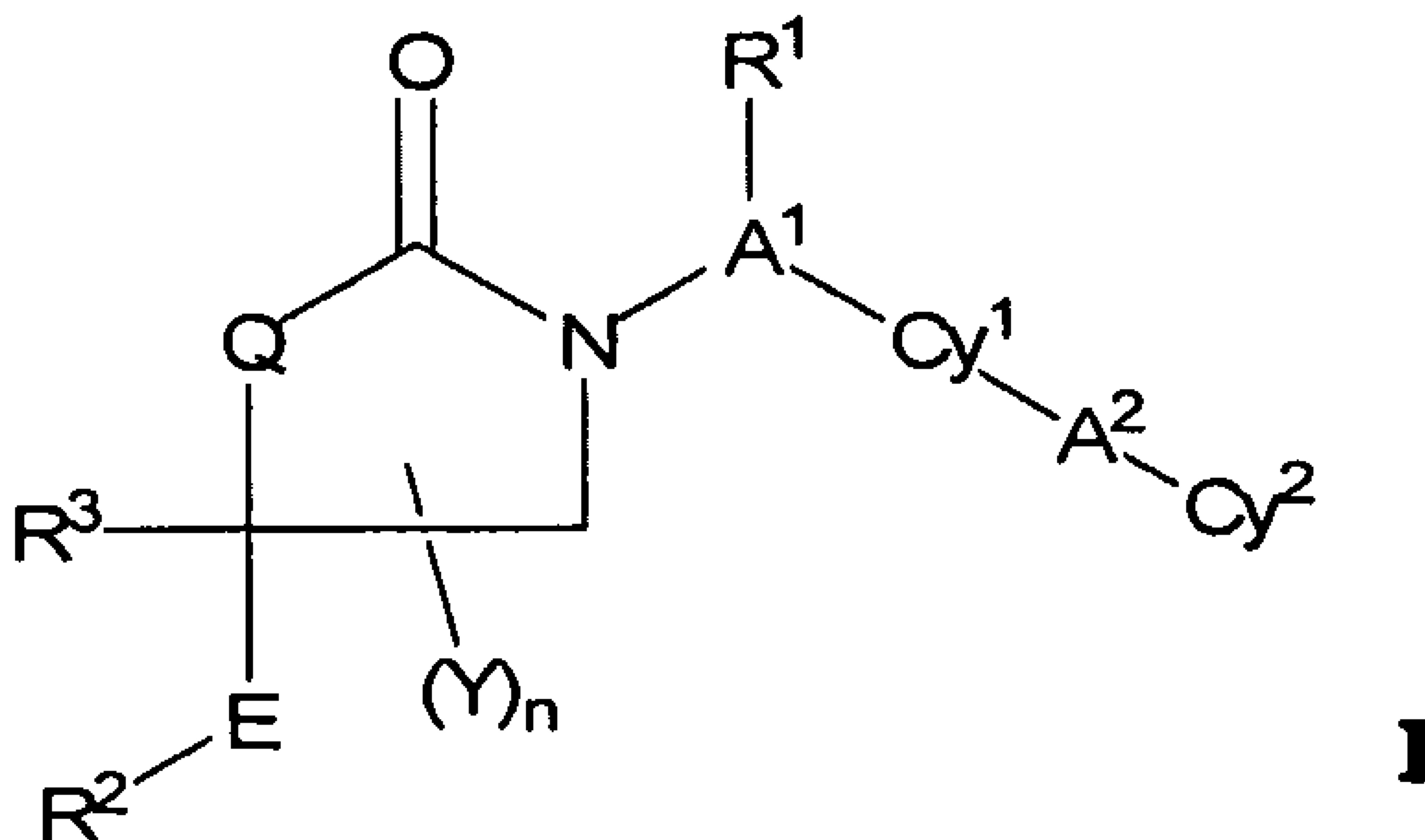
(51) Cl.Int./Int.Cl. *C07D 233/32* (2006.01),
A61K 31/445 (2006.01), *C07D 263/22* (2006.01),
C07D 263/24 (2006.01), *C07D 401/04* (2006.01),
C07D 403/06 (2006.01), *C07D 409/10* (2006.01),
C07D 413/04 (2006.01), *C07D 413/06* (2006.01),
C07D 413/10 (2006.01), *C07D 417/10* (2006.01)

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(54) Titre : INHIBITEURS DE LA 11-BETA-HYDROXYSTEROIDE DESHYDROGENASE DE TYPE 1

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



(57) Abrégé/Abstract:

This invention relates to novel compounds of the Formula (I) and 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.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
24 September 2009 (24.09.2009)

PCT

(10) International Publication Number
WO 2009/117109 A1

(51) International Patent Classification:

C07D 233/32 (2006.01) C07D 413/04 (2006.01)
C07D 263/22 (2006.01) C07D 413/06 (2006.01)
C07D 263/24 (2006.01) C07D 413/10 (2006.01)
C07D 401/04 (2006.01) C07D 417/10 (2006.01)
C07D 403/06 (2006.01) A61K 31/445 (2006.01)
C07D 409/10 (2006.01)

(21) International Application Number:

PCT/US2009/001712

(22) International Filing Date:

18 March 2009 (18.03.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/037,646 18 March 2008 (18.03.2008) US

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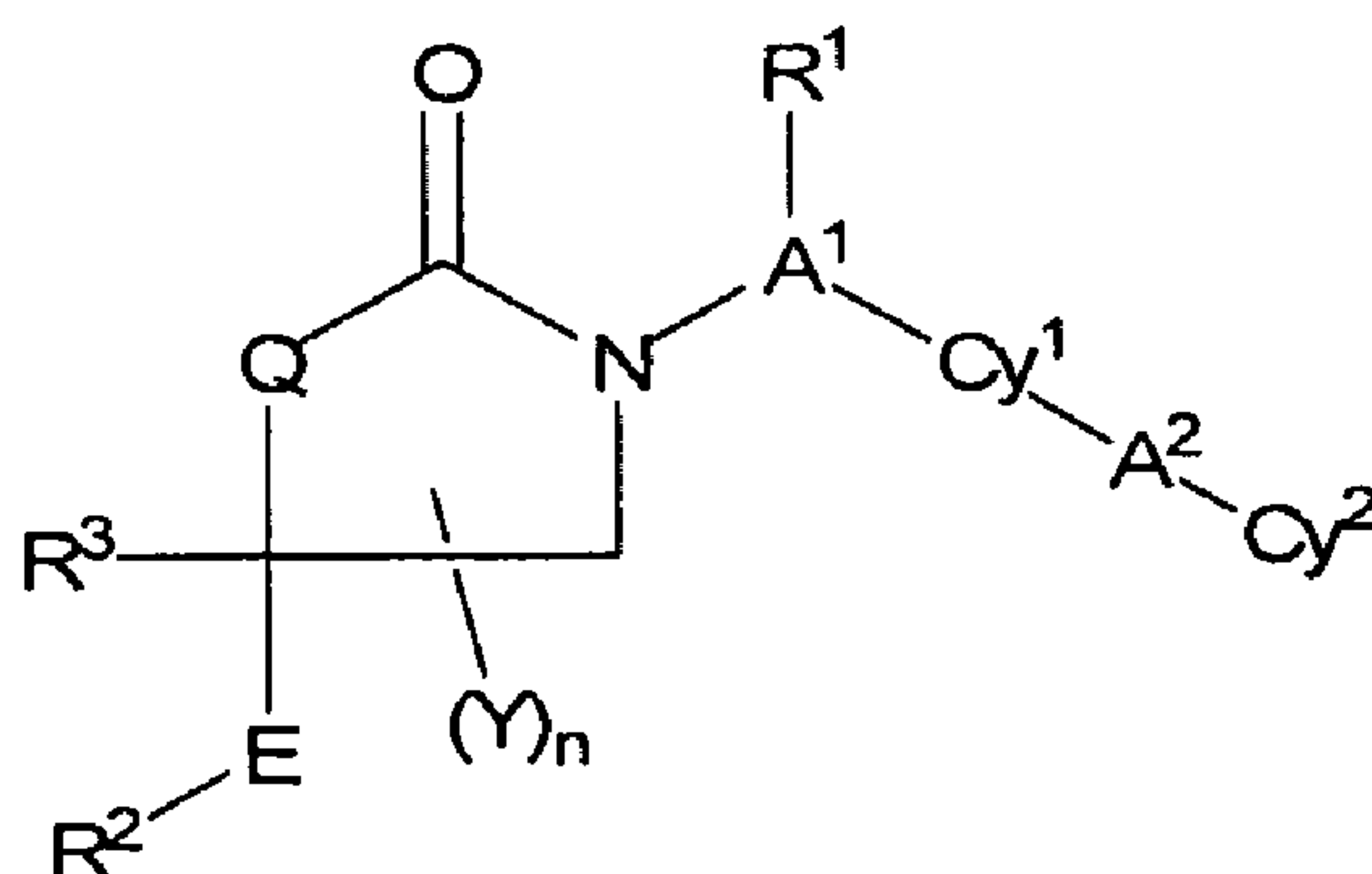
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

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

**I**

(57) Abstract: This invention relates to novel compounds of the Formula (I) and 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.

INHIBITORS OF 11BETA-HYDROXYSTEROID DEHYDROGENASE TYPE 1

RELATED APPLICATIONS

5 The application claims the benefit of U.S. Provisional Application No. 61/037,646, filed March 18, 2008, the entire teachings of which are incorporated herein by reference.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

15 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
20 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
25 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 11 β -
30 hydroxysteroid dehydrogenase (11 β -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: 11 β -HSD1 (also known as 11-beta-HSD type 1, 11betaHSD1, HSD11B1, and HSD11L) and 11 β -HSD2. 11 β -HSD1 is a bi-directional oxidoreductase that regenerates active cortisol from

inactive 11-keto forms, whereas 11 β -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. 11 β -HSD1 is widely distributed in rat
5 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, 11 β -HSD1 may regulate intraocular pressure and may contribute to glaucoma; some data suggests that inhibition
10 of 11 β -HSD1 may cause a drop in intraocular pressure in patients with intraocular hypertension (Kotelevtsev, *et al.*, (1997), Proc. Nat'l Acad. Sci. USA 94(26):14924-9). Although 11 β -HSD1 catalyzes both 11-beta-dehydrogenation and the reverse 11-oxoreduction reaction, 11 β -HSD1 acts predominantly as a NADPH-dependent oxoreductase in intact cells and tissues, catalyzing the formation of active cortisol from
15 inert cortisone (Low, *et al.*, (1994) J. Mol. Endocrin. 13: 167-174). In contrast, 11 β -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. 11 β -HSD2 acts as an NAD-dependent dehydrogenase catalyzing the inactivation of cortisol to cortisone (Albiston, *et al.*, (1994) Mol. Cell. Endocrin. 105:
20 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 11 β -HSD1 or the 11 β -HSD2 genes result in human pathology. For example, individuals with mutations in 11 β -HSD2 are deficient in this
25 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. Nat'l Acad. Sci. 95: 10200-10205). Similarly, mutations in 11 β -HSD1 and in the gene encoding a co-localized NADPH-generating enzyme, hexose 6-phosphate dehydrogenase (H6PD), can result in cortisone reductase deficiency (CRD);
30 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 & Chrousos, *Endocrinology and Metabolism* (Felig & Frohman eds., McGraw-Hill: New York, 4th Ed. (2001)) 387-524). Patients with Cushing's syndrome or
5 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
10 the role of glucocorticoids in human obesity is not fully characterized, there is mounting evidence that 11 β -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.*,
15 (2003) *J. Clin. Endocrinol. Metab.* 88, 3983-3988).

Data from studies in mouse transgenic models supports the hypothesis that adipocyte 11 β -HSD1 activity plays a central role in visceral obesity and metabolic syndrome (Alberts, *et al.*, (2002) *Diabetologia*. 45(11), 1526-32). Over-expression in
20 adipose tissue of 11 β -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 11 β -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 11 β HSD1-deficient mice produced by
25 homologous recombination demonstrate that the loss of 11 β -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. Nat'l Acad. Sci.* 94: 14924-14929; Morton, *et al.*, (2001) *J. Biol. Chem.* 276, 41293-41300; Morton, *et al.*, (2004) *Diabetes* 53, 931-938).

30 The published data supports the hypothesis that increased expression of 11 β -HSD1 contributes to increased local conversion of cortisone to cortisol in adipose tissue and hence that 11 β -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, 11 β -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 11 β -HSD1 activity may prove beneficial in treating numerous glucocorticoid-related disorders. For example, 11 β -HSD1 inhibitors could be effective in combating obesity and/or other aspects of the metabolic syndrome cluster, including glucose intolerance, insulin resistance, hyperglycemia, hypertension, and/or hyperlipidemia (Kotelevstev, *et al.*, (1997) *Proc. Nat'l 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 11 β -HSD1 activity may have beneficial effects on the pancreas, including the enhancement of glucose-stimulated insulin release (Billaudel & 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). Inter-individual differences in general cognitive function has 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. Such chronic exposure to glucocorticoid excess in certain brain subregions has been theorized to contribute to the decline of cognitive function (McEwen & Sapolsky (1995) *Curr. Opin. Neurobiol.* 5, 205-216). Therefore, inhibition of 11 β -HSD1 may reduce exposure to glucocorticoids in the brain and thereby protect against deleterious glucocorticoid effects on neuronal function, including cognitive impairment, dementia, and/or depression.

There is also evidence that glucocorticoids and 11 β -HSD1 play a role in regulation of 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 11 β -HSD1 in the eye could reduce local glucocorticoid concentrations and IOP, and hence could be used to treat or prevent glaucoma and other visual disorders.

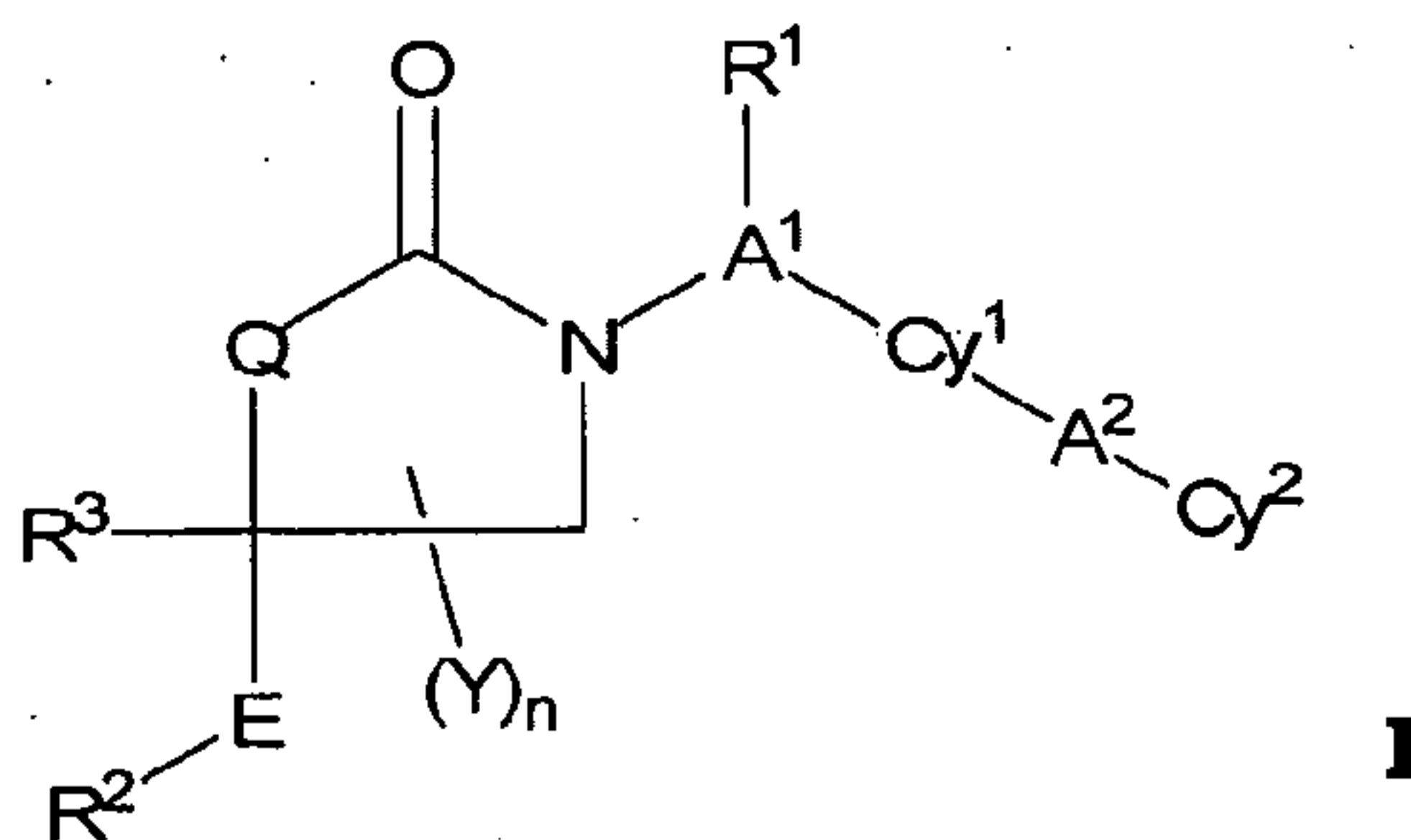
Transgenic aP2-11 β -HSD1 mice exhibit high arterial blood pressure and have increased sensitivity to dietary salt. Additionally, plasma angiotensinogen levels are elevated in the transgenic mice, as are angiotensin II and aldosterone. Treatment of the mice with an angiotensin II antagonist alleviates the hypertension (Masuzaki, *et al.*, (2003) *J. Clinical Invest.* 112, 83-90). This suggests that hypertension may be caused or exacerbated by 11 β -HSD1 activity. Thus, 11 β -HSD1 inhibitors may be useful for treatment of hypertension and hypertension-related cardiovascular disorders.

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, 11 β -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 11 β -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 11 β -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.

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

15 SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I:



wherein:

R¹ is (a) absent or (b) selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl and (C₁-C₃)alkoxy(C₁-C₃)alkyl, wherein each is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R⁴, R⁴O-, (R⁴)₂N-, R⁴O₂C-, R⁴S, R⁴S(=O)-, R⁴S(=O)₂-, R⁴C(=O)NR⁴-, (R⁴)₂NC(=O)-, (R⁴)₂NC(=O)O-, (R⁴)₂NC(=O)NR⁴-, R⁴OC(=O)NR⁴-, (R⁴)₂NC(=N)NR⁴-, (R⁴O)₂P(=O)O-, (R⁴O)₂P(=O)NR⁴-, R⁴OS(=O)₂NR⁴-, (R⁴)₂NS(=O)₂O-, (R⁴)₂NS(=O)₂NR⁴-, R⁴S(=O)₂NR⁴-, R⁴S(=O)₂NHC(=O)-, R⁴S(=O)₂NHC(=O)O-, R⁴S(=O)₂NHC(=O)NR⁴-, R⁴OS(=O)₂NHC(=O)-, R⁴OS(=O)₂NHC(=O)O-, R⁴OS(=O)₂NHC(=O)NR⁴-, (R⁴)₂NS(=O)₂NHC(=O)-, (R⁴)₂NS(=O)₂NHC(=O)O-, (R⁴)₂NS(=O)₂NHC(=O)NR⁴-, R⁴C(=O)NHS(=O)₂-, R⁴C(=O)NHS(=O)₂O-, R⁴C(=O)NHS(=O)₂NR⁴-, R⁴OC(=O)NHS(=O)₂-, R⁴OC(=O)NHS(=O)₂O-, R⁴OC(=O)NHS(=O)₂NR⁴-,

$(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, 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 ;

- 5 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 $(C_2-$
- 10 $C_4)$ 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) cycloalkylthio, (C_4-C_7) cycloalkylalkylthio, halo (C_1-C_6) alkylthio, halo (C_3-C_6) cycloalkylthio, halo (C_4-C_7) cycloalkylalkylthio, (C_1-C_6) alkanesulfinyl, (C_3-C_6) cycloalkanesulfinyl, $(C_4-$
- 15 $C_7)$ 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-
- 20 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, heterocyclosulfonyl, (C_1-C_6) alkylcarbonylamino, (C_1-C_6) alkyl-
- 25 carbonylamino (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, (C_1-C_6) alkylcarbonyl, (C_3-C_6) cycloalkylcarbonyl, (C_3-C_6) cycloalkylaminocarbonyl, $\{(C_3-C_6)$ cycloalkyl $\} \{(C_1-$
- 30 $C_6)$ 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 $(C_3-$
- 35 $C_6)$ cycloalkylaminocarbonyl (C_1-C_6) alkyl;

A² is (a) a bond, O, S or NR⁴; or (b) (C₁-C₃)alkylene or (C₁-C₂)alkyleneoxy, each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo;

- 5 Cy² 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, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl} {(C₁-C₆)alkyl} aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl} {(C₁-C₆)alkyl} aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-

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C₆)cycloalkyl} {(C₁-C₆)alkyl} aminocarbonyl(C₁-C₆)alkyl and di(C₃-

C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;

Y is (C₁-C₆)alkyl or halo(C₁-C₆)alkyl;

n is 0, 1 or 2;

- 5 E is (a) a bond or (b) (C₁-C₃)alkylene or (C₁-C₂)alkylenyloxy, wherein the O is attached to R², each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo;
- R² is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein each is optionally substituted with up to 4 groups independently selected from fluorine, chlorine, bromine,
- 10 iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio,
- 15 (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy,
- 20 heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl} {(C₁-C₆)alkyl} aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl} {(C₁-
- 25 30

- C₆alkyl} aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl} {(C₁-C₆)alkyl} aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;
- R³ is selected from (C₂-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl and (C₁-C₃)alkoxy(C₁-C₃)alkyl, wherein the (C₂-C₆)alkyl is substituted with, and each of the (C₂-C₆)alkenyl, (C₂-C₆)alkynyl and (C₁-C₃)alkoxy(C₁-C₃)alkyl is optionally substituted with, up to four groups independently selected from fluorine, cyano, oxo, halo(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, R⁴O-, (R⁴)₂N-, R⁴O₂C-, R⁴S, R⁴S(=O)-, R⁴S(=O)₂-, R⁴C(=O)NR⁴-, (R⁴)₂NC(=O)-, (R⁴)₂NC(=O)O-, (R⁴)₂NC(=O)NR⁴-, R⁴OC(=O)NR⁴-, (R⁴)₂NC(=N)NR⁴-, (R⁴O)₂P(=O)O-, (R⁴O)₂P(=O)NR⁴-, R⁴OS(=O)₂NR⁴-, (R⁴)₂NS(=O)₂O-, (R⁴)₂NS(=O)₂NR⁴-, R⁴S(=O)₂NR⁴-, R⁴S(=O)₂NHC(=O)-, R⁴S(=O)₂NHC(=O)O-, R⁴S(=O)₂NHC(=O)NR⁴-, R⁴OS(=O)₂NHC(=O)-, R⁴OS(=O)₂NHC(=O)O-, R⁴OS(=O)₂NHC(=O)NR⁴-, (R⁴)₂NS(=O)₂NHC(=O)-, (R⁴)₂NS(=O)₂NHC(=O)O-, (R⁴)₂NS(=O)₂NHC(=O)NR⁴-, R⁴C(=O)NHS(=O)₂-, R⁴C(=O)NHS(=O)₂O-, R⁴C(=O)NHS(=O)₂NR⁴-, R⁴OC(=O)NHS(=O)₂-, R⁴OC(=O)NHS(=O)₂O-, R⁴OC(=O)NHS(=O)₂NR⁴-, (R⁴)₂NC(=O)NHS(=O)₂-, (R⁴)₂NC(=O)NHS(=O)₂O-, (R⁴)₂NC(=O)NHS(=O)₂NR⁴-, heterocyclyl (which in turn may be optionally substituted with alkyl, haloalkyl or oxo), heteroaryl (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo), arylamino (which in turn may be optionally substituted with alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido) and heteroaryl-amino (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo);
- R⁴ is independently selected from H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl and (C₁-C₆)alkoxy(C₁-C₆)alkyl;
- Q = O, NR⁵; and
- R⁵ is H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl or hydroxy(C₁-C₆)alkyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the invention is a compound of Formula I wherein Cy¹ 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, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl;

Cy² 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, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-

- C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-
 C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkyl-
 alkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-
 C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-
 5 C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-
 C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl,
 (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-
 C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cyclo-
 alkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-
 10 C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO,
 H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-
 C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-
 C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-
 C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-
 15 C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-
 C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy,
 heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-
 C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy,
 di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl;
- 20 R² is (C₁-C₆)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, (C₁-C₆)alkyl,
 hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-
 C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-
 25 C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl,
 halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-
 C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-
 C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkyl-
 alkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-
 30 C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-
 C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-
 C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl,
 (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-
 C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cyclo-

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alkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl and the reminder of the variables are as defined above.

The present invention also provides a pharmaceutical composition comprising a disclosed 11 β -HSD1 inhibitor, including a compound of Formula I, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof, and a pharmaceutically acceptable carrier or diluent, wherein the values for the variables are as described above for the compounds of Formula I.

The present invention further provides a method of inhibiting 11 β -HSD1 activity, comprising administering to a mammal in need thereof an effective amount of a disclosed 11 β -HSD1 inhibitor, including a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the values for the variables are as described above for the compounds of Formula I.

Also included in the present invention is a method of treating a disease or disorder associated with activity or expression of 11 β -HSD1, comprising administering to a mammal in need thereof an effective amount of a disclosed 11 β -HSD1 inhibitor, including a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the values for the variables are as described above for the compounds of Formula I.

Also included in the present invention is the use of a disclosed 11 β -HSD1 inhibitor, including a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting 11 β -HSD1 activity in a mammal in need of such treatment.

Also included in the present invention is the use of a disclosed 11 β -HSD1 inhibitor, including a compound of Formula I, or a pharmaceutically acceptable salt

thereof, for the manufacture of a medicament for treating a disease or disorder related to the activity or expression of 11 β -HSD1, inhibiting the conversion of cortisone to cortisol in a cell, inhibiting production of cortisol in a cell, increasing insulin sensitivity in a mammal in need thereof, modulating 11 β -HSD1 activity in a mammal in need thereof,
 5 and/or inhibiting 11 β -HSD1 in a mammal in need thereof.

Also included in the present invention is a disclosed 11 β -HSD1 inhibitor, including a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in inhibiting 11 β -HSD1 activity in a mammal in need of such treatment.

Also included in the present invention is a disclosed 11 β -HSD1 inhibitor,
 10 including a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in therapy, e.g., treating a disease or disorder associated with activity or expression of 11 β -HSD1 in a subject.

DETAILED DESCRIPTION OF THE INVENTION

15 In one embodiment, the 11 β -HSD1 inhibitors of the invention are represented by Structural Formula I. Pharmaceutically acceptable salts of the 11 β -HSD1 inhibitors disclosed herein (including those represented by Structural Formula I) are also included in the invention. Values and alternative values for the variables in Structural Formula I are provided in the following paragraphs:

20 R^1 is (a) absent or (b) selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl and (C₁-C₃)alkoxy(C₁-C₃)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 , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$, $(R^4O)_2P(=O)O-$,
 25 $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$,
 30 $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, aryl, cycloalkyl, heterocyclyl, heteroaryl, arylamino and heteroarylamino. Alternatively, R^1 is absent. Alternatively, R^1 is unsubstituted or substituted (C₁-C₆)alkyl, wherein the substituents are as described above. Alternatively, R^1 is unsubstituted or substituted

methyl or ethyl, wherein the substituents are as described above. Alternatively, R¹ is unsubstituted methyl or ethyl.

A¹ is (a) a bond, or (b) (C₁-C₃)alkylene, CH₂CH₂O, wherein the oxygen is attached to Cy¹, or CH₂C(=O), wherein the carbonyl carbon is attached to Cy¹.

5 Alternatively, A¹ is a bond. Alternatively, A¹ is (C₁-C₃)alkylene. Alternatively, A¹ is methylene.

Cy¹ 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, (C₁-C₆)alkyl, hydroxy(C₁-
 10 C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy,
 15 (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-
 20 C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl,
 25 heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl oxo, amino(C₁-C₆)alkyl, (C₁-
 30 C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl.

Alternatively, Cy¹ is optionally substituted aryl or optionally substituted heteroaryl, wherein the substituents are as described above. Alternatively, Cy¹ is

optionally substituted phenyl or optionally substituted pyridyl, wherein the substituents are as described above. Alternatively, Cy¹ is optionally substituted phenyl, wherein the substituents are as described above. Alternatively, Cy¹ is optionally substituted monocyclic cycloalkyl, wherein the substituents are as described above. Alternatively, Cy¹ is optionally substituted cyclohexyl, wherein the substituents are as described above. Alternatively, Cy¹ is substituted with fluorine, chlorine, bromine, methoxy, difluoromethoxy, methoxycarbonyl, carboxy, methyl, or trifluoromethyl.

A² is (a) a bond, O, S or NR⁴; or (b) (C₁-C₃)alkylene or (C₁-C₂)alkyleneoxy, each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo. Alternatively, A² is a bond.

Cy² 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, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-

C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl.

Alternatively, Cy² is hydrogen. Alternatively, Cy² is optionally substituted aryl or heteroaryl, wherein the substituents are as described above. Alternatively, Cy² is optionally substituted cycloalkyl or heterocyclyl, wherein the substituents are as described above. Alternatively, Cy² is optionally substituted phenyl or pyridyl, wherein the substituents are as described above. Alternatively, Cy² is substituted with 1 to 4 groups independently selected from chlorine or fluorine. Alternatively, Cy² is difluorophenyl or monofluorophenyl. Alternatively, Cy² is 1,2-dihydro-2-oxopyridyl or 1,2-dihydro-1-methyl-2-oxopyridyl. Alternatively, Cy² is cyclopropyl.

Y is (C₁-C₆)alkyl or halo(C₁-C₆)alkyl.

n is 0, 1 or 2.

E is (a) a bond or (b) (C₁-C₃)alkylene or (C₁-C₂)alkylenyloxy, wherein the O is attached to R², 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 alkylene. Alternatively, E is a bond.

R² is (C₁-C₆)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, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-

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C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl.

Alternatively, R² is optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclyl, wherein the substituents are as described above; or R² is (C₁-C₆)alkyl substituted with up to 4 groups independently selected from fluorine, cyano, nitro, amino, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl.

Alternatively, R² is optionally substituted (C₁-C₆)alkyl, wherein the substituents are as described above; or R² is aryl, heteroaryl, cycloalkyl or heterocyclyl substituted with up to 4 groups independently selected from fluorine, bromine, iodine, cyano, amino, hydroxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl.

Alternatively, R² is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocyclyl, wherein the substituents are as described above.

Alternatively, R² is (a) isopropyl or (b) selected from optionally substituted phenyl, optionally substituted pyridyl and optionally substituted thienyl, wherein the substituents are as described above.

Alternatively, R² is optionally substituted phenyl, wherein the substituents are as described above.

Alternatively, R^2 is fluorophenyl.

R^3 is selected from (C₂-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl and (C₁-C₃)alkoxy(C₁-C₃)alkyl, wherein the (C₂-C₆)alkyl is substituted with, and each of the (C₂-C₆)alkenyl, (C₂-C₆)alkynyl and (C₁-C₃)alkoxy(C₁-C₃)alkyl is optionally substituted with,
 5 up to four groups independently selected from fluorine, cyano, oxo, halo(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, R^4O- , $(R^4)_2N-$, R^4O_2C- , R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$,
 10 $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$,
 15 $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, heterocyclyl (which in turn may be optionally substituted with alkyl, haloalkyl or oxo), heteroaryl (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo), aryl-amino (which in turn may be optionally substituted with alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido) and heteroaryl-amino (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio,
 20 alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo).

Alternatively, R^3 is substituted (C₂-C₆)alkyl, wherein the substituents are as described above. Alternatively, R^3 is hydroxy(C₂-C₅)alkyl. Alternatively, R^3 is dihydroxy(C₃-C₅)alkyl. Alternatively, R^3 is ω -H₂NCO(C₁-C₃)alkyl. Alternatively, R^3 is (C₁-C₂)alkoxy(C₁-C₃)alkyl. Alternatively, R^3 is H₂NSO₂O(C₂-C₄)alkyl. Alternatively,
 30 R^3 is H₂NSO₂NH(C₂-C₄)alkyl. Alternatively, R^3 is oxo(C₂-C₄)alkyl. Alternatively, R^3 is MeC(=O)NH(C₂-C₄)alkyl. Alternatively, R^3 is 2-hydroxy-2-methylpropyl. Alternatively, R^3 is 2-(4-morpholino)ethyl. Alternatively, R^3 is MeSO₂NH(C₂-C₄)alkyl. Alternatively, R^3 is MeSO₂NHCH₂CH₂CH₂-.

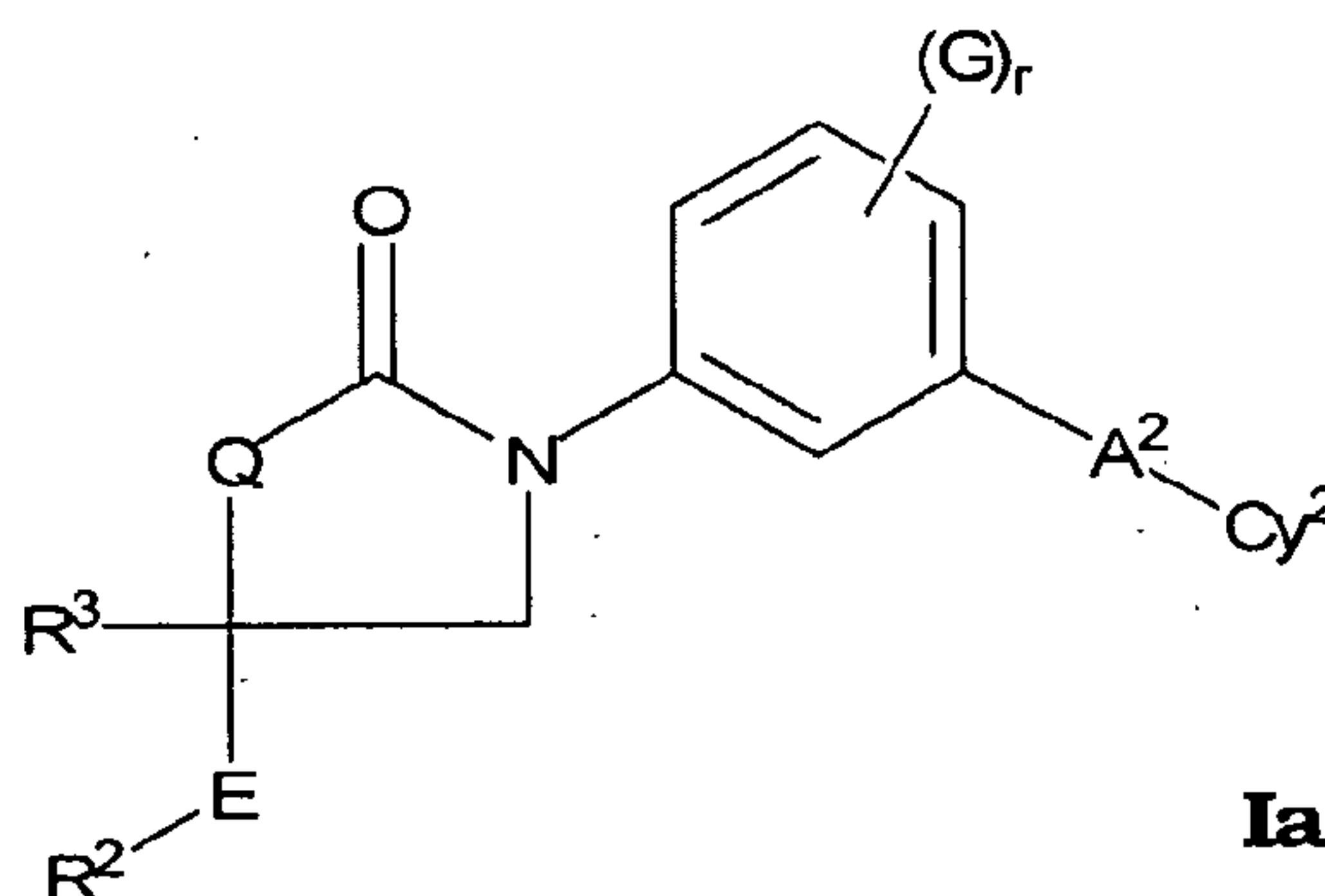
- 20 -

R^4 is independently selected from H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl and (C₁-C₆)alkoxy(C₁-C₆)alkyl.

Q = O, NR⁵. Alternatively, Q is O. Alternatively, Q is NR⁵. Alternatively, Q is
5 NH.

R^5 is H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl or hydroxy(C₁-C₆)alkyl.

In a second embodiment, the 11 β -HSD1 inhibitors of the invention are represented by Structural Formula Ia:



10

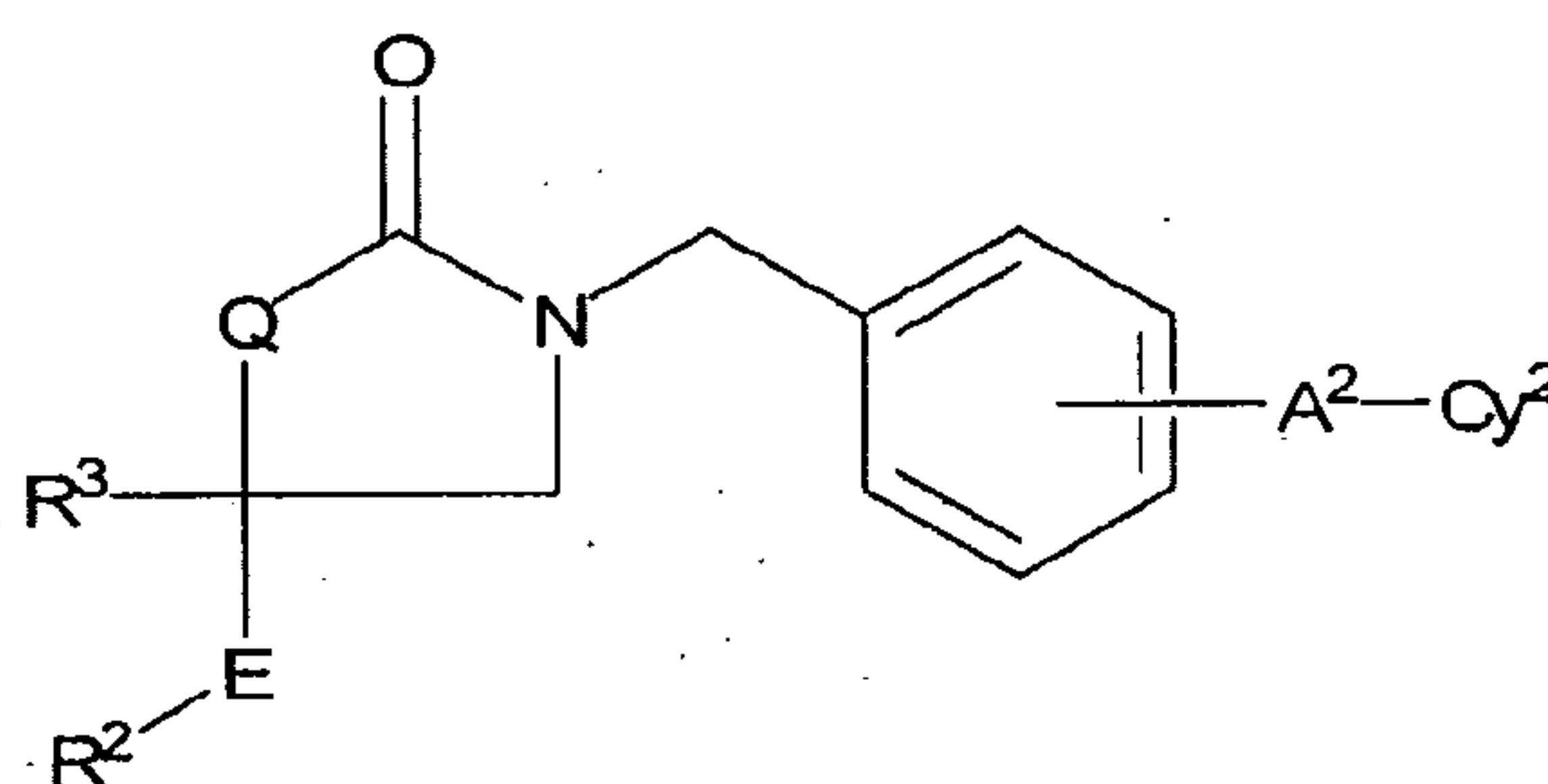
wherein:

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkynyl, (C₃-
15 C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-
20 C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkane-sulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl,
25

- 21 -

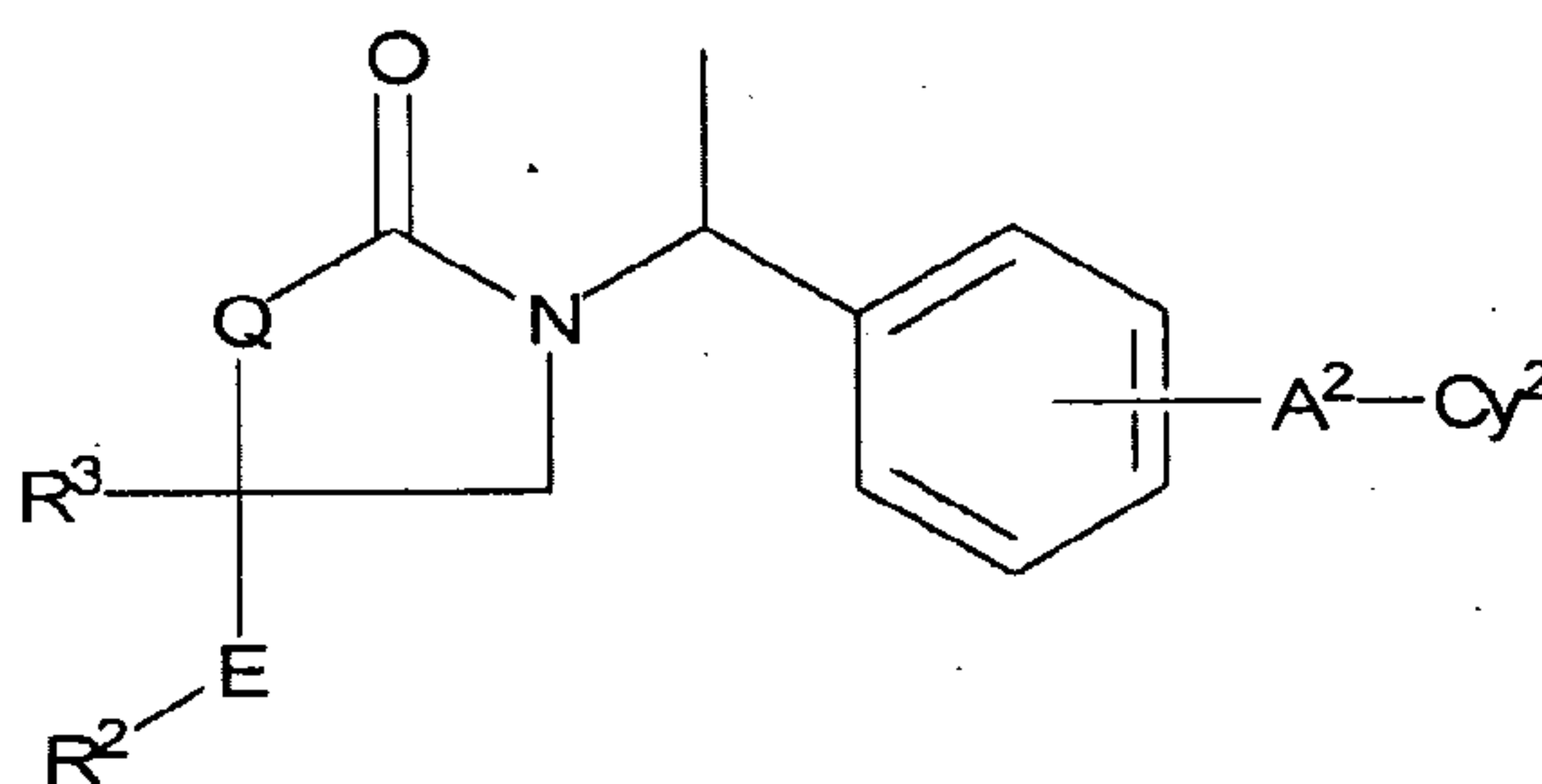
heterocyclsulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxyl or (C₁-C₆)alkylcarbonyl; and
 5 r is 0, 1, 2, 3 or 4. Values and alternative values for the remainder of the variables in Structural Formula Ia are as described for Structural Formula I.

In a third embodiment, the 11 β -HSD1 inhibitors of the invention are represented
 10 by Structural Formula Ib:

**Ib**

Values and alternative values for the variables in Structural Formula Ib are as described above for Structural Formula I.

In a fourth embodiment, the 11 β -HSD1 inhibitors of the invention are represented
 15 by Structural Formula Ic:

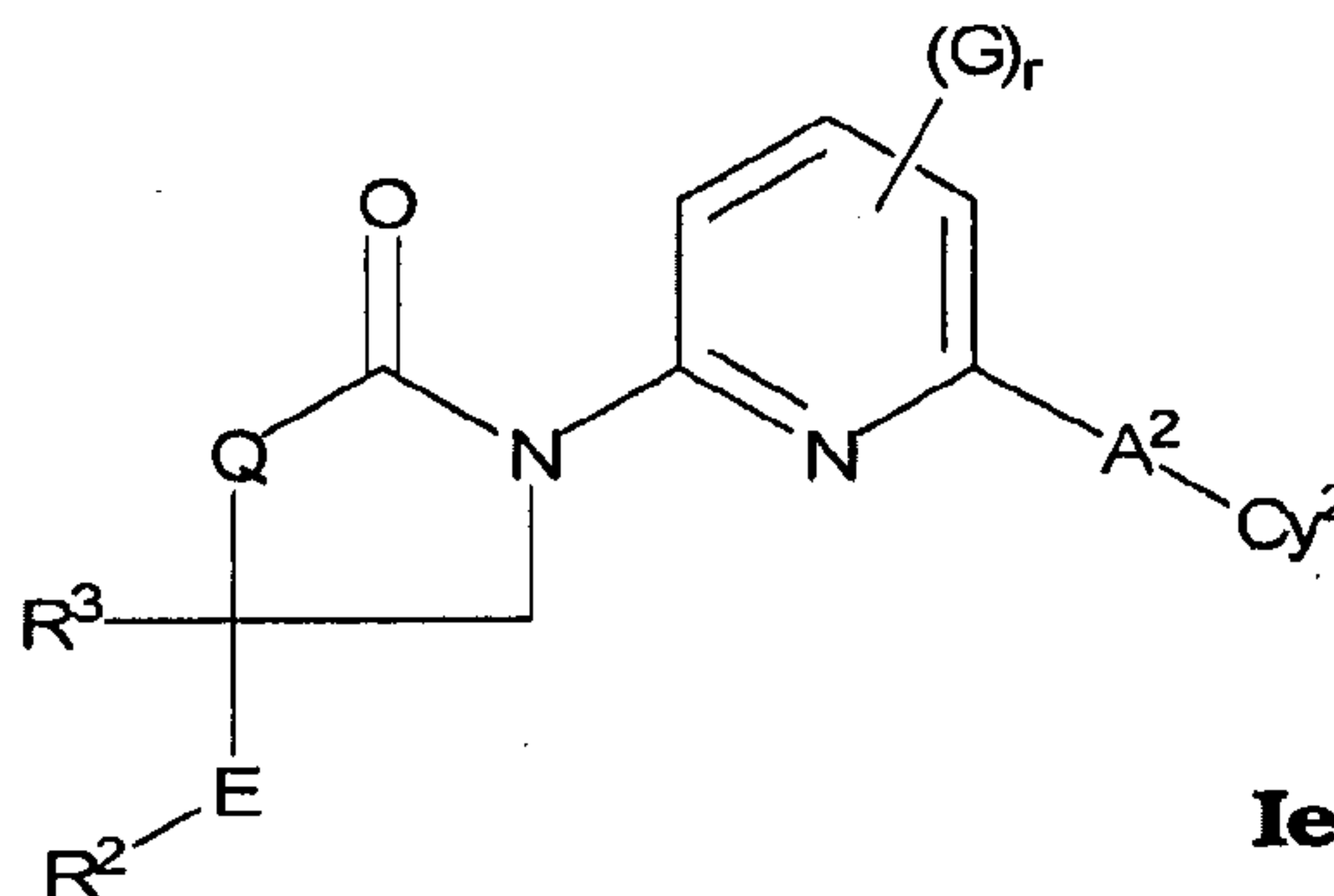
**Ic**

Values and alternative values for the variables in Structural Formula Ic are as described above for Structural Formula I.

In a fifth embodiment, the 11 β -HSD1 inhibitors of the invention are represented
 20 by Structural Formula Id:

m is 0, 1, 2, 3 or 4. Values and alternative values for the remainder of the variables in Structural Formula Id are as described above for Structural Formula I.

In a sixth embodiment, the 11 β -HSD1 inhibitors of the invention are represented by Structural Formula Ie:

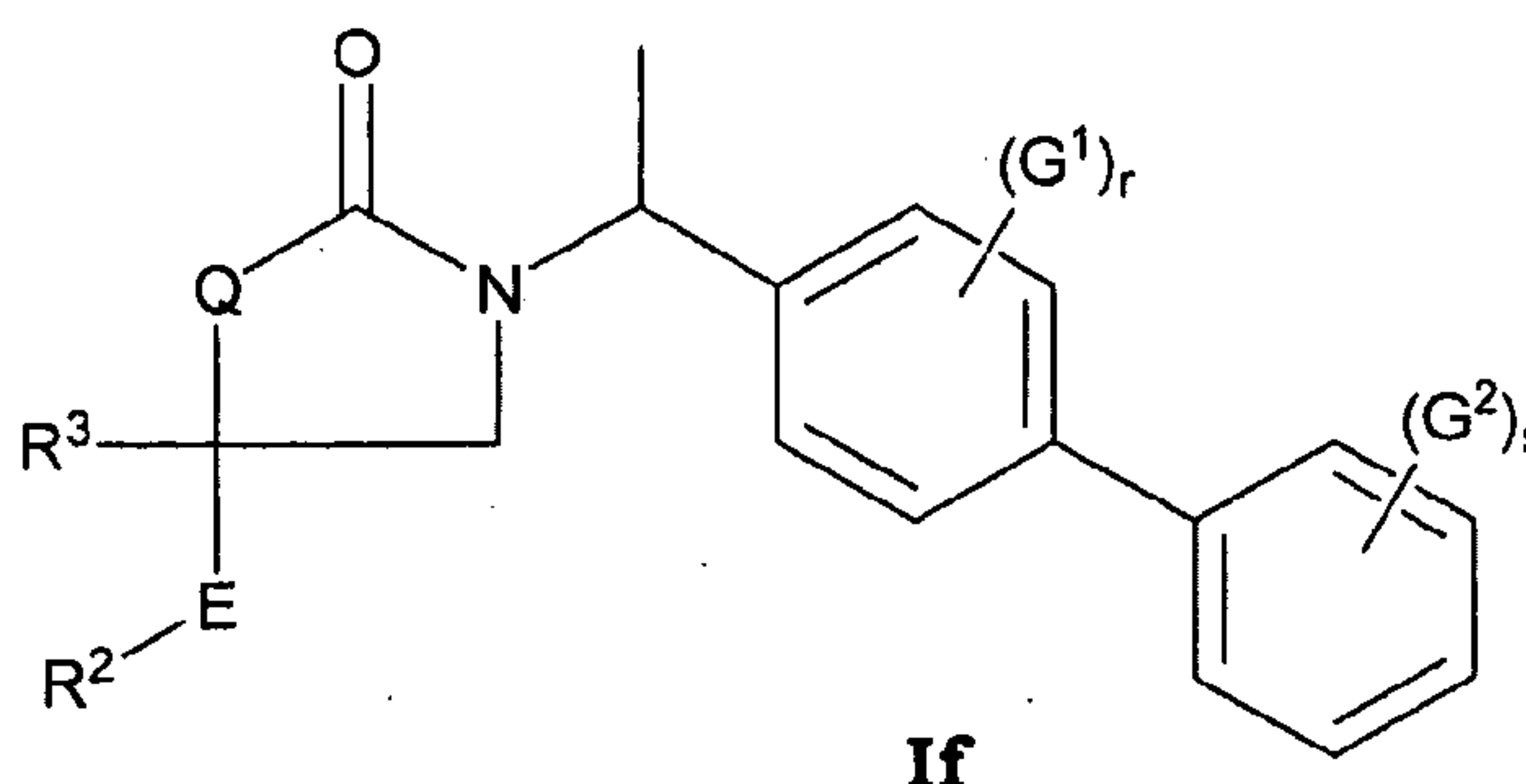


wherein:

- 5 G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkane-sulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclsulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxyl and (C₁-C₆)alkylcarbonyl; and

r is 0, 1, 2, 3 or 4. Values and alternative values for the remainder of the variables in Structural Formula Ie are as described above for Structural Formula I.

In a seventh embodiment, the 11 β -HSD1 inhibitors of the invention are represented by Structural Formula If:



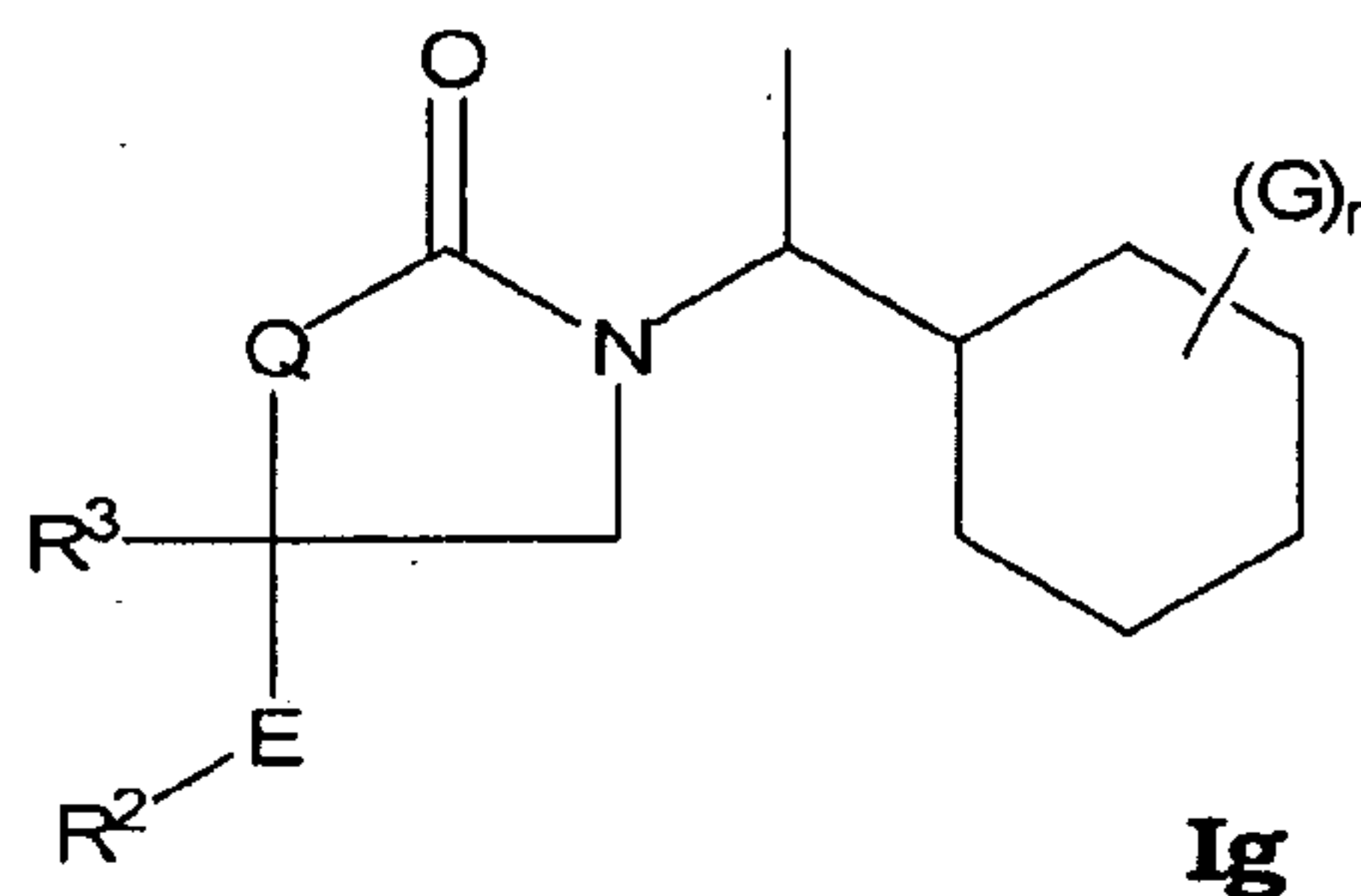
wherein:

G^1 and G^2 are each independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkane-sulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclsulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxyl or (C₁-C₆)alkylcarbonyl;

- 25 -

R^5 is H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or hydroxy(C₁-C₆)alkyl; and
 r and s are independently 0, 1, 2, 3 or 4. Values and alternative values for the remainder
 of the variables in Structural Formula If are as described above for Structural Formula I.

In an eighth embodiment, the 11 β -HSD1 inhibitors of the invention are
 5 represented by Structural Formula Ig:



wherein:

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino,
 hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-
 10 C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-
 C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl,
 halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-
 C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy,
 halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-
 15 C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-
 C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-
 C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-
 C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl,
 (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-
 20 C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cyclo-
 alkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-
 C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO,
 H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-
 C₃)alkylaminocarbonyl, heterocyclcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-
 25 C₆)alkylaminosulfonyl, heterocyclsulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-
 C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-
 C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-
 C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy,
 heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-

C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxyl and (C₁-C₆)alkylcarbonyl; and

r is 0, 1, 2, 3 or 4. Values and alternative values for the remainder of the variables in Structural Formula Ig are as described above for Structural Formula I.

- 5 Pharmaceutically acceptable salts of the 11 β -HSD1 inhibitors disclosed herein (including those represented by any one of Structural Formulae Ia-Ig) are also included in the invention.

10 In a ninth embodiment, the 11 β -HSD1 inhibitors of the invention are represented by any one of Structural Formulae I and Ia-Ig, wherein values and alternative values for the variables in each of Structural Formulae I and Ia-Ig are as described above for each of Structural Formulae I and Ia-Ig, respectively, provided that if Q is NR⁵, A¹ is methylene, R¹ is absent, Cy¹ is optionally substituted phenyl, A² is a bond, Cy² is hydrogen, E is a bond and R² is optionally substituted phenyl, then R³ is not hydroxyethyl or hydroxypropyl.

- 15 In a tenth embodiment, the 11 β -HSD1 inhibitors of the invention are represented by any one of Structural Formulae I and Ia-Ig, wherein values and alternative values for the variables in each of Structural Formulae I and Ia-Ig are as described above for each of Structural Formulae I and Ia-Ig, respectively, provided that:

20 if A¹ is optionally substituted methylene and A² is a bond, then Cy² is not ortho to the ring atom of Cy¹ that is bonded to A¹, and Cy¹ is not substituted with an optionally substituted amine or aminomethyl group at a ring atom ortho to the ring atom of Cy¹ that is bonded to A¹;

 if Q is NR⁵ and R³ is (C₂-C₆)alkyl substituted with one to three groups independently selected from fluorine, halo(C₁-C₆)alkyl, hydroxy and hydroxy(C₁-C₆)alkyl, then (a) E is (C₁-C₂)alkylenyloxy; (b) E is a bond or (C₁-C₃)alkylene and R² is (C₁-C₆)alkyl substituted with up to 4 groups independently selected from cyano, nitro, amino, carboxy, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-

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C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl,
 (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-
 C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cyclo-
 alkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-
 5 C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO,
 H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-
 C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-
 C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-
 C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-
 10 C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-
 C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy,
 heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-
 C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy,
 di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl; (c) E is a bond and R² is
 15 optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclyl; or (d) E is (C₁-
 C₃)alkylene and R² is optionally substituted heteroaryl, cycloalkyl or heterocyclyl; and
 if Q is NR⁵ and E-R² is (a) (C₁-C₆)alkyl optionally substituted with one to three
 groups independently selected from fluorine, chlorine, bromine, iodine, hydroxy, (C₁-
 C₆)alkyl, hydroxy(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (b) benzyl, then R³ is (a) (C₂-
 20 C₆)alkyl substituted up to four groups independently selected from cyano, oxo,
 amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl,
 (C₁-C₆)alkoxy(C₁-C₆)alkyl, R⁴O- (except hydroxy), (R⁴)₂N-, R⁴O₂C-, R⁴S, R⁴S(=O)-,
 R⁴S(=O)₂-, R⁴C(=O)NR⁴-, (R⁴)₂NC(=O)-, (R⁴)₂NC(=O)O-, (R⁴)₂NC(=O)NR⁴-,
 R⁴OC(=O)NR⁴-, (R⁴)₂NC(=NCN)NR⁴-, (R⁴O)₂P(=O)O-, (R⁴O)₂P(=O)NR⁴-,
 25 R⁴OS(=O)₂NR⁴-, (R⁴)₂NS(=O)₂O-, (R⁴)₂NS(=O)₂NR⁴-, R⁴S(=O)₂NR⁴-,
 R⁴S(=O)₂NHC(=O)-, R⁴S(=O)₂NHC(=O)O-, R⁴S(=O)₂NHC(=O)NR⁴-,
 R⁴OS(=O)₂NHC(=O)-, R⁴OS(=O)₂NHC(=O)O-, R⁴OS(=O)₂NHC(=O)NR⁴-,
 (R⁴)₂NS(=O)₂NHC(=O)-, (R⁴)₂NS(=O)₂NHC(=O)O-, (R⁴)₂NS(=O)₂NHC(=O)NR⁴-,
 R⁴C(=O)NHS(=O)₂-, R⁴C(=O)NHS(=O)₂O-, R⁴C(=O)NHS(=O)₂NR⁴-,
 30 R⁴OC(=O)NHS(=O)₂-, R⁴OC(=O)NHS(=O)₂O-, R⁴OC(=O)NHS(=O)₂NR⁴-,
 (R⁴)₂NC(=O)NHS(=O)₂-, (R⁴)₂NC(=O)NHS(=O)₂O-, (R⁴)₂NC(=O)NHS(=O)₂NR⁴-,
 heterocyclyl (which in turn may be optionally substituted with alkyl, haloalkyl or oxo),
 heteroaryl (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy,
 alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H,

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CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo), aryl-amino (which in turn may be optionally substituted with alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido) and heteroarylamino
5 (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); or (b) optionally substituted (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₃)alkoxy(C₁-C₃)alkyl.

In an eleventh embodiment, the 11 β -HSD1 inhibitors of the invention are
10 represented by any one of Structural Formulae I and Ia-Ig, wherein values and alternative values for the variables in each of Structural Formulae I and Ia-Ig are as described above for each of Structural Formulae I and Ia-Ig, respectively, and wherein the provisos in the ninth and the tenth embodiments apply.

In a twelfth embodiment, the 11 β -HSD1 inhibitors of the invention are
15 represented by any one of Structural Formulae I and Ia-Ig, wherein values and alternative values for the variables in each of Structural Formulae I and Ia-Ig are as described above for each of Structural Formulae I and Ia-Ig, respectively, wherein E is (C₁-C₃)alkylene or (C₁-C₂)alkylenyloxy, and wherein the provisos in the tenth embodiment apply.

In a thirteenth embodiment, the 11 β -HSD1 inhibitors of the invention are
20 represented by any one of Structural Formulae I and Ia-Ig, wherein values and alternative values for the variables in each of Structural Formulae I and Ia-Ig are as described above for each of Structural Formulae I and Ia-Ig, respectively, and wherein the provisos in the tenth embodiment apply, further provided that if E is a bond, then R² is optionally substituted (C₁-C₆)alkyl.

In a fourteenth embodiment, the 11 β -HSD1 inhibitors of the invention are
25 represented by any one of Structural Formulae I and Ia-Ig, wherein values and alternative values for the variables in each of Structural Formulae I and Ia-Ig are as described above for each of Structural Formulae I and Ia-Ig, respectively, and wherein the provisos in the ninth and the tenth embodiments apply, further provided that if E is a bond, then R² is
30 optionally substituted (C₁-C₆)alkyl.

In a fifteenth embodiment, the 11 β -HSD1 inhibitors of the invention are represented by any one of Structural Formulae I and Ia-Ig, wherein values and alternative values for the variables in each of Structural Formulae I and Ia-Ig are as described above for each of Structural Formulae I and Ia-Ig, respectively, and wherein the provisos in the

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tenth embodiment apply, further provided that if E is a bond, and R² is optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclyl, then the optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclyl represented by R² is not substituted with heteroaryl, amine or aminomethyl at a ring atom ortho to the ring atom of R² that is
5 bonded to E.

In a sixteenth embodiment, the 11 β -HSD1 inhibitors of the invention are represented by any one of Structural Formulae I and Ia-Ig, wherein values and alternative values for the variables in each of Structural Formulae I and Ia-Ig are as described above for each of Structural Formulae I and Ia-Ig, respectively, and wherein the provisos in the
10 ninth and the tenth embodiments apply, further provided that if E is a bond, and R² is optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclyl, then the optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclyl represented by R² is not substituted with heteroaryl, amine or aminomethyl at a ring atom ortho to the ring atom of R² that is bonded to E.

15 In a seventeenth embodiment, the 11 β -HSD1 inhibitors of the invention are represented by any one of Structural Formulae I and Ia-Ig, wherein values and alternative values for the variables in each of Structural Formulae I and Ia-Ig are as described above for each of Structural Formulae I and Ia-Ig, respectively, wherein E is a bond or alkylene, and wherein the provisos in the tenth embodiment apply.

20 In an eighteenth embodiment, the 11 β -HSD1 inhibitors of the invention are represented by any one of Structural Formulae I and Ia-Ig, wherein values and alternative values for the variables in each of Structural Formulae I and Ia-Ig are as described above for each of Structural Formulae I and Ia-Ig, respectively, wherein E is a bond or alkylene, and wherein the provisos in the ninth and the tenth embodiments apply.

25 Specific 11 β -HSD1 inhibitors of the invention and pharmaceutically acceptable salts thereof are provided in Examples 1-3 and Prophetic Examples 1a-221a and 1b-221b below.

Specific examples of compounds of Formulae I and Ia-Ig may exist in various stereoisomeric or tautomeric forms. The invention encompasses all such forms,
30 including active compounds in the form of essentially pure enantiomers, racemic mixtures, and tautomers, including those forms not depicted structurally.

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When any variable (e.g., aryl, heterocyclyl, R¹, R², etc.) occurs more than once in a compound, its definition on each occurrence is independent of any other occurrence.

The term "alkyl", used alone or as part of a larger moiety such as "alkoxy", "hydroxyalkyl", "alkoxyalkyl", "alkylamine", "dialkyamine", "alkoxycarbonyl" or
5 "alkylaminocarbonyl", means a saturated straight or branched hydrocarbon radical having (unless otherwise specified) 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
10 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 means a 6-10 membered carbocyclic aromatic monocyclic or polycyclic ring system, such as phenyl or naphthyl. The term "aryl" may be used
15 interchangeably with the terms "aryl ring" "aromatic ring", "aryl group" and "aromatic group".

"Heteroaromatic group", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", means a 5-10 membered monovalent monocyclic and polycyclic aromatic group radical containing 1 to 4 heteroatoms independently
20 selected from N, O, and S. Heteroaryl groups include furyl, thienyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridinyl-N-oxide, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, indolyl, isoindolyl, benzo[b]furyl, benzo[b]thienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinoliziny, quinoliny, isoquinoliny,
25 quinazolinyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzodioxolyl, benzimidazolyl, indazolyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, cinnoliny, phthalziny, quinazolinyl, quinoxaliny, 1,8-naphthyridiny, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,2,5-thiadiazolyl, 1,2,5-thiadiazolyl-1-oxide, 1,2,5-thiadiazolyl-1,1-dioxide, 1,3,4-thiadiazolyl, 1,2,4-triazinyl, 1,3,5-triazinyl, tetrazolyl, and
30 pteridinyl. The terms "heteroaryl", "heteroaromatic", "heteroaryl ring", "heteroaryl group" and "heteroaromatic group" are used interchangeably herein.

The term "heterocyclic group" 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, and include pyrrolidine, pyrrolidin-2-one, 1-methylpyrrolidin-

2-one, piperidine, piperidin-2-one, dihydropyridine, tetrahydropyridine, piperazine, 1-(2,2,2-trifluoroethyl)piperazine, 1,2-dihydro-2-oxopyridine, 1,4-dihydro-4-oxopyridine, piperazin-2-one, 3,4,5,6-tetrahydro-4-oxopyrimidine, 3,4-dihydro-4-oxopyrimidine, 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-thioxazole 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. The terms "heterocyclyl", "heterocycle", "heterocyclic group" and "heterocyclic ring" are used interchangeably herein.

The term "ring atom" is an atom such as C, N, O or S that is in the ring of an aryl group, heteroaryl group, cycloalkyl group or heterocyclic group. A "substitutable ring atom" in an aryl, heteroaryl cycloalkyl or heterocyclic is a carbon or nitrogen atom in the aryl, heteroaryl, cycloalkyl or heterocyclic group that is bonded to at least one hydrogen atom. The hydrogen(s) can be optionally replaced with a suitable substituent group. Thus, the term "substitutable ring atom" does not include ring carbon or nitrogen atoms when the structure depicts that they are not attached to any hydrogen atoms.

Suitable substituents for an alkyl, aryl, heteroaryl and heterocyclic group are those which do not significantly reduce the ability of the compound to inhibit the activity of 11 β -HSD1. Unless otherwise specified, suitable substituents for an alkyl, aryl, heteroaryl and heterocyclyl include fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-

C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cyclo-
 alkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-
 C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO,
 H₂NSO₂, CONH₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-
 5 C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl,
 di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-
 C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-
 C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-
 C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy,
 10 heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-
 C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy,
 di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl. Preferred substituents an
 alkyl, aryl, heteroaryl and heterocyclyl include, unless otherwise specified, halogen, (C₁-
 C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, NO₂, CN,
 15 CONH₂, halo(C₁-C₆)akyl or halo(C₁-C₆)alkoxy.

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.

20 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, hexylresorcinatate,
 hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate,
 25 lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate,
 nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate,
 stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, and
 triethiodide salts.

The compounds of the invention include pharmaceutically acceptable anionic
 30 salt forms, wherein the 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, hexylresorcinatate, hydrobromide, hydrochloride,
 hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate,

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mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, and triethiodide salts.

Salts of the disclosed 11β -HSD1 inhibitors containing an acidic functional group
5 can be prepared by reacting with a suitable base. Such a pharmaceutically acceptable salt may be made with a base which affords a pharmaceutically acceptable cation, which includes alkali metal salts (especially sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from physiologically acceptable organic bases such as trimethylamine,
10 triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine, collidine, quinine, quinoline, and basic amino acids such as lysine and arginine.

15 The invention also includes various isomers and mixtures thereof. "Isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light (stereoisomers).

20 Certain of the disclosed 11β -HSD1 inhibitors 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
25 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.
30 Thus, "R*" and "S*" denote the relative configurations of substituents around one or more chiral carbon atoms. When a chiral center is not defined as R or S, a mixture of both configurations is present.

“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.

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 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 inhibitor free from the corresponding optical isomer, a racemic mixture of the inhibitor and mixtures enriched in one enantiomer relative to its corresponding optical isomer.

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%, 95%, 98%, 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%, 95%, 98%, 99% or 99.9% by weight optically pure.

Percent optical purity by weight is the ratio of the weight of the enantiomer over the weight of the enantiomer plus the weight of its optical isomer. When a single geometric isomer, e.g., a geometric isomer with a double bond, is depicted by name or structure and the stereochemistry about the double is indicated, the compound is considered to be at least 60%, 70%, 80%, 90%, 95%, 98%, 99% or 99.9% stereochemically pure by

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weight. Percent stereochemically purity by weight is the ratio of the weight of the geometric isomer over the weight of the both geometric isomers. For example, 99% stereochemically pure means that at least 99% by weight of the compound is the indicated stereoisomer.

5 A pharmaceutical composition of the invention may, alternatively or in addition to a compound of Formulae I and Ia-Ig, comprise a pharmaceutically acceptable salt of a compound of Formulae I and Ia-Ig, or a prodrug or pharmaceutically active metabolite of such a compound or salt and one or more pharmaceutically acceptable carriers therefor.

10 “Effective amount” means that amount of active compound agent that elicits the desired biological response in a subject. Such response includes alleviation of the symptoms of the disease or disorder being treated. The effective amount of a compound of the invention in such a therapeutic method is from about 0.01 mg/kg/day to about 10 mg/kg/day, preferably from about 0.5 mg/kg/day to 5 mg/kg/day.

“Inhibiting 11 β -HSD1” means to decrease the activity of the 11 β -HSD1 enzyme.

15 “Modulating 11 β -HSD1” means to impact the activity of the 11 β -HSD1 enzyme by altering its natural activity. Modulation can be analogous to inhibition when a disease or disorder relating to the activity 11 β -HSD1 would be effectively treated by suppressing the activity of the enzyme.

20 “Pharmaceutically acceptable carrier” means compounds and compositions that are of sufficient purity and quality for use in the formulation of a composition of the invention and that, when appropriately administered to an animal or human, do not produce an adverse reaction.

25 “Treatment” or “treating”, as used herein, includes prophylactic and therapeutic treatment. “Therapeutic treatment” includes partially or totally inhibiting, delaying, or reducing the severity of the disease or disorder related to 11 β -HSD1. “Prophylactic treatment” encompasses administration of a compound of the invention to a subject susceptible to a disease or disorder related to the activity or expression of 11 β -HSD1 in an effort to reduce the likelihood of a subject developing the disease or disorder, or slowing or preventing progression of the disease. Prophylactic treatment includes 30 suppression (partially or completely) of the disease or disorder, and further includes reducing the severity of the disease or disorder, if onset occurs. Prophylactic treatment is particularly advantageous for administration to mammals at risk for developing a disease or disorder related to 11 β -HSD1.

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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 carboxymethylcellulose, 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 carboxymethyl cellulose, and other well-known suspending agents.

5 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
10 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.
15 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 11 β -HSD1 or an inhibitor in the production of cortisol in the cell, the active ingredient is preferably
20 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.

 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.
25 Thus, the compounds of the invention can be used in the treatment or prevention of diabetes mellitus, obesity, metabolic syndrome, insulin resistance, cardiovascular disease, dyslipidemia, atherosclerosis, lipodystrophy, osteoporosis, glaucoma, Cushing's syndrome, depression, anxiety and Alzheimer's disease, cognitive decline (including age-related cognitive decline), polycystic ovarian syndrome and infertility. In addition,
30 compounds modulate the function of B and T cells of the immune system.

 A pharmaceutical composition of the invention may, alternatively or in addition to a compound of Formulae I and Ia-Ig, comprise a pharmaceutically acceptable salt of a compound of Formulae I and Ia-Ig, or a prodrug or pharmaceutically active metabolite of such a compound or salt and one or more pharmaceutically acceptable carriers therefor.

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The invention includes a therapeutic method for treating or ameliorating an 11 β -HSD1 mediated disorder in a mammal in need thereof comprising administering to a subject in need thereof an effective amount of a compound of Formulae I and Ia-Ig, or the enantiomers, diastereomers, or salts thereof or composition thereof.

5 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, hyperglycemia, hypertension, hyperlipidemia, insulin resistance, cardiovascular disease,
10 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
15 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.

Additional diseases or disorders that are related to 11 β -HSD1 activity include those selected from the group consisting of lipid disorders, hypertriglyceridemia,
20 hypercholesterolemia, low HDL levels, high LDL levels, vascular restenosis, pancreatitis, abdominal obesity, neurodegenerative disease, retinopathy, nephropathy, neuropathy, diabetes, coronary heart disease, stroke, peripheral vascular disease, Cushing's syndrome, hyperinsulinemia, viral diseases, and Syndrome X.

The term "mammal" is preferably a human, but can also be an animal in need of
25 veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

The disclosed 11 β -HSD1 inhibitors can be used alone or in a combination therapy with one or more additional agents for the treatment of diabetes, dyslipidemia,
30 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® (rosiglitazone maleate, GSK) and Actos® (pioglitazone hydrochloride, Takeda/Eli Lilly); sulfonylureas, such as Amaryl® (glimepiride, Sanofi Aventis),

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Diabeta® (glyburide, Sanofi Aventis), Micronase®/Glynase® (glyburide, Pfizer), and Glucotrol®/Glucotrol XL® (glipizide, Pfizer); meglitinides, such as Prandin®/NovoNorm® (repaglinide, Novo Nordisk), Starlix® (nateglinide, Novartis), and Glufast® (mitiglinide, Takeda); biguanides, such as Glucophage®/Glucophage XR® (metformin HCl, Bristol Myers Squibb) and Glumetza (metformin HCl, Depomed);

5 thiazolidinediones; amylin analogs; GLP-1 analogs; DPP-IV inhibitors, such as Januvia® (sitagliptin, Merck); PTB-1B inhibitors; protein kinase inhibitors (including AMP-activated protein kinase inhibitors); glucagon antagonists; glycogen synthase kinase-3 beta inhibitors; glucose-6-phosphatase inhibitors; glycogen phosphorylase inhibitors;

10 sodium glucose co-transporter inhibitors, and α -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 ezetimibe. Agents for the treatment of hypertension include α -blockers, β -blockers, calcium channel blockers, diuretics, angiotensin converting enzyme

15 (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 11 β -HSD1 inhibiting

20 compound of any one of Structural Formulae I and Ia-Ig or composition thereof in a combination therapy with one or more other 11 β -HSD1 inhibitors (whether such inhibitors are also compounds of any one of Structural Formulae 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

25 maleate, GSK); Metaglip® (glipizide and metformin HCl, Bristol Myers Squibb); Janumet® (sitagliptin and metformin, Merck) and Glucovance® (glyburide and metformin HCl, Bristol Myers Squibb).

The following abbreviations have the indicated meanings:

Abbreviation	Meaning
Boc	<i>tert</i> -butoxy carbonyl or <i>t</i> -butoxy carbonyl
(Boc) ₂ O	di- <i>tert</i> -butyl dicarbonate
Cbz	Benzyloxycarbonyl

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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
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

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 ₂ SO ₄	sodium sulfate
NMM	N-methylmorpholine
NMP	N-methylpyrrolidinone
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
PE	petroleum ether
Quant	quantitative yield
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 ₃ N
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Teoc	1-[2-(trimethylsilyl)ethoxycarbonyloxy]-

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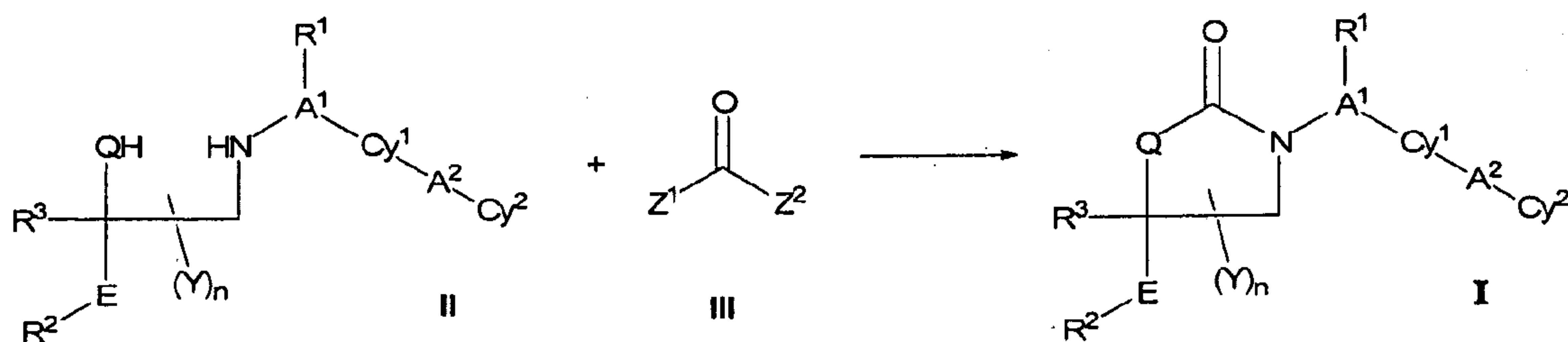
Teoc-OSu	1-[2-(trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione
TFA	trifluoroacetic acid
Tlc, TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane or trimethylsilyl chloride
t_R	retention time
TsOH	p-toluenesulfonic acid

GENERAL DESCRIPTION OF SYNTHETIC METHODS

Compounds of Formula I can be prepared by several processes. In the discussion below, A^1 , A^2 , Cy^1 , Cy^2 , E, Q, R^1 , R^2 , R^3 , R^5 , Y, and n have the meanings indicated
5 above unless otherwise noted. In cases where the synthetic intermediates and final products of Formula 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
10 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
15 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).

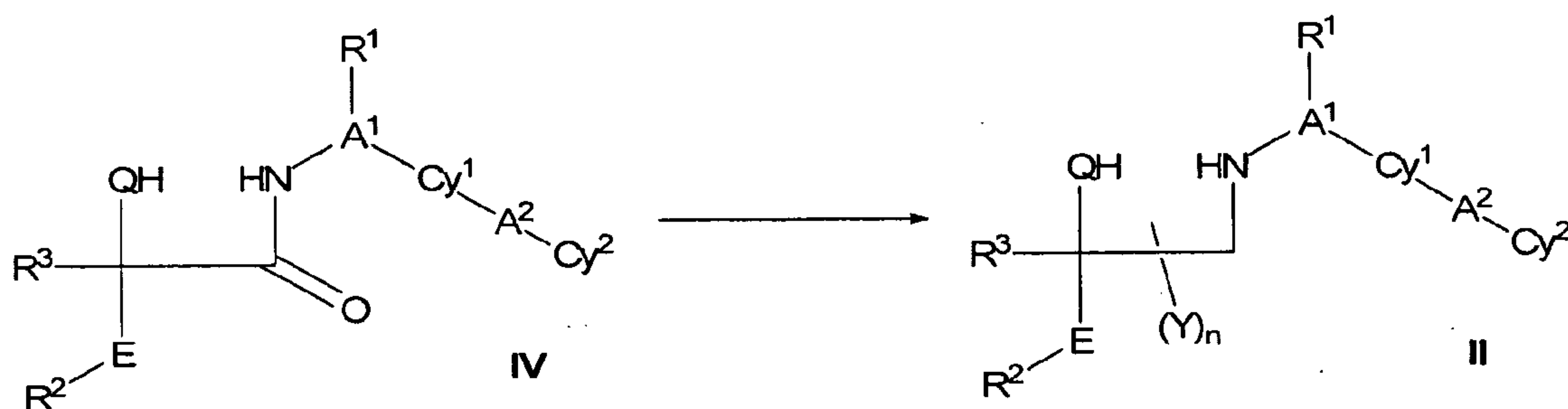
In a first process, compounds of Formula I can be prepared by reaction of intermediates of Formula II with reagents of Formula III, wherein Z^1 and Z^2 are leaving
20 groups such as chloride, 1-imidazolyl or aryloxy, in an inert solvent such as THF, CH_2Cl_2 , toluene or MeCN, usually in the presence of an organic or inorganic base such as triethylamine or $NaHCO_3$ respectively, at -10 °C to 120 °C:

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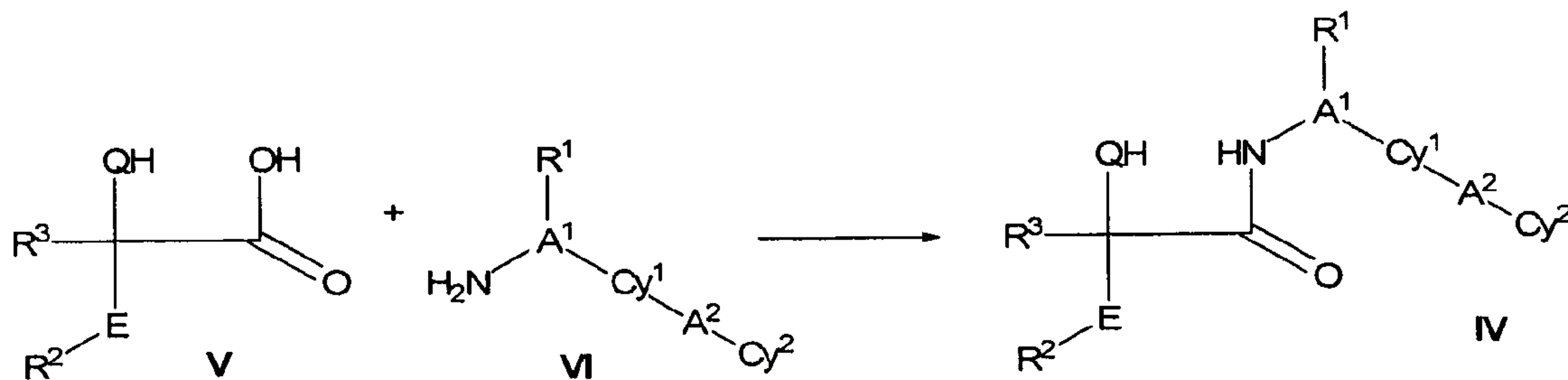


Certain instances of reagent III are especially convenient because they are commercially available. For example when Z^1 and Z^2 are both chloride, III is phosgene. When Z^1 and Z^2 are both 1-imidazolyl, III is carbonyl diimidazole. When Z^1 is chloride and Z^2 is p-nitrophenoxide, III is p-nitrophenyl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

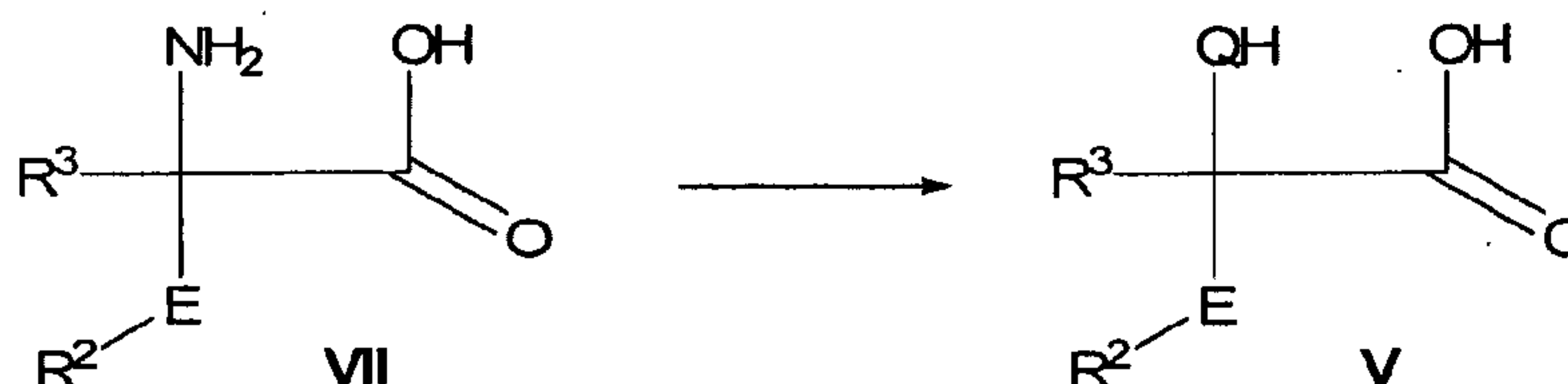
Intermediates of Formula II, wherein $n = 0$, can be prepared by reduction of amides of Formula IV using a hydride reagent such as BH_3 .THF solution, BH_3 . Me_2S or LiAlH_4 in an ethereal solvent such as THF or DME at 20°C to 100°C for between 1 h and 48 h:



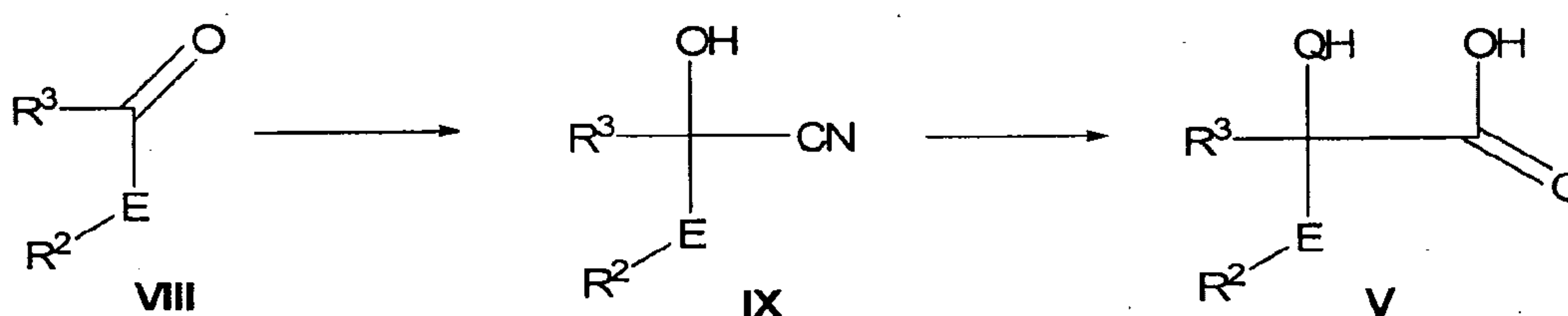
Intermediates of Formula IV can be prepared by coupling of α -hydroxyacids of Formula V ($\text{Q} = \text{OH}$) or suitably protected α -aminoacids of Formula V ($\text{Q} = \text{NR}^5$) with amines of Formula VI using standard peptide coupling reagents such as EDC in the presence of HOBt and N,N-diisopropylethylamine in an inert solvent such as CH_2Cl_2 at $0 - 30^\circ\text{C}$ for between 1 h and 24 h:



Certain α -hydroxyacids of Formula V, wherein Q = O, are commercially available. α -Hydroxyacids of Formula V can be prepared by diazotization of α -amino acids of Formula VII using NaNO_2 in H_2SO_4 :

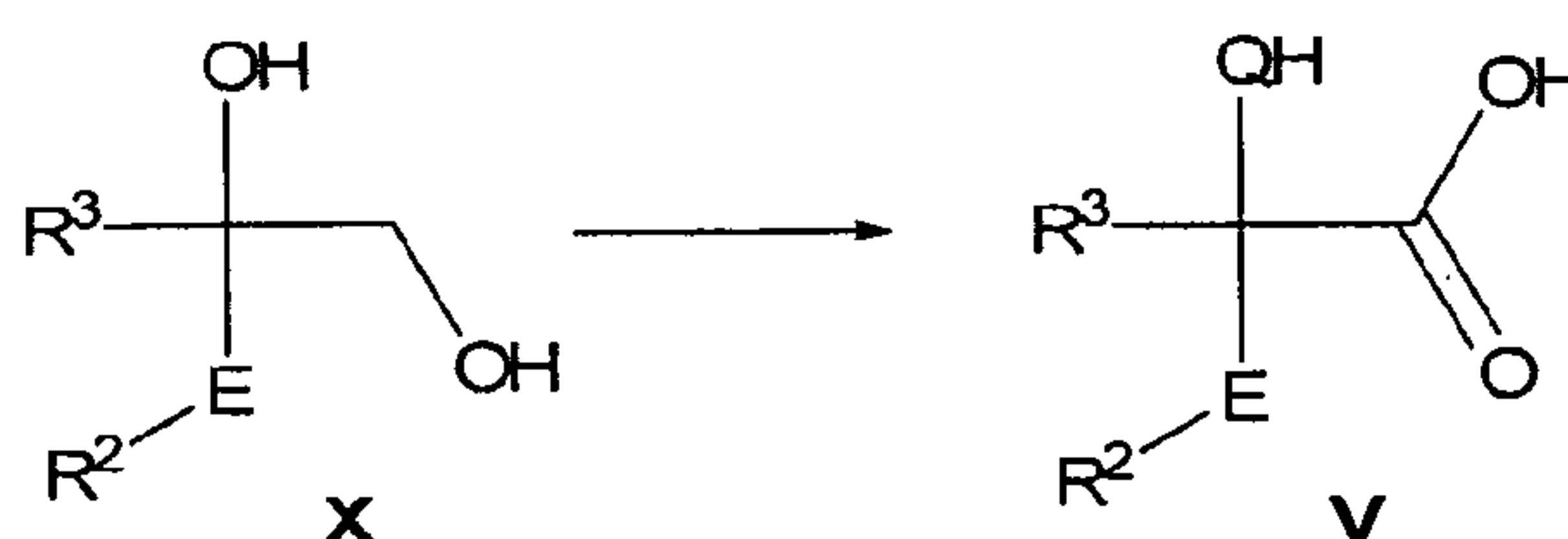


5 α -Hydroxyacids of Formula V, wherein Q = O, can also be prepared from ketones Formula VIII via cyanohydrins of Formula IX:



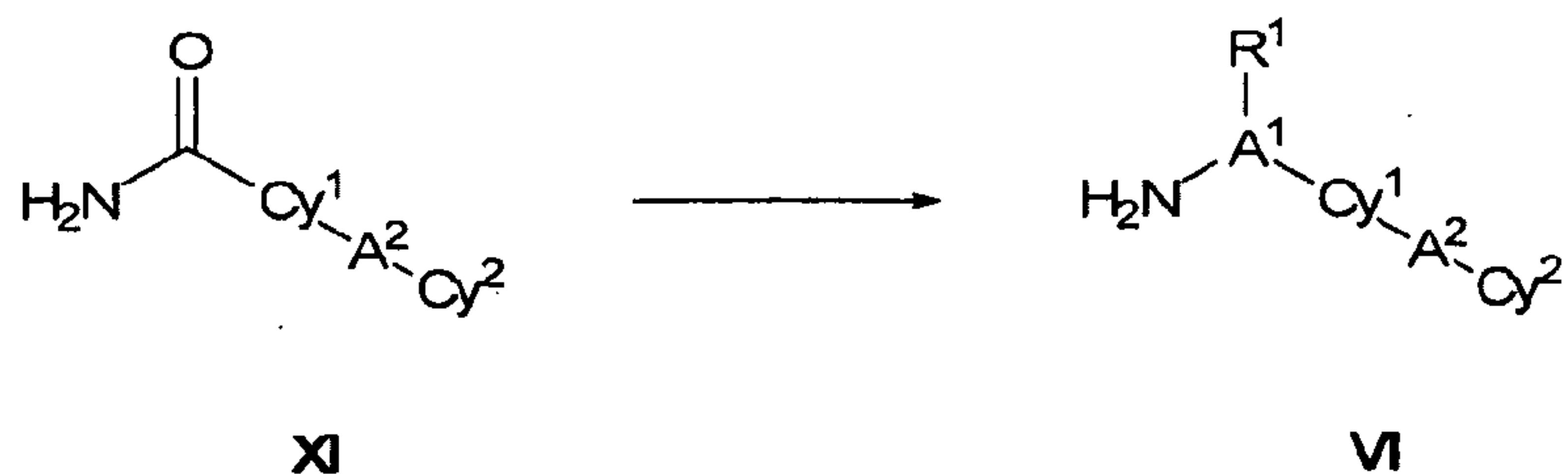
Methods for the conversion of ketones to cyanohydrins are described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" pp 1239-1240, 5th Edition, Wiley, New York, NY, 2001. Methods for the hydrolysis of cyanohydrins to α -hydroxyacids are described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" p 1179, 5th Edition, Wiley, New York, NY, 2001

15 α -hydroxyacids of Formula V, wherein Q = O, can also be prepared by oxidation of diols of Formula X with for example oxygen in the presence of a catalyst or using sodium chlorite and TEMPO:

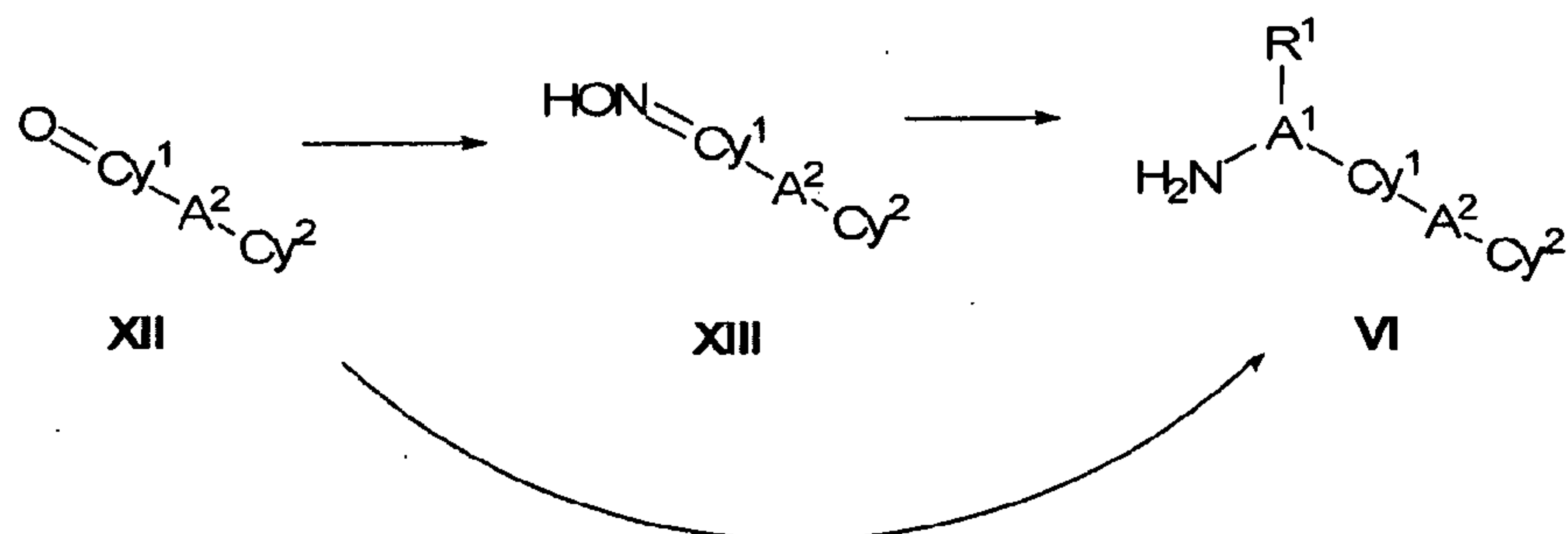


Amine intermediates of Formula VI, wherein $\text{A}^1 = \text{CH}_2$ and R^1 is absent, can be prepared by reduction of amides of Formula XI using a hydride reagent such as BH_3 .THF solution, BH_3 . Me_2S or LiAlH_4 in an ethereal solvent such as THF or DME at 20 $^\circ\text{C}$ to 100 $^\circ\text{C}$ for between 1 h and 48 h:

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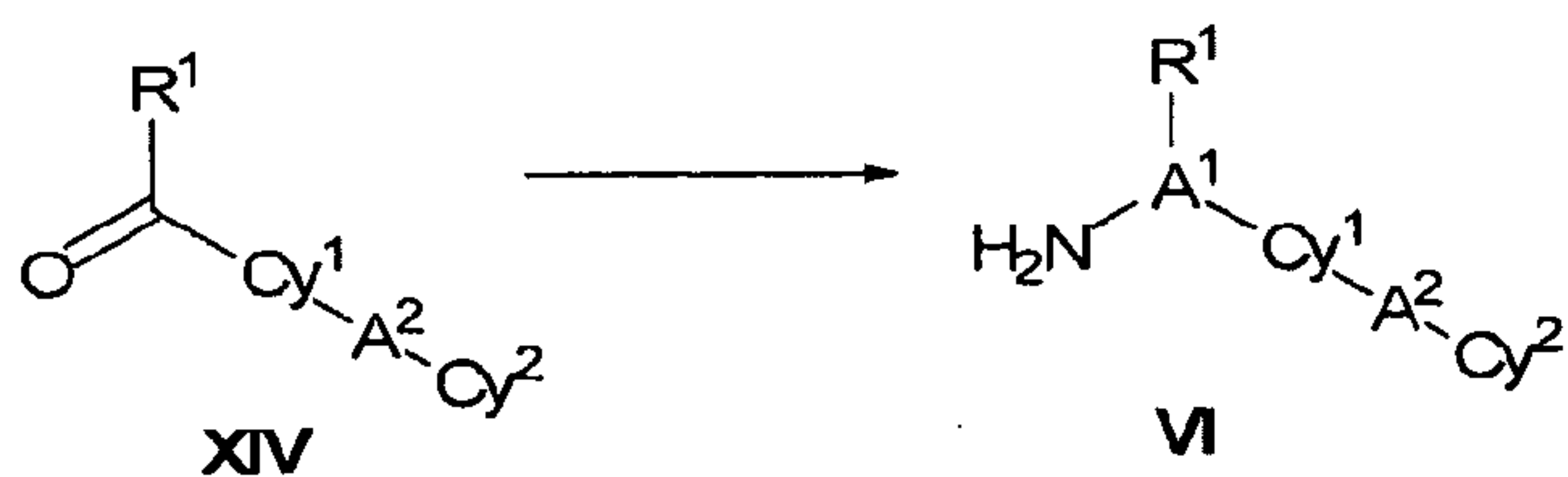


Amine intermediates of Formula VI, wherein A¹ is a bond, R¹ is absent and Cy¹ is not an aromatic or heteroaromatic ring, can be prepared from ketones of formula XII via oximes of Formula XIII or by reductive amination of ketones of Formula XII with ammonia:



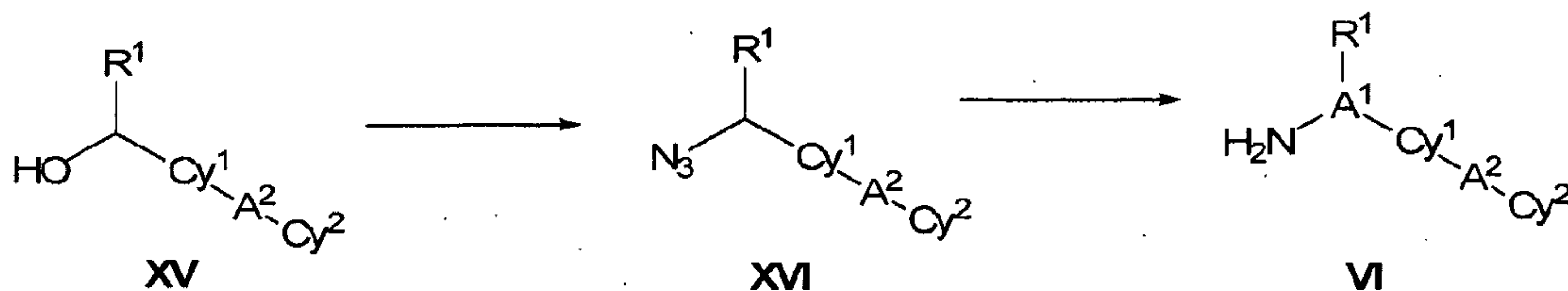
Methods for the conversion of ketones to oximes are described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" pp 1194-1195, 5th Edition, Wiley, New York, NY, 2001. Methods for the reduction of oximes to primary amines are described in Smith, M. B. and March, J. "March's Advanced Organic 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 VI, wherein A¹ is CH, can be prepared from ketones of Formula XIV by reductive amination with ammonia.

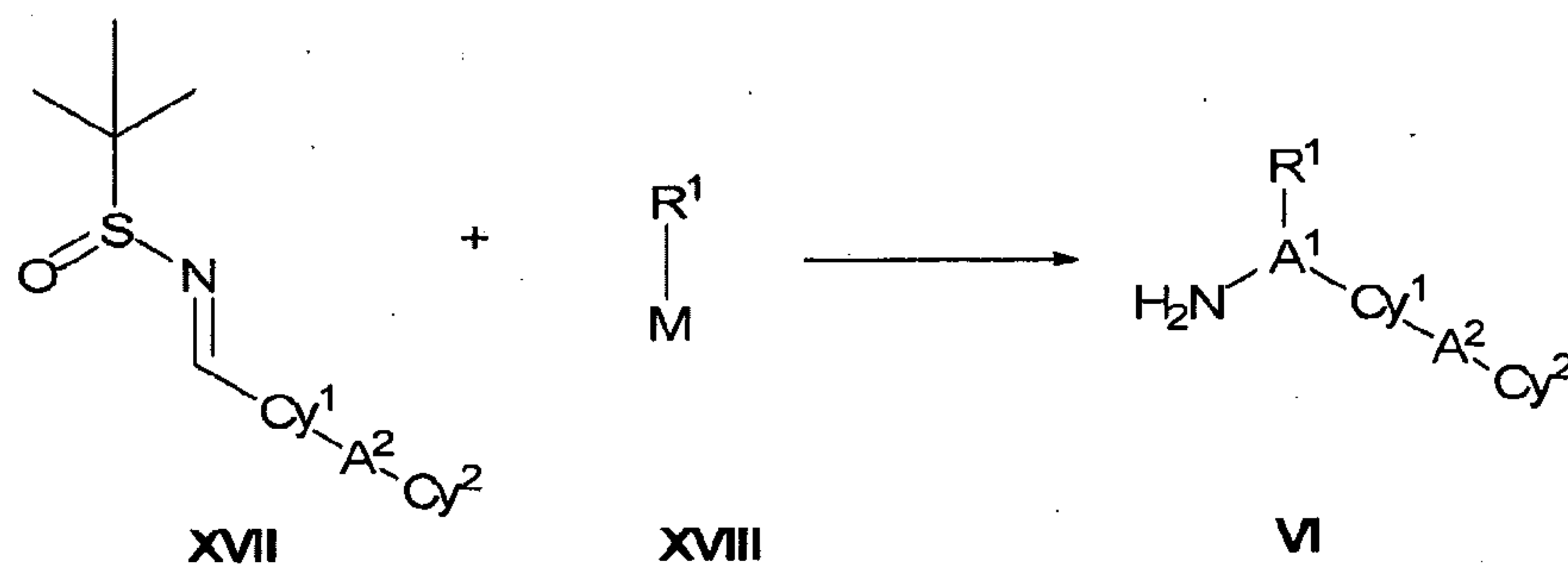


Amine intermediates of Formula VI, wherein A¹ is CH, can be prepared from alcohols of Formula XV via azides of Formula XVI. The conversion of alcohols of Formula XV to azides of Formula XVI can be accomplished with, for example, diphenylphosphoryl azide. Reduction of azides of Formula XVI to amines of Formula VII can be effected, for example, by hydrogenation in the presence of a palladium catalyst or by reaction with triphenylphosphine in wet THF.

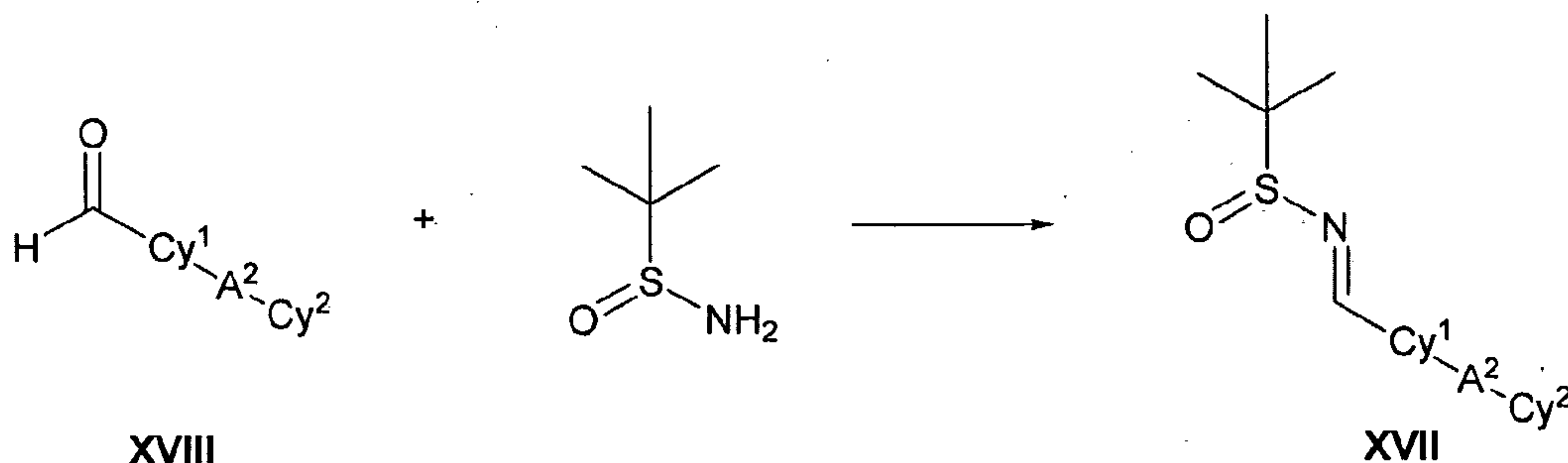
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Amine intermediates of Formula VI, wherein A^1 is CH, can be prepared by reaction of sulfinyl imine intermediates of Formula XVII with organometallic reagents of Formula XVIII, wherein M is Li, MgCl, MgBr or MgI, followed by treatment with acid to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

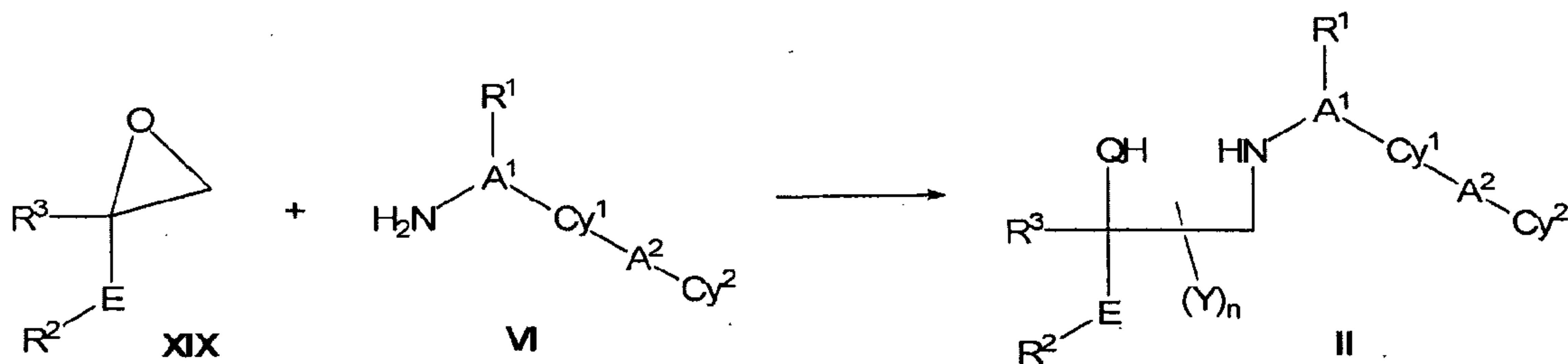


Sulfinyl imines of Formula XVII can be prepared by treatment of aldehyde intermediates of Formula XVIII with 2-methylpropane-2-sulfinamide.



10

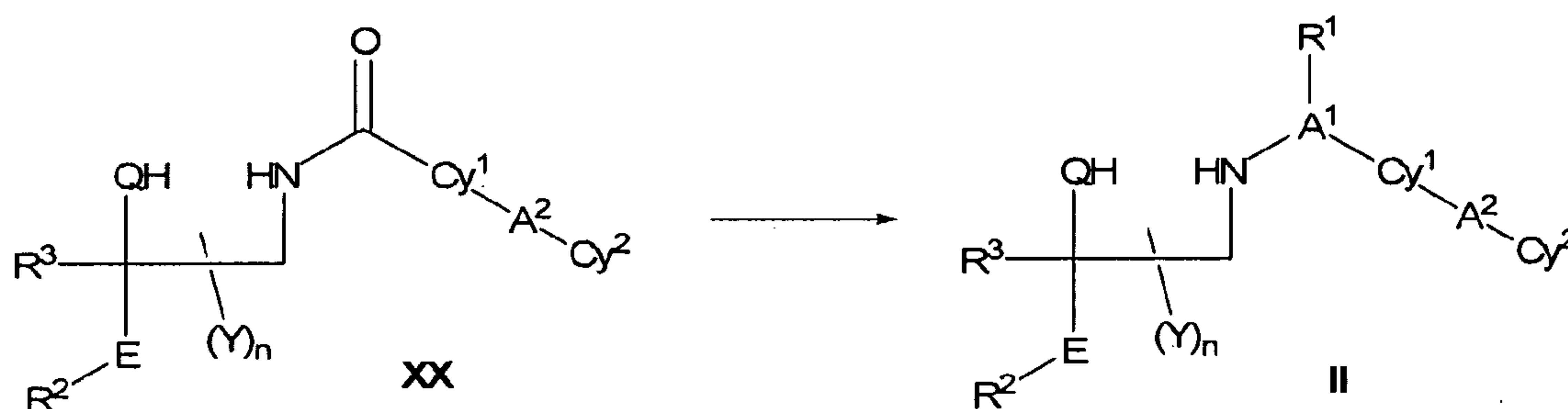
Intermediates of Formula II, wherein $Q = O$ and $n = 0$, can be prepared by reaction of epoxides of Formula XIX with amines of Formula VI as described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" p 504, 5th Edition, Wiley, New York, NY, 2001:



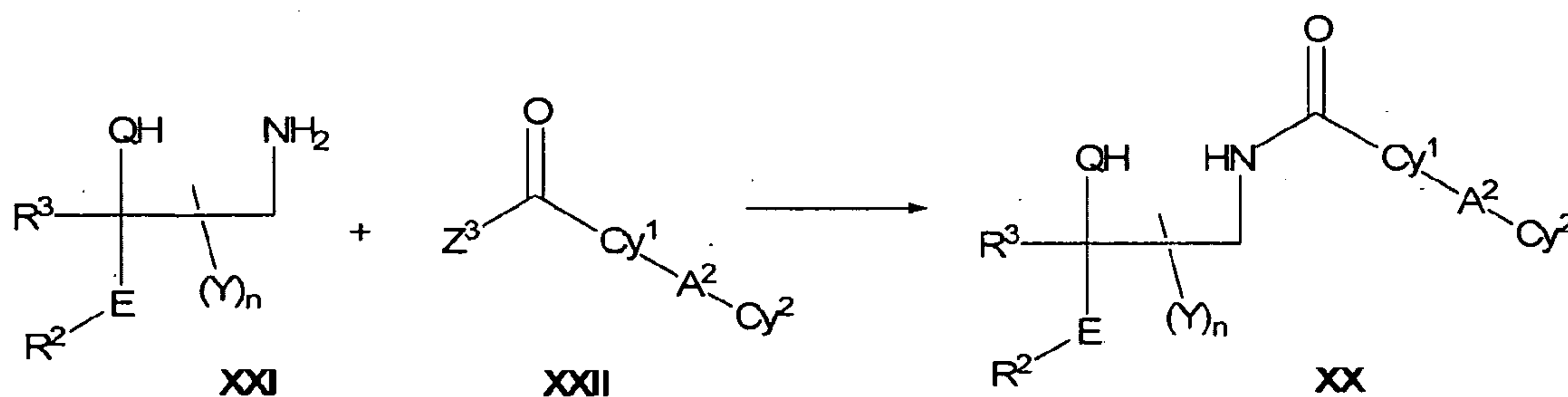
15

Epoxide compounds of formula XIX can, in turn, be prepared in a number of ways including those described in Aube, J. "Epoxidation and Related Processes" Chapter 3.2 in Volume 1 of "Comprehensive Organic Synthesis" Edited by B. M. Trost, I. Fleming and Stuart L. Schreiber, Pergamon Press, New York, 1992).

- 5 Intermediates of Formula II, wherein A^1 is CH_2 and R^1 is absent, can be prepared by reduction of amide intermediates of formula XX using a hydride reagent such as BH_3 .THF solution, $BH_3.Me_2S$ or $LiAlH_4$ in an inert solvent ethereal such as THF or DME at 20 °C to 100 °C for between 1 h and 48 h:

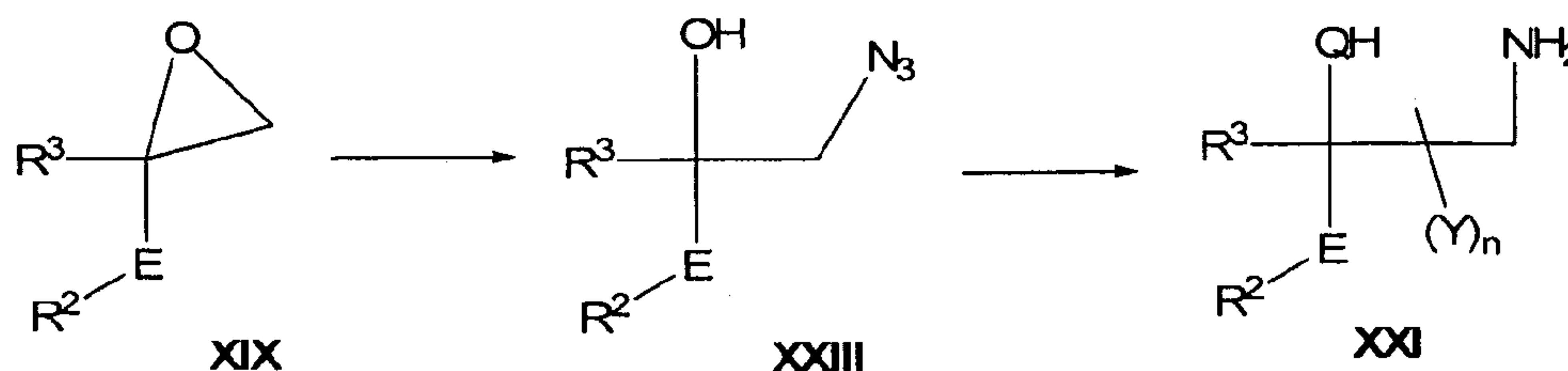


- 10 Amide intermediates of Formula XX can be prepared by reaction of an amine of Formula XXI with activated carboxylic acid of Formula XXII wherein Z^3 = chloride or an activated ester, such as an N-hydroxysuccinimide ester:



15

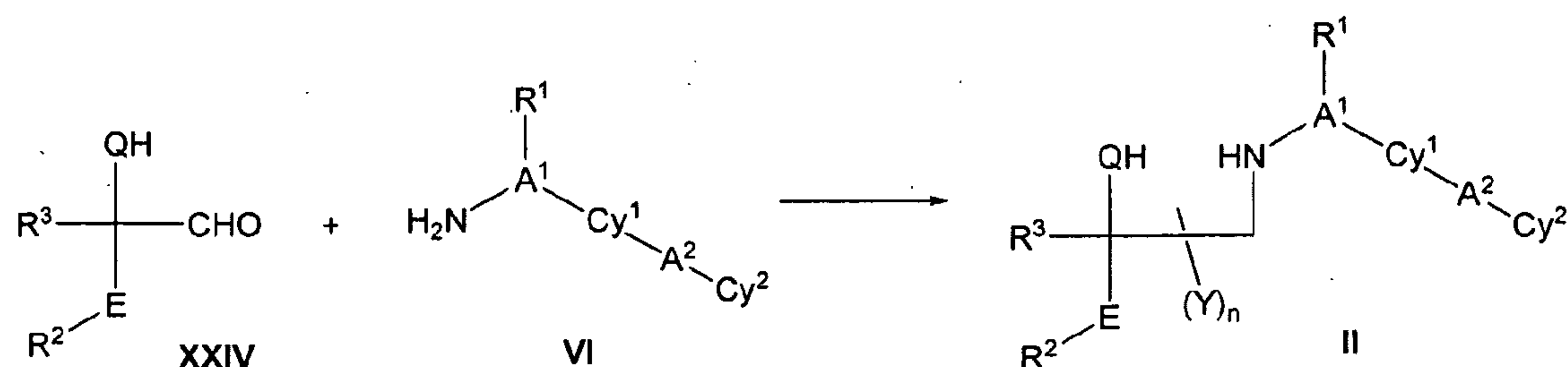
Amines of Formula XXI, wherein $n = 0$, can be prepared by reaction of epoxides of Formula XIX with azide ion to give azidoalcohols of Formula XXIII followed by reduction of the azide moiety with hydrogen gas or using triphenylphosphine in the presence of water:



20

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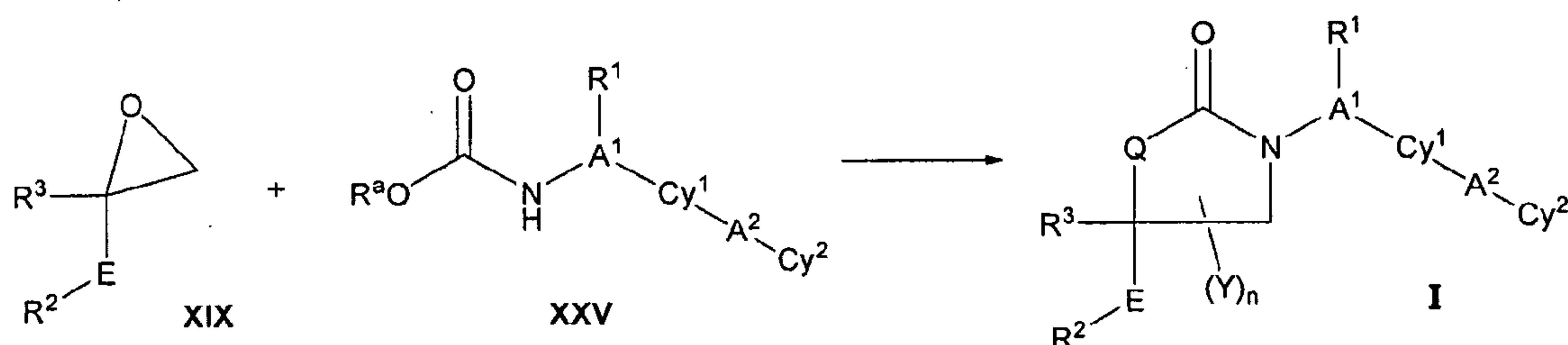
Intermediates of Formula II, wherein $n = 0$, can also be prepared by reductive amination of aldehyde intermediates of Formula XXIV with amines of Formula VI using for example NaCNBH_3 or $\text{NaBH}(\text{OAc})_3$ as reducing agent:



5

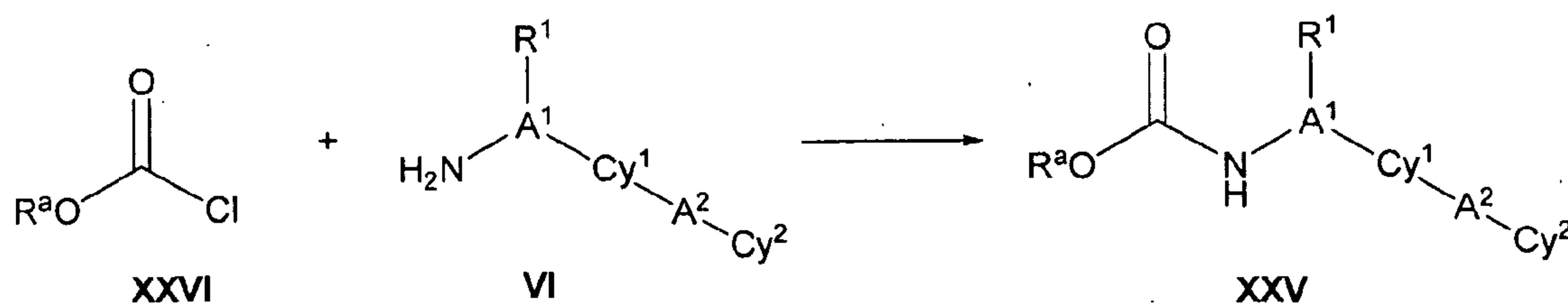
Additional methods for the synthesis of 1,2-diamines, certain of which are applicable to intermediates of Formula II wherein $Q = \text{NR}^3$, are described in Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, 37, 2580-2617.

In a second process, a compound of Formula I, wherein $Q = \text{O}$ and $n = 0$, can be prepared by reaction of a carbamate intermediate of Formula XXV, wherein $R^a = \text{alkyl}$ or benzyl, with an epoxide intermediate of Formula XIX in the presence of a strong base such as NaH in a solvent such as THF or DMF at 0 °C to 80 °C:



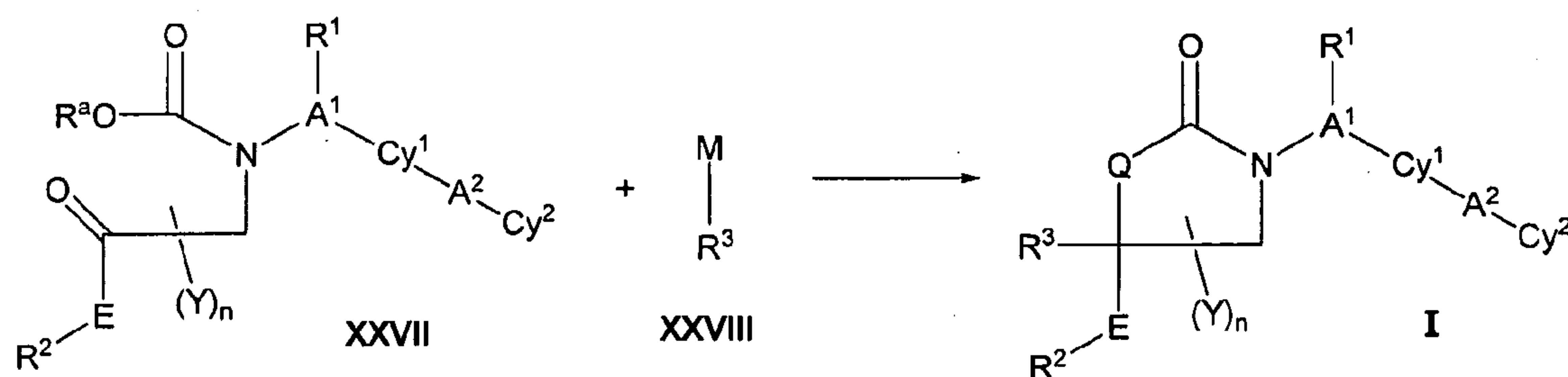
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Carbamate intermediates of Formula XXV can be prepared by reaction of amines of Formula VI with chloroformates of Formula XXVI in the presence of a base such as pyridine or triethylamine in an inert solvent such as CH_2Cl_2 or THF at 0 °C to 25 °C for between 1 h and 24 h:



20

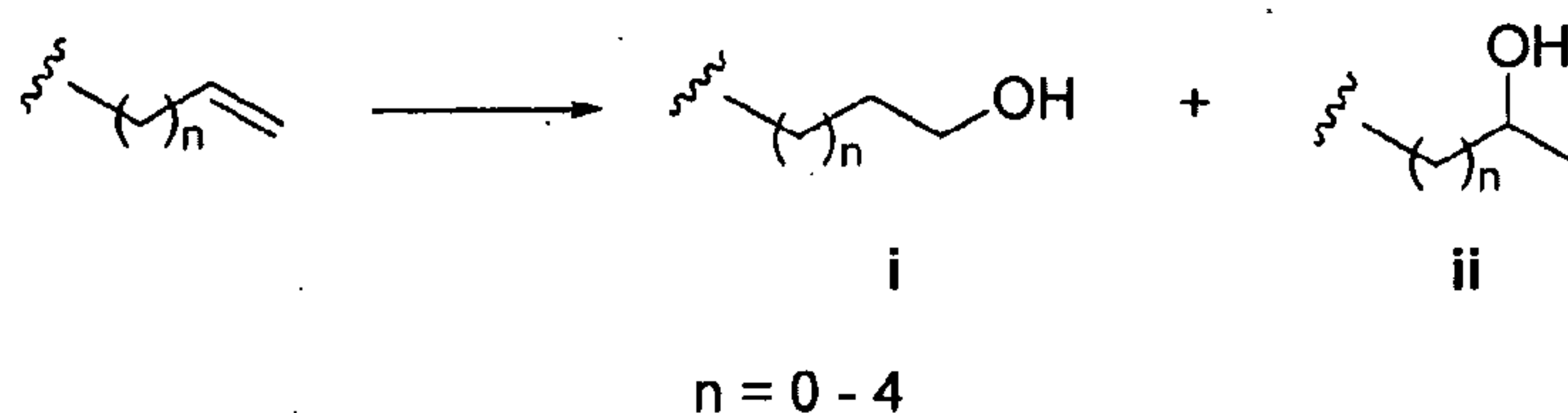
In a third process, compounds of Formula I, wherein R^3 is not hydrogen, Q is O and $n = 0$, can be prepared by reaction of ketocarbamates of Formula XXVII with organometallic reaction of Formula XXVIII, wherein M is Li, MgCl, MgBr or MgI.



In a fourth process a compound of Formula I can be prepared from another compound of Formula I. For example:

- 5 (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.
- 10 (2) a compound of Formula I wherein R^1 or R^3 is ω -hydroxy(C_2 - C_6)alkyl can be oxidized to a compound of Formula I wherein R^1 or R^3 is ω -carboxy(C_1 - C_5)alkyl using Jones reagent.
- (3) a compound of Formula I wherein R^1 or R^3 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 or R^3 is ω - $\text{H}_2\text{NC}(=\text{O})(\text{C}_1$ - C_6)alkyl or ω - $\{(\text{C}_1$ - C_6)alkyl $\text{NHC}(=\text{O})\}(\text{C}_1$ - C_6)alkyl.
- 15 (4) a compound of Formula I wherein R^1 or R^3 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 or R^3 is ω -amino(C_1 - C_6)alkyl.
- 20 (5) a compound of Formula I wherein R^1 or R^3 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 or R^3 is {acetylamino}(C_1 - C_6)alkyl.
- (6) a compound of Formula I wherein R^1 or R^3 is amino(C_1 - C_6)alkyl can be reacted with methanesulfonyl chloride to give a compound of Formula I wherein R^1 or R^3 is {methanesulfonylamino}(C_1 - C_6)alkyl.
- 25 (7) a compound of Formula I, wherein R^1 or R^3 is (C_2 - C_6)alkenyl is hydroborated to afford a compound of Formula I wherein R^1 or R^3 is hydroxy(C_2 - C_6)alkyl. When the

alkene is at the terminus of the (C₂-C₆)alkenyl group, the major product is generally the primary ω-hydroxy(C₂-C₆)alkenyl **i** and the minor product is the secondary alcohol **ii**.



(8) a compound of Formula I, wherein R¹ is (C₂-C₆)alkenyl, can be reacted with osmium tetroxide and N-methylmorpholine-N-oxide to afford a compound of Formula I wherein R¹ is vicinal dihydroxy(C₂-C₆)alkyl.

(9) a compound of Formula I, wherein R³ is (C₂-C₆)alkenyl, can be reacted with osmium tetroxide and N-methylmorpholine-N-oxide to afford a vicinal diol compound of Formula I wherein R³ is vicinal dihydroxy(C₂-C₆)alkyl.

10 (10) a compound of Formula I, wherein R¹ is (C₂-C₆)alkenyl, can be reacted with ozone followed by NaBH₄ to give a compound of Formula I wherein R¹ is ω-hydroxy(C₁-C₅)alkyl.

(11) a compound of Formula I, wherein R³ is (C₂-C₆)alkenyl, can be reacted with ozone followed by NaBH₄ to give a compound of Formula I wherein R³ is ω-hydroxy(C₁-C₅)alkyl.

(12) a compound of Formula I wherein R¹ or R³ is amino(C₁-C₆)alkyl can be reacted with an (C₁-C₆)alkyl isocyanate to give a compound of Formula I wherein R¹ or R³ is (C₁-C₆)alkylaminocarbonylamino(C₁-C₆)alkyl.

(13) a compound of Formula I wherein R¹ or R³ is amino(C₁-C₆)alkyl can be
20 reacted with an (C₁-C₆)alkyl chloroformate to give a compound of Formula I wherein R¹
or R³ is (C₁-C₆)alkoxycarbonylamino(C₁-C₆)alkyl.

(14) a compound of Formula I wherein R¹ or R³ is amino(C₁-C₆)alkyl can be reacted with chlorosulfonyl isocyanate or sulfamide to give a compound of Formula I wherein R¹ or R³ is aminosulfonylamino(C₁-C₆)alkyl.

25 (15) a compound of Formula I wherein R¹ or R³ is amino(C₁-C₆)alkyl can be reacted with a (C₁-C₆)alkylsulfamoyl chloride to give a compound of Formula I wherein R¹ or R³ is (C₁-C₆)alkylaminosulfonylamino(C₁-C₆)alkyl.

(16) a compound of Formula I wherein R¹ or R³ is hydroxy(C₁-C₆)alkyl can be reacted with chlorosulfonyl isocyanate to give a compound of Formula I wherein R¹ or R³ is aminosulfonyloxy(C₁-C₆)alkyl.

(17) a compound of Formula I wherein R^1 or R^3 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 or R^3 is aminocarboxy(C_1 - C_6)alkyl, (C_1 -
5 C_6)alkyl aminocarboxy(C_1 - C_6)alkyl or di(C_1 - C_6)alkyl aminocarboxy(C_1 - C_6)alkyl.

(18) a compound of Formula I wherein R^1 or R^3 is hydroxy(C_1 - C_6)alkyl can be reacted with $POCl_3$ to give a compound of Formula I wherein R^1 or R^3 is $(HO)_2P(=O)O(C_1-C_6)alkyl$.

(19) a compound of Formula I wherein Cy^1 is substituted with bromine or iodine,
10 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.

(20) a compound of Formula I wherein R^3 is $MeO_2C(C_1-C_5)alkyl$ can be treated with $MeMgBr$ to afford a compound of Formula I wherein R^3 is $Me_2(HO)C(C_1-C_5)alkyl$.

(21) a compound of Formula I wherein R^1 or R^3 is ω - $H_2NCO(C_1-C_5)alkyl$ can be
15 reacted with TFAA in the presence of pyridine to afford a compound of Formula I wherein R^1 or R^3 is ω -cyano(C_1-C_5)alkyl.

(22) a compound of Formula I wherein R^3 is amino(C_1 - C_6)alkyl can be reacted with a 2-fluoropyridine to give a compound of Formula I wherein R^3 is 2-
20 pyridylamino(C_1 - C_6)alkyl.

(23) a compound of Formula I wherein R^3 is ω -hydroxy(C_1 - C_6)alkyl can be converted to its methanesulfonate or trifluoromethanesulfonate, treated with a (C_1 - C_6)alkylthiol followed by oxidation with m-CPBA to give a compound of Formula I wherein R^3 is (C_1 - C_6)alkylsulfonyl(C_1 - C_6)alkyl.

(24) a compound of Formula I, wherein Q is NH, can be reacted with sodium hydride and methyl iodide in an inert solvent to give a compound of Formula I, wherein Q is NMe.

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:

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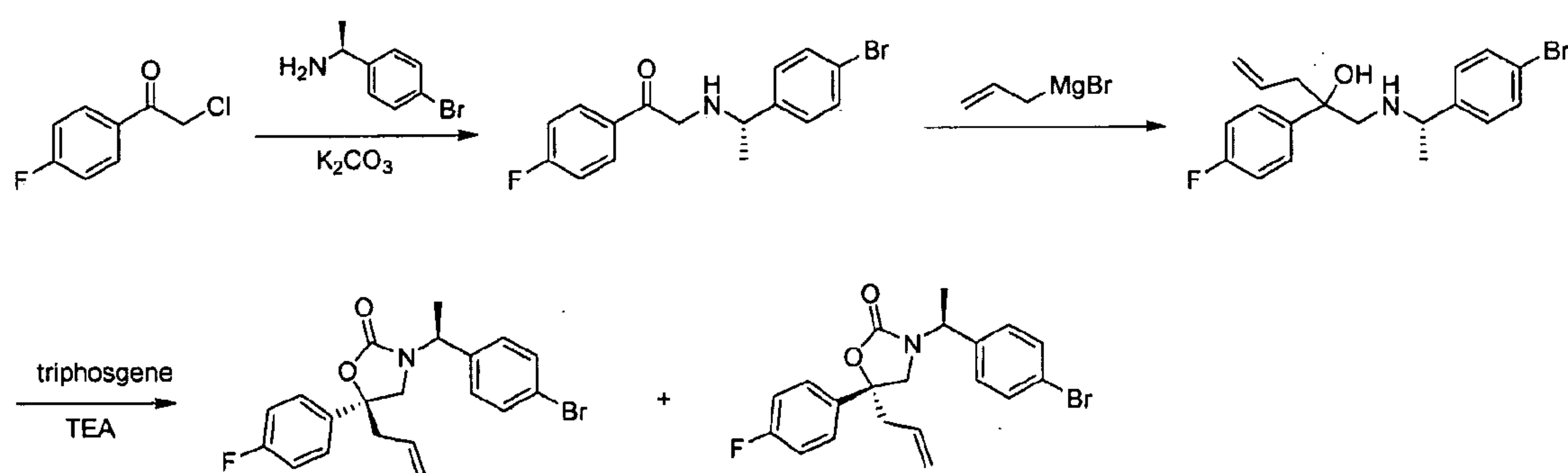
Time (min)	A%	B%
0.0	90	10
2.0	10	90
2.4	10	90
2.5	90	10
3.0	90	10

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		

5 EXAMPLE 1

5-allyl-3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)oxazolidin-2-one



Step 1

To a solution of (S)-1-(4-bromophenyl)ethanamine (2 g, 0.01 mol) and K_2CO_3 (4.2 g, 0.03 mol) in acetonitrile (50 mL) was added 2-chloro-1-(4-fluorophenyl)ethanone (1.72 g, 0.01 mol). The formed mixture was stirred overnight at rt. The solid was
 5 filtered, and the filtrate was concentrated to give (S)-2-(1-(4-bromophenyl) ethylamino) - 1-(4-fluorophenyl)ethanone (2 g, 60%), which was used for the next step without further purification.

Step 2

To a solution of (S)-2-(1-(4-bromophenyl)ethylamino)-1-(4-
 10 fluorophenyl)ethanone (2 g, 0.006 mol) in THF (300 mL) was added allylmagnesium bromide (1 M, 20 mL, 0.02 mol) under nitrogen at $-78^\circ C$. The mixture was stirred at this temperature till the reaction was over. The reaction was quenched with satd aq NH_4Cl . The organic phase was separated and concentrated to give crude 1-((S)-1-(4-bromophenyl)ethylamino)-2-(4-fluorophenyl) pent-4- en-2-ol (1.8 g, 80%), which was
 15 used for the next step without further purification.

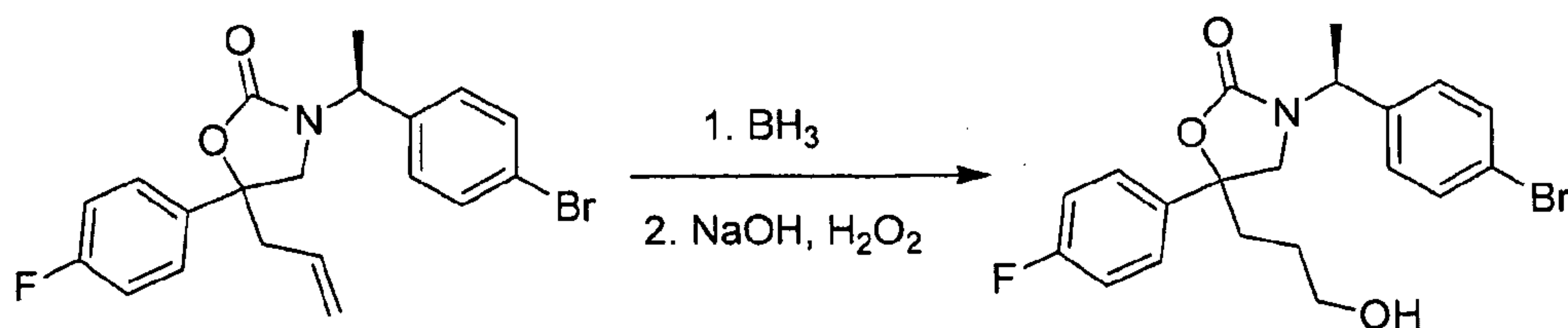
Step 3

To a solution of 1-((S)-1-(4-bromophenyl)ethylamino)-2-(4-fluorophenyl)pent-4- en-2-ol (0.9 g, 0.003 mol) in CH_2Cl_2 (50 mL) and Et_3N (0.8 g, 0.009 mol) was added
 20 triphosgene (0.84 g, 0.003 mol) at $0^\circ C$. The resulting mixture was stirred overnight. The mixture was washed with water. The organic layer was separated, and concentrated to give the crude product, which was purified by preparative TLC to afford 5-allyl-3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)oxazolidin-2-one isomer 1 (403 mg, 33%) and 5-allyl -3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)oxazolidin-2-one
 25 isomer 2 (392 mg, 32%).

EXAMPLE 2

3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)-5-(3-hydroxypropyl)oxazolidin-2-one

30

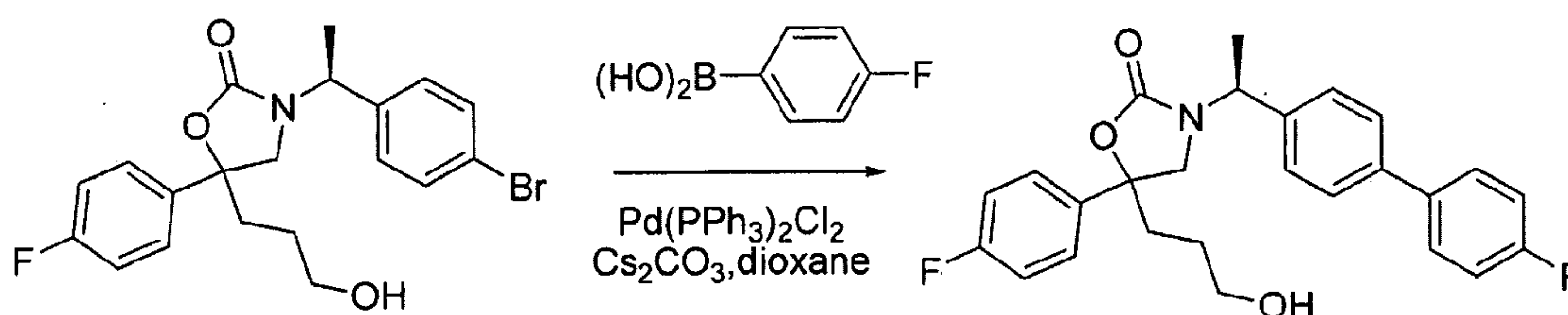


To a solution of 5-allyl-3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)oxazolidin-2-one isomer 1 (50 mg, 0.13 mmol) in THF (10 mL) was added 1 M BH_3 in THF (2 mL, 2.0 mmol) at 0 °C under nitrogen atmosphere. The formed
 5 mixture was stirred for 2 h. The reaction was quenched with water. Then 3 M aq NaOH (1 mL, 3 mmol) and H_2O_2 (2 mL) were added to the above mixture. When the reaction was over, the mixture was extracted with EtOAc. The combined organic phase was concentrated to give the crude product, which was purified by preparative TLC to give 3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)-5-(3-hydroxypropyl)oxazolidin-2-one
 10 isomer 1 (15 mg, 30%). ^1H NMR (CDCl_3): 1.38 (m, 2H), 1.50 (m, 3H), 1.61 (m, 2H), 2.00 (m, 2H), 3.11 (m, 1H), 3.52 (m, 3H), 5.12 (m, 1H), 6.98 (m, 4H), 7.18 (m, 2H), 7.30 (m, 2H).

Reaction of 5-allyl-3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)oxazolidin-2-one isomer 2 under analogous conditions afforded 3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)-5-(3-hydroxypropyl)oxazolidin-2-one isomer
 15 2. ^1H NMR (CDCl_3): 1.18 (m, 2H), 1.39 (m, 3H), 1.41 (m, 1H), 1.86 (m, 2H), 3.18 (m, 1H), 3.48 (m, 3H), 5.12 (m, 1H), 6.98 (m, 2H), 7.17 (m, 2H), 7.23 (m, 2H), 7.48 (m, 2H).

EXAMPLE 3

20 3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)-5-(3-hydroxypropyl)oxazolidin-2-one



25 A mixture of 3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)-5-(3-hydroxypropyl)oxazolidin-2-one isomer 1 (84 mg, 0.2 mmol), 4-fluorophenylboronic acid (34 mg, 0.24 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (30 mg), and aq. Cs_2CO_3 solution (2 mL, 2 M) in 1,4-dioxane (6 mL) was stirred and heated to reflux for 2 h. The organic phase was separated, and concentrated to give the crude product, which was purified by preparative
 30 HPLC to give 3-((1S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-5-(4-fluorophenyl)-5-(3-hydroxypropyl)oxazolidin-2-one isomer 1 (23.2 mg, 27%). ^1H NMR (CDCl_3): 1.28 (m,

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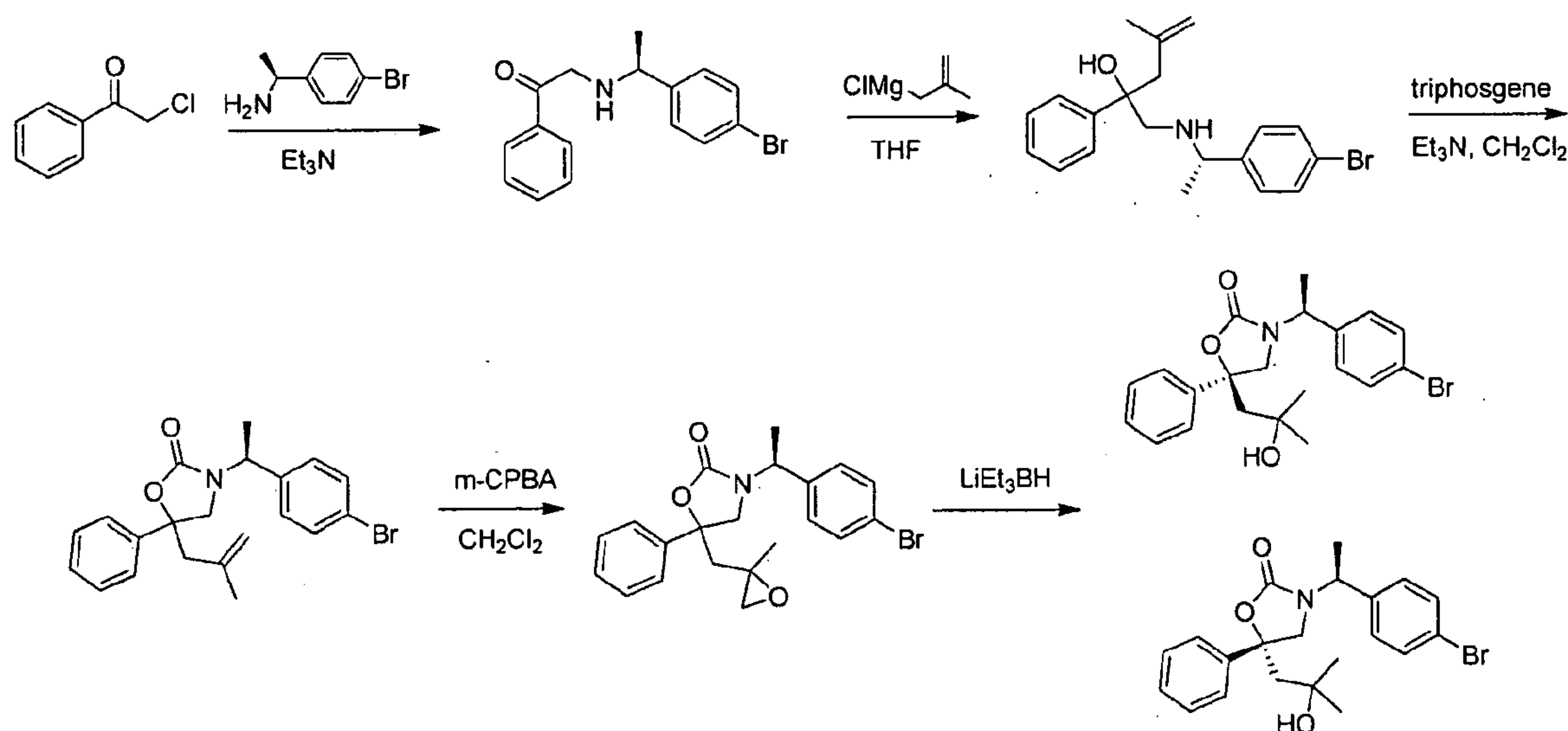
1H), 1.55 (m, 3H), 1.59 (m, 1H), 2.00 (m, 2H), 3.18 (m, 1H), 3.54 (m, 3H), 5.18 (m, 1H), 6.88 (m, 2H), 7.07 (m, 2H), 7.18 (m, 2H), 7.20 (m, 2H), 7.36 (m, 2H), 7.45 (m, 2H).

Reaction of 3-((1S)-1-(4-bromophenyl)ethyl)-5-(4-fluorophenyl)-5-(3-hydroxypropyl)oxazolidin-2-one isomer 2 under analogous conditions afforded 3-((1S)-
 5 1-(4'-fluorobiphenyl-4-yl)ethyl)-5-(4-fluorophenyl)-5-(3-hydroxypropyl)oxazolidin-2-one isomer 2. ¹H NMR (CDCl₃): 1.22 (m, 1H), 1.45 (m, 3H), 1.49 (m, 1H), 1.86 (m, 2H), 3.22 (m, 1H), 3.48 (m, 3H), 5.22 (m, 1H), 7.00 (m, 4H), 7.25 (m, 2H), 7.36 (m, 2H), 7.51 (m, 4H).

10

EXAMPLE 4

3-((S)-1-(4-bromophenyl)ethyl)-5-(2-hydroxy-2-methylpropyl)-5-phenyloxazolidin-2-one



15

Step 1

To a solution of 2-bromo-1-phenylethanone (1.54 g, 0.01 mol) in dry THF (50 mL) was added (S)-1-(4-bromophenyl)-ethyl amine (1.99 g, 0.01 mol) and Et₃N (3 g, 0.03 mol). The mixture was stirred at room temperature for 4 h, and filtered. The filtrate
 20 was concentrated to give the crude (S)-2-(1-(4-bromophenyl)ethylamino)-1-phenylethanone (2.85 g, 90%) as an oil, which was used for the next step without purification.

25 Step 2

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To a solution of crude (S)-2-(1-(4-bromophenyl)ethylamino)-1-phenylethanone (1 g, 3.15 mmol) in THF (20 mL) was added (2-methylallyl)magnesium chloride (10 mL, 1 mol/L) at -78 °C. The mixture was stirred at rt for 1 h, and TLC showed disappearance of the starting material. The mixture was quenched with satd aq NH₄Cl and extracted with EtOAc. The combined organic phase was dried over Na₂SO₄ and concentrated to give the crude product, which was purified by chromatography to afford 1-((S)-1-(4-bromophenyl)ethylamino)-4-methyl-2-phenylpent-4-en-2-ol (1.06 g, 90%).

Step 3

To a solution of 1-((S)-1-(4-bromophenyl)-ethylamino)-4-methyl-2-phenylpent-4-en-2-ol (800 mg, 2.14 mmol) in CH₂Cl₂ (30 mL) was added triphosgene (630 mg, 2.14 mmol) and Et₃N (650 mg, 6.42 mmol) at 0 °C. The mixture was stirred at rt overnight. TLC showed disappearance of the starting material. The mixture was washed with 1 N aq HCl and extracted by DCM. The combined organic phase was dried over Na₂SO₄ and concentrated to give the crude product, which was purified by chromatography to afford 3-((S)-1-(4-bromophenyl)-ethyl)-5-(2-methylallyl)-5-phenyloxazolidin-2-one (700 mg, 82%).

Step 4

To a solution of 3-((S)-1-(4-bromophenyl)-ethyl)-5-(2-methylallyl)-5-phenyloxazolidin-2-one (700 mg, 1.75 mmol) in dry CH₂Cl₂ (100 mL) was added *m*-CPBA (1.5 g, 8.75 mmol) at rt. The reaction mixture was stirred until the starting material had been consumed (monitored by TLC). The mixture was diluted with (CH₃)₃COCH₃ (70 mL), washed with 30% aq Na₂S₂O₃ and aq NaHCO₃, dried over Na₂SO₄, filtered, and concentrated to give 3-((S)-1-(4-bromophenyl)-ethyl)-5-((2-methyloxiran-2-yl)-methyl)-5-phenyloxazolidin-2-one (650 mg, 90%), which was used directly for the next step without further purification..

Step 5

To a solution of 3-((S)-1-(4-bromophenyl)-ethyl)-5-((2-methyloxiran-2-yl)-methyl)-5-phenyloxazolidin-2-one (650 mg, 1.57 mmol) in THF (32 mL) was added dropwise Super-Hydride (13.6 mL, 13.6 mmol) at 0 °C under N₂ over 30 min, and the resulting solution was stirred at 10~13°C for 4 h. To the mixture was added dropwise H₂O₂ (20 mL), diluted with (CH₃)₃COCH₃ (380 mL), washed with water, followed by

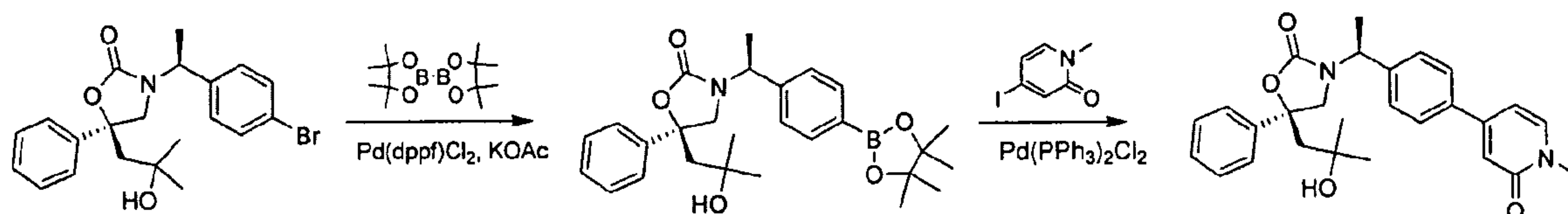
addition of 30% aq $\text{Na}_2\text{S}_2\text{O}_3$ and brine. The organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product, which was purified by prep TLC to afford the the two isomers of the title compound:

Isomer 1: (*S*)-3-((*S*)-1-(4-bromophenyl)ethyl)-5-(2-hydroxy-2-methylpropyl)-5-phenyl oxazolidin-2-one (300 mg, 46%).

Isomer 2: (*R*)-3-((*S*)-1-(4-bromophenyl)-ethyl)-5-(2-hydroxy-2-methylpropyl)-5-phenyloxazolidin-2-one (300 mg, 46%).

10 EXAMPLE 5 Isomer 1

(*S*)-5-(2-hydroxy-2-methylpropyl)-3-((*S*)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-5-phenyloxazolidin-2-one



15 Step 1

To a solution of (*S*)-3-((*S*)-1-(4-bromophenyl)-ethyl)-5-(2-hydroxy-2-methylpropyl)-5-phenyloxazolidin-2-one (300 mg, 0.72 mmol) in DMSO (10 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-1,3,2-dioxaborolane (560 mg, 2.16 mmol), CH_3COOK (995 mg, 10.13 mmol), and Pd(dppf)Cl_2 (60 mg, 0.076 mmol) under N_2 . The mixture was stirred at 90 °C for 2 h. The reaction was quenched with H_2O , and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product, which was purified by preparative TLC to give (*S*)-5-(2-hydroxy-2-methylpropyl)-5-phenyl-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-phenyl)-ethyl)-oxazolidin-2-one (150 mg, 45%).

25

Step 2

A mixture of compound (*S*)-5-(2-hydroxy-2-methylpropyl)-5-phenyl-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)phenyl)ethyl)oxazolidin-2-one (120 mg, 0.26 mmol), 4-iodo-1-methylpyridin-2(1H)-one (67 mg, 0.28 mmol), $\text{Pd(PPh}_3)_2\text{Cl}_2$ (30 mg) and aq Cs_2CO_3 (2 N, 2 mL) solution in 1,4-dioxane (8 mL) was stirred under N_2 atmosphere at 100 °C for 2 h. LC-MS showed the reaction was complete. Water (5 mL)

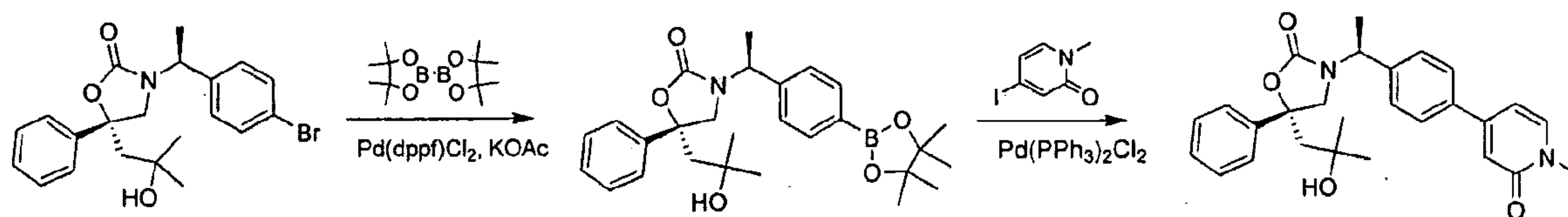
30

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was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by preparative TLC to give (*S*)-5-(2-hydroxy-2-methylpropyl)-3-((*S*)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-5-phenyloxazolidin-2-one (65 mg, yield 56%). ¹H NMR (CDCl₃ 400 MHz): δ 1.05 (s, 3H), 1.07 (s, 3H), 1.53 (d, 3H), 1.68 (s, 1H), 2.28 (s, 2H), 3.15 (d, 1H), 3.50 (s, 3H), 3.71 (m, 1H), 5.14 (m, 1H), 5.23 (s, 1H), 6.28 (d, 1H), 6.63 (s, 1H), 7.03 (d, 2H), 7.19-7.29 (m, 8H).

EXAMPLE 5 Isomer 2

(*R*)-5-(2-hydroxy-2-methylpropyl)-3-((*S*)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-5-phenyloxazolidin-2-one



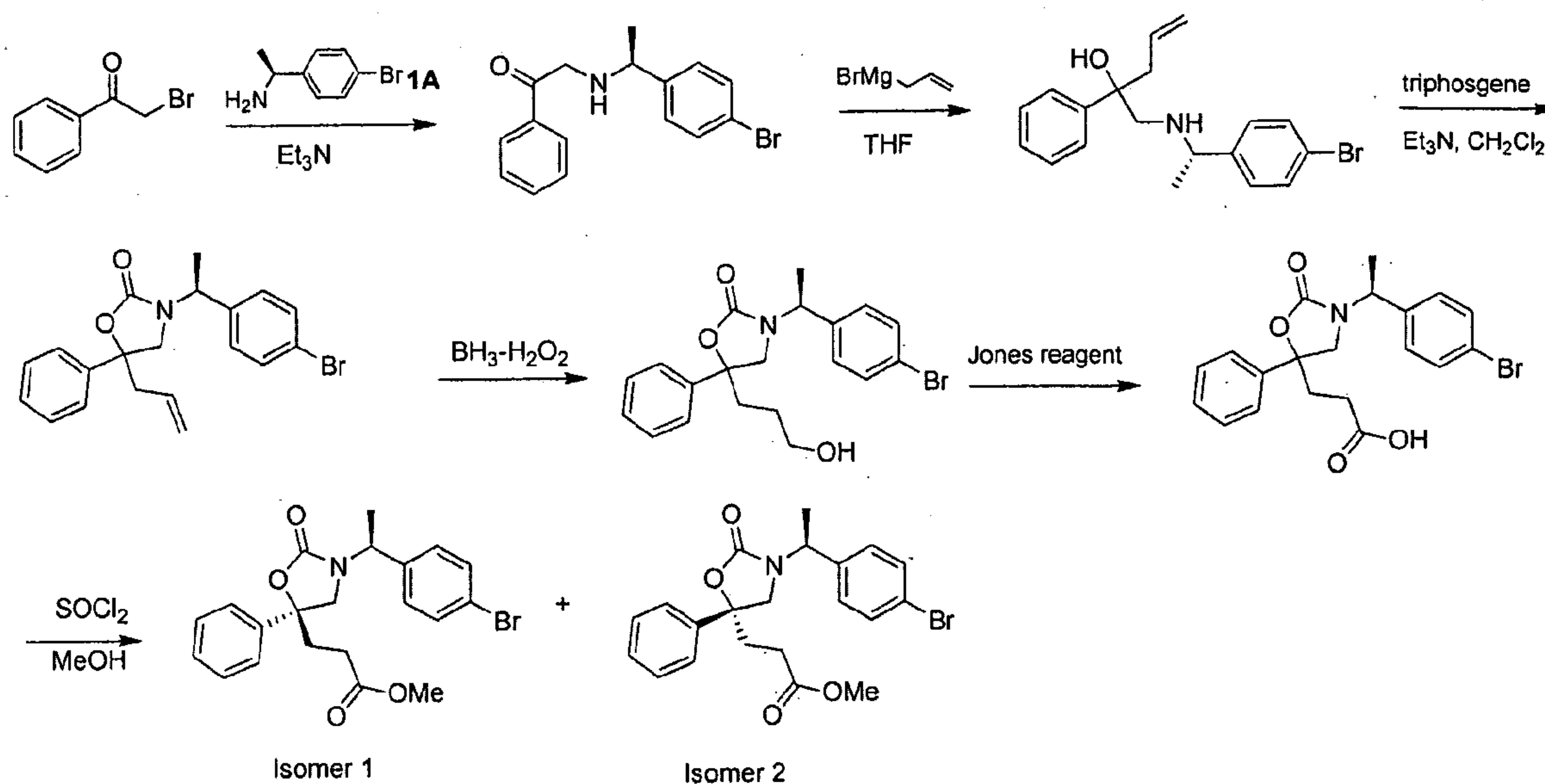
The title compound was prepared following a procedure analogous to that described in for Example 5 Isomer 1, using (*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-5-(2-hydroxy-2-methylpropyl)-5-phenyloxazolidin-2-one in Step 1. ¹H NMR (CDCl₃ 400 MHz): δ 1.02 (s, 3H), 1.06 (s, 3H), 1.45 (d, 3H), 1.71 (s, 1H), 2.20 (m, 2H), 3.40 (d, 1H), 3.48 (d, 1H), 3.60 (s, 3H), 5.28 (m, 1H), 6.45 (d, 1H), 6.80 (s, 1H), 7.28-7.45 (m, 8H), 7.58 (d, 2H).

20

EXAMPLE 6

5-(3-hydroxy-3-methylbutyl)-3-((*S*)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-5-phenyloxazolidin-2-one

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Steps 1-3

Procedures analogous to those described in Example 4 Steps 1-3 were followed using allylmagnesium bromide in Step 2.

Step 4

To a solution of 5-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-5-phenyloxazolidin-2-one (1 g, 2.59 mmol) in THF (10 mL) was added $\text{BH}_3\text{-THF}$ (10 mL, 10 mmol) at 0 °C under nitrogen. The mixture was stirred for 2 h, and quenched with water. The aqueous NaOH solution (2 mL, 3 M) and H_2O_2 (5 mL) was added into the mixture. When the reaction was finished, the mixture was extracted with EtOAc and concentrated to give 3-((*S*)-1-(4-bromophenyl)ethyl)-5-(3-hydroxypropyl)-5-phenyloxazolidin-2-one (0.98 g, yield 93.63%).

15

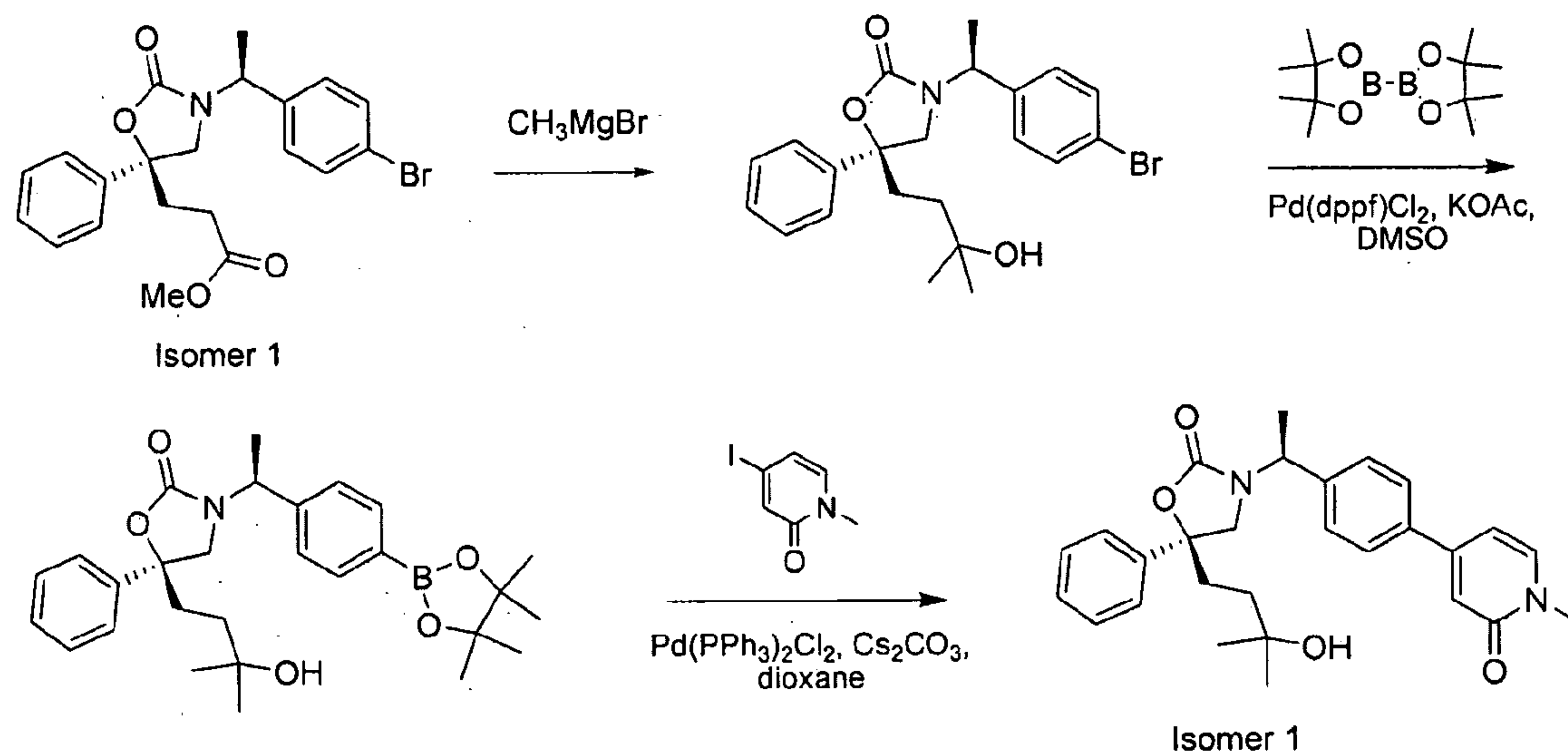
Step 5

To a solution of 3-((*S*)-1-(4-bromophenyl)ethyl)-5-(3-hydroxypropyl)-5-phenyloxazolidin-2-one (0.98 g, 2.42 mmol) in acetone (20 mL) was added Jones reagent (8 mL, 2.5 mol/L) at 0 °C. The solution was stirred at room temperature for 30 min. Solvent was removed in vacuum, and the residue was dissolved in a mixture of CH_2Cl_2 and water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give 3-(3-((*S*)-1-(4-bromophenyl)ethyl)-2-oxo-5-phenyloxazolidin-5-yl)propanoic acid (270 mg, 26.60%).

20

Step 6

To a solution of 3-(3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-5-phenyloxazolidin-5-yl)propanoic acid (270 mg, 0.645 mmol) in MeOH (10 mL) was added SOCl₂ (5 mL) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 2 h, concentrated, and purified by prep TLC (3:1 PE/EA) to afford methyl 3-(3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-5-phenyloxazolidin-5-yl)propanoate (74 mg, 53%) & methyl 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-5-phenyloxazolidin-5-yl)propanoate (73 mg, 52.32%).



10

Step 7

To a solution of methyl 3-(3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-5-phenyloxazolidin-5-yl)propanoate isomer 1 (74 mg, 0.171 mmol) in THF (5 mL) was added MeMgBr (0.57 mL, 1.71 mmol) dropwise at -78 °C under nitrogen. The reaction mixture was stirred at -78°C for 30 min., at room temperature for 30 min. The reaction mixture was quenched with water, and extracted with EtOAc. The combined organic layer was concentrated to give an oil, which was purified by prep TLC to give 3-((S)-1-(4-bromophenyl)ethyl)-5-(3-hydroxy-3-methylbutyl)-5-phenyloxazolidin-2-one isomer 1 (70 mg, yield 94.59%).

20

Steps 8 and 9

Procedures analogous to those described in Example 5 Steps 1 and 2 were followed starting with 3-((S)-1-(4-bromophenyl)ethyl)-5-(3-hydroxy-3-methylbutyl)-5-phenyloxazolidin-2-one isomer 1 to afford 5-(3-hydroxy-3-methylbutyl)-3-((S)-1-(4-(1-

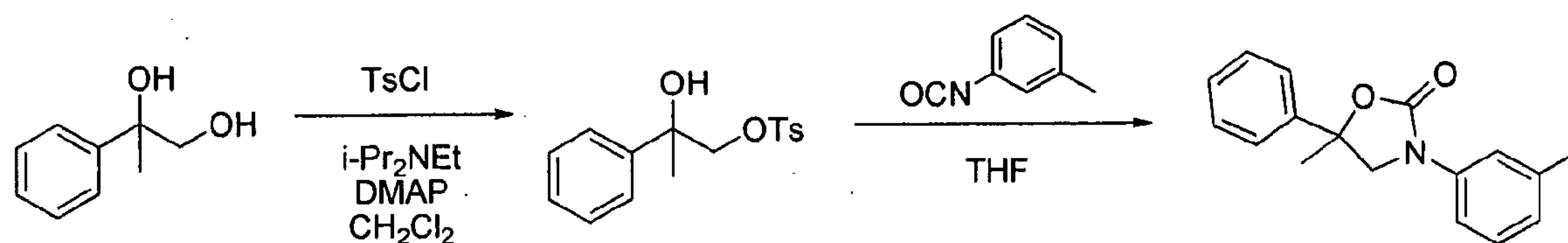
25

methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-5-phenyloxazolidin-2-one isomer 1.
LC-MS Method 2 t_R = 1.00 min, m/z = 461, 443.

Procedures analogous to those described in Example 5 Steps 1 and 2, were
5 followed starting with 3-((S)-1-(4-bromophenyl)ethyl)-5-(3-hydroxy-3-methylbutyl)-5-phenyloxazolidin-2-one isomer 2 to afford 5-(3-hydroxy-3-methylbutyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-5-phenyloxazolidin-2-one isomer 2.
LC-MS Method 2 t_R = 0.95 min, m/z = 461.

10 EXAMPLE 7

5-Methyl-5-phenyl-3-m-tolyloxazolidin-2-one



Step 1

15 To a stirred solution of 2-phenylpropane-1,2-diol (1.56 g, 10.3 mmol) and $i\text{-Pr}_2\text{NEt}$ (1.5 mL, 11.4 mmol) and DMAP (1 crystal) in CH_2Cl_2 (40 mL) was added solid $p\text{-toluenesulfonyl chloride}$ (1.95 g, 10.3 mmol). The mixture was stirred at rt for 3 d. The mixture was diluted with ether (150 mL), washed with 5% aq HCl (2 x 30 mL) and satd aq NaHCO_3 (30 mL), and dried over MgSO_4 . Removal of the salt left an oil (2.29 g)
20 which was purified by chromatography on a 12-g silica cartridge eluted with a 0-50% EtOAc in hexanes gradient to afford 2-hydroxy-2-phenylpropyl 4-methylbenzenesulfonate (1.17 g, 37%).

Step 2

25 To a stirred solution of 2-hydroxy-2-phenylpropyl 4-methylbenzenesulfonate (125 mg, 0.41 mmol) in THF (5 mL) was added 3-methylphenyl isocyanate (0.058 mL, 0.45 mmol), followed by DBU (0.075 mL, 0.49 mmol). The mixture was stirred at rt for 4 h and heated at reflux for 20 h. The mixture was diluted with ether (80 mL), washed with 5% aq HCl (20 mL) and satd aq NaHCO_3 (20 mL), and dried over MgSO_4 .
30 Removal of the solvent left an oil (70 mg) which was applied to a 2-g silica SPE cartridge which was eluted sequentially with 0, 10, 25, 50, 75 and 100% EtOAc in hexanes to give six fractions. Fractions 1 and 2 were pooled and concentrated to leave

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an oil (19 mg) which was purified prep HPLC to afford 5-methyl-5-phenyl-3-m-tolyloxazolidin-2-one (2.4 mg, 2%). LC-MS Method 1 t_R = 1.92 min, m/z = 268; ^1H NMR ($CDCl_3$) 1.87 (s, 3H), 2.35 (s, 3H), 4.12 (m, 2H), 6.94 (d, 1H), 7.2-7.5 (8H).

5 BIOLOGICAL TEST EXAMPLE 1

The inhibition of microsomal preparation of 11 β -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 room temperature in 96 well clear flexible PET Microbeta plates (PerkinElmer). The assay begins by dispensing 49 μ l of substrate solution (50mM HEPES, pH 7.4, 100mM KCl, 5mM NaCl, 2mM $MgCl_2$, 2 mM NADPH and 160 nM [^3H]cortisone (1 Ci/mmol)) and mixing in 1 μ L of the test compounds in DMSO

15 previously diluted in half-log increments (8 points) starting at 0.1 mM. After a 10 minute pre-incubation, 50 μ L of enzyme solution containing microsomes isolated from CHO cells overexpressing human 11 β -HSD1 (10-20 μ g/ml of total protein) was added, and the plates were incubated for 90 minutes at room temperature. The reaction was stopped by adding 50 μ l of the SPA beads suspension containing 10 μ M 18 β -

20 glycyrrhetic acid, 5 mg/ml protein A coated YSi SPA beads (GE Healthcare) and 3.3 μ g/ml of anti-cortisol antibody (East Coast Biologics) in Superblock buffer (Bio-Rad). The plates were shaken for 120 minutes at room temperature, and the SPA signal corresponding to [^3H]cortisol was measured on a Microbeta plate reader.

25 BIOLOGICAL TEST EXAMPLE 2

The inhibition of 11 β -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

30 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% CO₂.

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% CO₂. 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 [³H] 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% CO₂. Negative controls were incubated without radioactive substrate and received the same amount of [³H] cortisone at the end of the incubation. Formation of [³H] 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

25

Compound	Biological Test Example 1 ^a	
	IC ₅₀ Range	Average % inhibition at 100 nM
Example 1 Isomer 1	nt	nt
Example 1 Isomer 2	nt	nt
Example 2 Isomer 1	++	78.3
Example 2 Isomer 2	#	16.9
Example 3 Isomer 1	++	91.4

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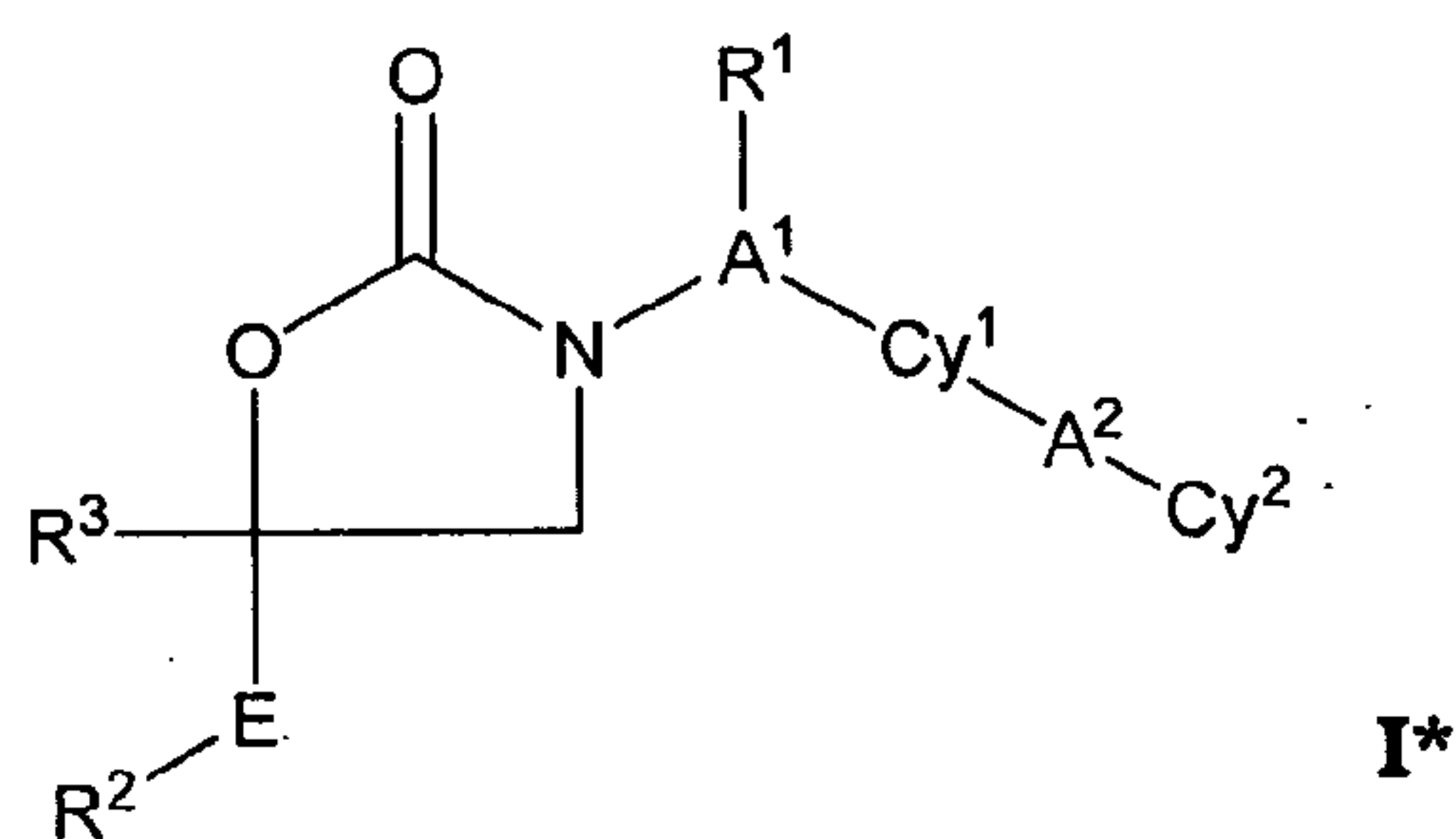
Example 3 Isomer 2	#	19.1
Example 4 Isomer 1	nt	nt
Example 4 Isomer 2	nt	nt
Example 5 Isomer 1	++	51.9
Example 5 Isomer 2	#	3.4
Example 6 Isomer 1	#	18.4
Example 6 Isomer 2	#	19.8
Example 7	-	5.4

^a ++ means IC₅₀ = <100 nM, + means IC₅₀ = 100 – 1000 nM, # means IC₅₀ > 100 nM, nt means not tested.

PROPHETIC COMPOUND TABLES

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TABLE 1



Prophetic Example No.	A ¹ -R ¹	Cy ¹	A ²	Cy ²	E	R ²	R ³
1a	CHMe	3-Me-Ph	bond	H	bond	Ph	Me
2a	CHMe	3-Br-Ph	bond	H	bond	Ph	Me
3a	bond	1,3-C ₆ H ₄	bond	Ph	bond	Ph	Me
4a	bond	1,3-C ₆ H ₄	bond	2-Cl-Ph	bond	Ph	Me
5a	bond	1,3-C ₆ H ₄	bond	2-NC-Ph	bond	Ph	Me
6a	bond	1,3-C ₆ H ₄	bond	2-MeO-Ph	bond	Ph	Me
7a	bond	1,3-C ₆ H ₄	bond	2,6-diCl-Ph	bond	Ph	Me
8a	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	Me
9a	bond	1,3-C ₆ H ₄	bond	3-Cl-Ph	bond	Ph	Me
10a	bond	1,3-C ₆ H ₄	bond	3-F-Ph	bond	Ph	Me
11a	bond	1,3-C ₆ H ₄	bond	2,5-diF-Ph	bond	Ph	Me
12a	bond	1,3-C ₆ H ₄	bond	3,5-diF-Ph	bond	Ph	Me

13a	bond	1,3-C ₆ H ₄	bond	4-F-Ph	bond	Ph	Me
14a	bond	1,3-C ₆ H ₄	bond	2-F-Ph	bond	Ph	Me
15a	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
16a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)CH ₂
17a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH(OH)CH ₂
18a	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	allyl
19a	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂
20a	bond	1,3-(4-F)C ₆ H ₃	bond	4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
21a	bond	1,3-(4-F)C ₆ H ₃	bond	4-F-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
22a	bond	1,3-C ₆ H ₄	bond	2-Cl-4-F-Ph	bond	Ph	HOCH ₂ CH ₂
23a	bond	1,3-C ₆ H ₄	bond	2,6-diCl-Ph	bond	Ph	HOCH ₂ CH ₂
24a	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	H ₂ NC(=O)CH ₂
25a	CH	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH(OH)CH ₂
26a	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
27a	bond	1,3-C ₆ H ₄	bond	Ph	bond	3-Cl-Ph	Me
28a	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	2-pyridyl	Me
29a	CHMe	Ph	bond	H	bond	Ph	Me
30a	CHMe	3-MeO-Ph	bond	H	bond	Ph	Me
31a	CHMe	4-MeO-Ph	bond	H	bond	Ph	Me
32a	CHMe	Ph	bond	H	bond	2-Me-Ph	Me
33a	CHMe	Ph	bond	H	bond	4-Me-Ph	Me
34a	CHMe	Ph	bond	H	bond	4-MeS-Ph	Me
35a	CHMe	Ph	bond	H	bond	4-F-Ph	allyl
36a	bond	1,3-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂
37a	CHMe	Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂
38a	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	MeSO ₂ NHCH ₂ CH ₂
39a	bond	1,3-(4-F)C ₆ H ₃	bond	2-Cl-4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
40a	bond	1,3-C ₆ H ₄	bond	2-Cl-4-F-Ph	bond	Ph	HOCH ₂ CH ₂
41a	bond	2,6-pyridyl	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂
42a	bond	2,6-pyridyl	bond	4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
43a	bond	2,6-pyridyl	bond	4-F-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
44a	bond	1,3-(4-F)C ₆ H ₃	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂

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45a	bond	1,3-(4-F)C ₆ H ₃	bond	2,4-diF-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
46a	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂
47a	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
48a	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
49a	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	allyl
50a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	allyl
51a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
52a	CHMe	Ph	bond	H	bond	4-F-Ph	vinyl
53a	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂
54a	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	Ph	HOCH ₂ CH ₂
55a	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
56a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
57a	CHMe	c-hex	bond	H	bond	4-F-Ph	allyl
58a	CHMe	c-hex	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
59a	CHMe	1,4-C ₆ H ₄	bond	c-Pr	bond	4-F-Ph	allyl
60a	CHMe	4-MeO ₂ C-Ph	bond	H	bond	4-F-Ph	allyl
61a	CHMe	1,3-C ₆ H ₄	bond	c-Pr	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
62a	CHMe	4-MeO ₂ C-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
63a	CH ₂ Et	4-Br-Ph	bond	H	bond	4-F-Ph	allyl
64a	bond	2,6-(5-Cl)-pyridyl	bond	4-F-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
65a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NCH ₂ CH ₂
66a	bond	2,6-(5-Cl)-pyridyl	bond	2,4-diF-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
67a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
68a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeCH(OH)CH ₂
69a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeC(=O)CH ₂
70a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOC(Me) ₂ CH ₂
71a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeOCH ₂ CH ₂
72a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHC(=O)NHCH ₂ CH ₂
73a	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂
74a	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH(OH)CH ₂
75a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
76a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHC(=O)CH ₂ CH ₂

77a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeCONHCH ₂ CH ₂
78a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHC(=O)OCH ₂ CH ₂
79a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NSO ₂ NHCH ₂ CH ₂
80a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NSO ₂ OCH ₂ CH ₂
81a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	(HO) ₂ P(=O)OCH ₂ CH ₂
82a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NCH ₂ C(=O)NHCH ₂ CH ₂
83a	CHMe	4-HOCH ₂ -Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
84a	CHMe	4-HOC(Me) ₂ -Ph	bond	H	bond	4-F-Ph	allyl
85a	CHMe	4-Br-Ph	bond	H	bond	2-thienyl	allyl
86a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂
87a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-thienyl	allyl
88a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
89a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂
90a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	2-thienyl	allyl
91a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-thienyl	HOCH ₂ CH ₂ CH ₂
92a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-thienyl	MeCH(OH)CH ₂
93a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH(OH)CH ₂
94a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
95a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	MeCH(OH)CH ₂
96a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	2-thienyl	HOCH ₂ CH ₂ CH ₂
97a	CHMe	Ph	bond	2,4-diF-Ph	bond	4-F-Ph	NCCH ₂ CH ₂
98a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH(OH)CH ₂
99a	CH ₂ Et	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
100a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOC(=O)CH ₂ CH ₂
101a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ NHCH ₂ CH ₂
102a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ C(=O)NHCH ₂ CH ₂
103a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeOC(=O)NHCH ₂ CH ₂
104a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	2-(4-morpholino)ethyl
105a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	EtNHCONHCH ₂ CH ₂
106a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHC(=NCN)NHCH ₂ CH ₂
107a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH ₂ CH ₂
108a	CHMe	4-Cl-Ph	bond	H	bond	i-Pr	HOCH ₂ CH ₂ CH ₂

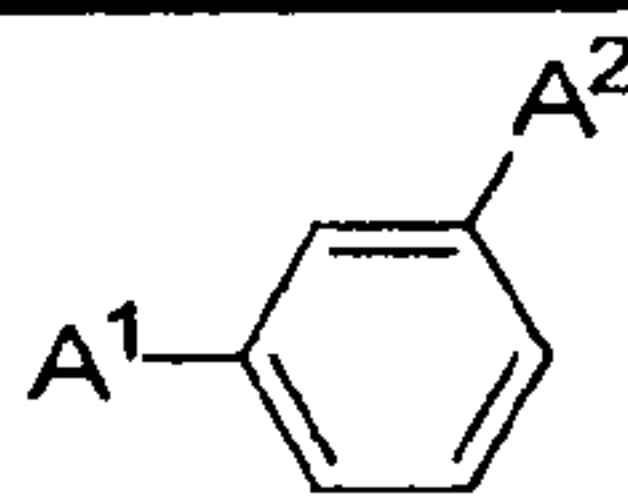
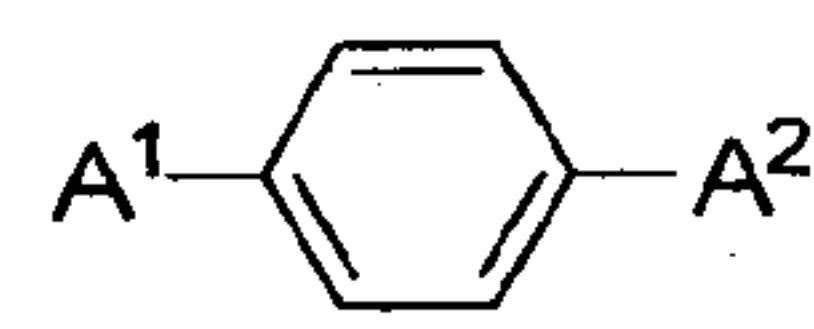
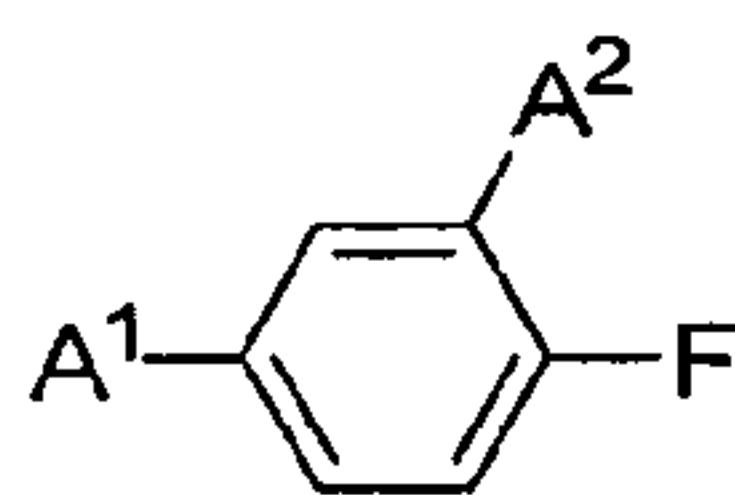
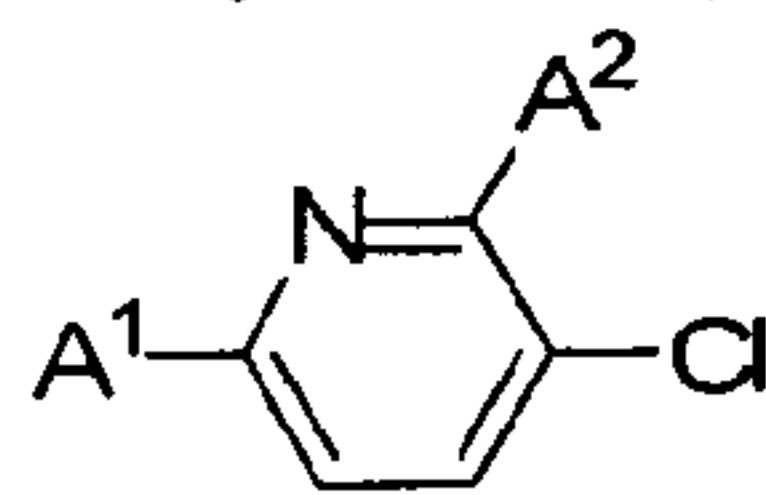
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110a	CHMe	4-MeO-Ph	bond	H	bond	Ph	HOCH ₂ CH ₂
111a	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	allyl
112a	CHMe	4-HOCH ₂ -Ph	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
113a	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂
114a	CHMe	4-Cl-Ph	bond	H	bond	4-F-Ph	allyl
115a	CHMe	c-hex	bond	H	bond	Ph	HOCH ₂ CH(OH)CH ₂
116a	CHMe	4-HOCH ₂ CH ₂ -Ph	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
117a	CHMe	4-MeOCH ₂ -Ph	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
118a	CHMe	4-Br-Ph	bond	H	bond	i-Pr	HOCH ₂ CH ₂ CH ₂
119a	CHMe	4-Cl-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
120a	CHMe	4-Cl-Ph	bond	H	bond	4-F-Ph	MeCH(OH)CH ₂
121a	CHMe	4-Br-Ph	bond	H	bond	Ph	allyl
122a	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	Ph	HOCH ₂ CH ₂
123a	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH(OH)CH ₂
124a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	i-Pr	HOCH ₂ CH ₂
125a	bond	1-(<i>t</i> -BuOC(=O))pyrrolidin-3-yl	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
126a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH ₂
127a	CHMe	1,4-C ₆ H ₄	bond	4-pyridyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
128a	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
129a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	i-Pr	HOCH ₂ CH ₂ CH ₂
130a	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂
131a	CHMe	1,4-C ₆ H ₄	bond	2-thienyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
132a	CHMe	1,4-C ₆ H ₄	bond	4-morpholinyl	bond	4-F-Ph	allyl
133a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-thienyl	HOCH ₂ CH ₂
134a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	NCCH ₂ CH ₂
135a	CH ₂ Et	4-Br-Ph	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
136a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
137a	CHMe	1,4-C ₆ H ₄	bond	1-oxo-3-pyridyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
138a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	i-Pr	HOCH ₂ CH(OH)CH ₂
139a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	MeCH(OH)CH ₂
140a	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂

141a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	Pr
142a	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
143a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeSO ₂ CH ₂ CH ₂
144a	CHMe	1,4-C ₆ H ₄	bond	5-Me-1,3,4-thiadiazol-2-yl	bond	4-F-Ph	allyl
145a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-thienyl	HOCH ₂ CH ₂ CH ₂
146a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	2-thienyl	HOCH ₂ CH ₂
147a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	H ₂ NCOCH ₂ CH ₂
148a	CHMe	1,4-C ₆ H ₄	bond	2-MeO-5-pyridyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
149a	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
150a	CHEt	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
151a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOC(Me) ₂ CH ₂
152a	CHEt	4-Br-Ph	bond	H	bond	Ph	HOCH ₂ CH(OH)CH ₂
153a	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
154a	CHEt	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
155a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	NCCH ₂
156a	CHMe	1,4-C ₆ H ₄	bond	2,4-diMe-5-thiazolyl	bond	4-F-Ph	allyl
157a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
158a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-F-Ph	HOCH ₂ CH ₂ CH ₂
159a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	3-F-Ph	HOCH ₂ CH ₂ CH ₂
160a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOC(Me) ₂ CH ₂ CH ₂
161a	CHMe	1,4-C ₆ H ₄	bond	5-MeCO-2-thienyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
162a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	H ₂ NCOCH ₂ CH ₂
163a	CHMe	1,4-C ₆ H ₄	bond	5-(H ₂ NCHMe)-2-thienyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
164a	CHEt	1,4-C ₆ H ₄	bond	4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
165a	CHEt	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
166a	CHMe	1,4-C ₆ H ₄	bond	5-(HOCHMe)-2-thienyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
167a	CHEt	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH(OH)CH ₂
168a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NCH ₂ CH ₂ CH ₂
169a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHCH ₂ CH ₂
170a	CHMe	1,4-C ₆ H ₄	bond	3-(CF ₃)-1-pyrazolyl	bond	4-F-Ph	allyl
171a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOC(Me) ₂ CH ₂ CH ₂
172a	CHEt	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂

173a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeSCH ₂ CH ₂
174a	CHMe	Ph	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)NHCH ₂ CH ₂
175a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)OCH ₂ CH ₂
176a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ OCH ₂ CH ₂
177a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	2-(1-imidazolyl)ethyl
178a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeCONMeCH ₂ CH ₂
179a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	MeSO ₂ NHCH ₂ CH ₂ CH ₂
180a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)NHCH ₂ CH ₂ CH ₂
181a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)OCH ₂ CH ₂ CH ₂
182a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	2-(1-aminoimidazol-1-yl)ethyl
183a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHC(=O)NHCH ₂ CH ₂ CH ₂
184a	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)NHCH ₂ CH(OH)CH ₂
185a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH(OH)CH ₂
186a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	4-F-Ph	MeSO ₂ NMeCH ₂ CH(OH)CH ₂
187a	CHMe	1,4-C ₆ H ₄	bond	6-CF ₃ -3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
188a	CHMe	4-MeO-Ph	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
189a	CHMe	3-F-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
190a	CHMe	2-F-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
191a	CHMe	4-F-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
192a	CHMe	4-MeO-Ph	bond	H	bond	Ph	HOCH ₂ CH(OH)CH ₂
193a	CHMe	4-Cl-Ph	bond	H	bond	Ph	H ₂ NCOCH ₂ CH ₂
194a	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
195a	CHMe	4-F ₂ HCO-Ph	bond	H	bond	4-F-Ph	allyl
196a	CHMe	Ph	bond	3-pyrazolyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
197a	CHMe	1,4-C ₆ H ₄	bond	5-F-3-pyridyl	bond	Ph	allyl
198a	CHMe	3-CF ₃ -Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
199a	CHMe	4-CF ₃ -Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
200a	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	Ph	H ₂ NCOCH ₂ CH ₂
201a	CHMe	1,4-C ₆ H ₄	bond	4-pyridyl	bond	Ph	H ₂ NCOCH ₂ CH ₂
202a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
203a	CHMe	1,4-C ₆ H ₄	bond	5-F-3-pyridyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
204a	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH ₂

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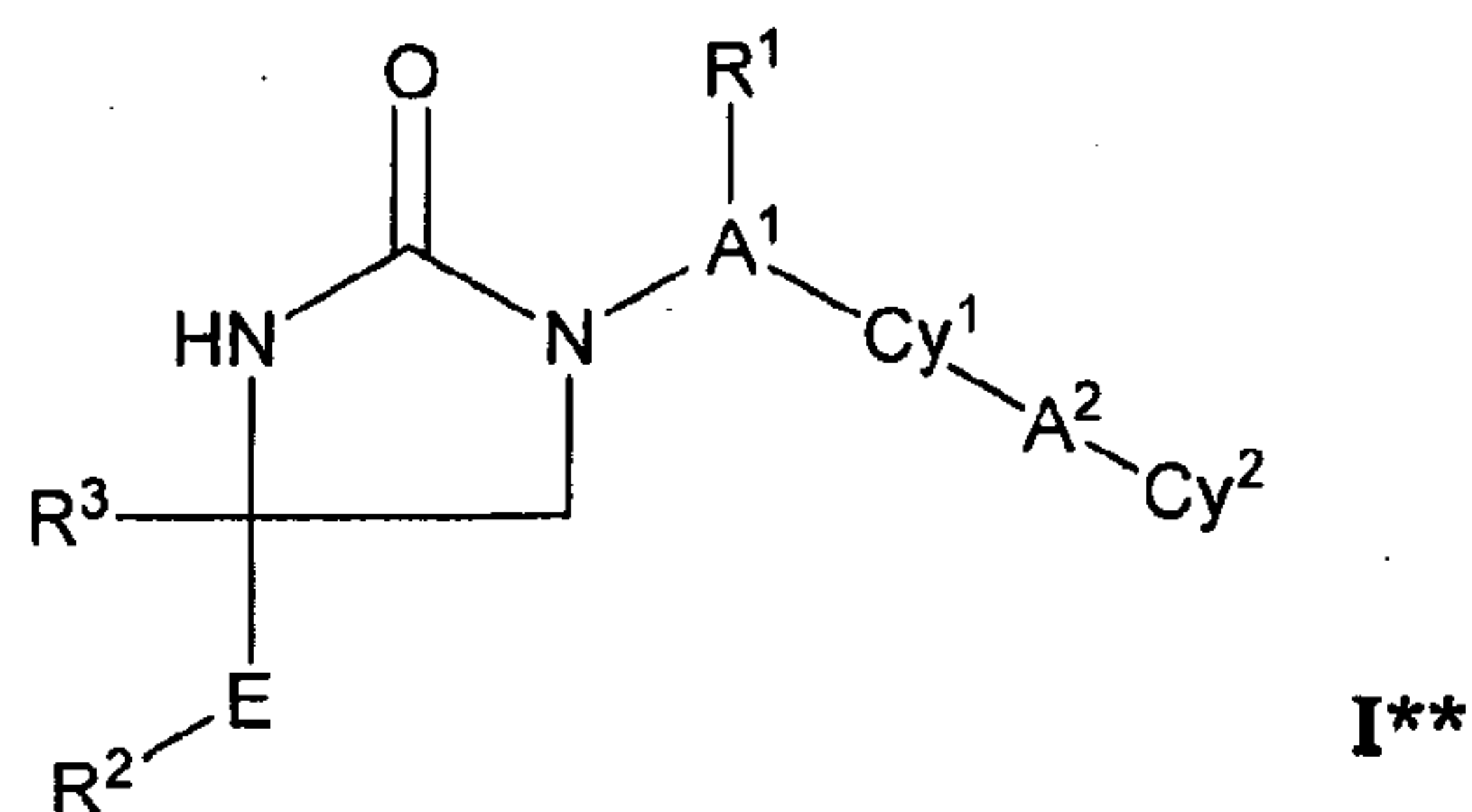
205a	CHMe	1,4-C ₆ H ₄	bond	5-F-3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
206a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	NCC(Me)2CH ₂
207a	CHMe	1,4-C ₆ H ₄	bond	6-MeO-3-pyridyl	bond	Ph	H ₂ NCOCH ₂ CH ₂
208a	CHMe	1,4-C ₆ H ₄	bond	5-MeO-3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
209a	CHMe	1,4-C ₆ H ₄	bond	5-Cl-3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
210a	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	Ph	MeSO ₂ NHCH ₂ CH ₂
211a	CHMe	4-F ₂ HCO-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
212a	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	(HO) ₂ P(=O)OCH ₂ CH ₂ CH ₂
213a	CHMe	1,4-C ₆ H ₄	bond	2-Me-4-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
214a	CHMe	1,4-C ₆ H ₄	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
215a	CHMe	1,4-C ₆ H ₄	bond	1-Me-6-oxo-3-(1,6-dihydropyridyl)	bond	Ph	HOCH ₂ CH ₂ CH ₂
216a	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH ₂ CH ₂
217a	CHMe	4-MeO-Ph	bond	H	bond	Ph	H ₂ NCOCH ₂ CH ₂
218a	CHMe	4-F-Ph	bond	H	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
219a	CHMe	c-hex	bond	H	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
220a	bond	1,3-(4-F)C ₆ H ₃	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
221a	CHMe	c-hex	bond	H	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH ₂ CH ₂

^a Cy¹ = 1,3-C₆H₄ meansCy¹ = 1,4-C₆H₄ meansCy¹ = 1,3-(4-F)C₆H₃ meansCy¹ = 2,6-(5-Cl)-pyridyl means

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TABLE 2



Prophetic Example No.	A ¹ -R ¹	Cy ¹	A ²	Cy ²	E	R ²	R ³
1b	CHMe	3-Me-Ph	bond	H	bond	Ph	Me
2b	CHMe	3-Br-Ph	bond	H	bond	Ph	Me
3b	bond	1,3-C ₆ H ₄	bond	Ph	bond	Ph	Me
4b	bond	1,3-C ₆ H ₄	bond	2-Cl-Ph	bond	Ph	Me
5b	bond	1,3-C ₆ H ₄	bond	2-NC-Ph	bond	Ph	Me
6b	bond	1,3-C ₆ H ₄	bond	2-MeO-Ph	bond	Ph	Me
7b	bond	1,3-C ₆ H ₄	bond	2,6-diCl-Ph	bond	Ph	Me
8b	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	Me
9b	bond	1,3-C ₆ H ₄	bond	3-Cl-Ph	bond	Ph	Me
10b	bond	1,3-C ₆ H ₄	bond	3-F-Ph	bond	Ph	Me
11b	bond	1,3-C ₆ H ₄	bond	2,5-diF-Ph	bond	Ph	Me
12b	bond	1,3-C ₆ H ₄	bond	3,5-diF-Ph	bond	Ph	Me
13b	bond	1,3-C ₆ H ₄	bond	4-F-Ph	bond	Ph	Me
14b	bond	1,3-C ₆ H ₄	bond	2-F-Ph	bond	Ph	Me
15b	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
16b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)CH ₂
17b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH(OH)CH ₂
18b	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	allyl
19b	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂
20b	bond	1,3-(4-F)C ₆ H ₃	bond	4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
21b	bond	1,3-(4-F)C ₆ H ₃	bond	4-F-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
22b	bond	1,3-C ₆ H ₄	bond	2-Cl-4-F-Ph	bond	Ph	HOCH ₂ CH ₂
23b	bond	1,3-C ₆ H ₄	bond	2,6-diCl-Ph	bond	Ph	HOCH ₂ CH ₂
24b	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	H ₂ NC(=O)CH ₂
25b	CH	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH(OH)CH ₂

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26b	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
27b	bond	1,3-C ₆ H ₄	bond	Ph	bond	3-Cl-Ph	Me
28b	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	2-pyridyl	Me
29b	CHMe	Ph	bond	H	bond	Ph	Me
30b	CHMe	3-MeO-Ph	bond	H	bond	Ph	Me
31b	CHMe	4-MeO-Ph	bond	H	bond	Ph	Me
32b	CHMe	Ph	bond	H	bond	2-Me-Ph	Me
33b	CHMe	Ph	bond	H	bond	4-Me-Ph	Me
34b	CHMe	Ph	bond	H	bond	4-MeS-Ph	Me
35b	CHMe	Ph	bond	H	bond	4-F-Ph	allyl
36b	bond	1,3-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂
37b	CHMe	Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂
38b	bond	1,3-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	MeSO ₂ NHCH ₂ CH ₂
39b	bond	1,3-(4-F)C ₆ H ₃	bond	2-Cl-4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
40b	bond	1,3-C ₆ H ₄	bond	2-Cl-4-F-Ph	bond	Ph	HOCH ₂ CH ₂
41b	bond	2,6-pyridyl	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂
42b	bond	2,6-pyridyl	bond	4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
43b	bond	2,6-pyridyl	bond	4-F-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
44b	bond	1,3-(4-F)C ₆ H ₃	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
45b	bond	1,3-(4-F)C ₆ H ₃	bond	2,4-diF-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
46b	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂
47b	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
48b	bond	2,6-pyridyl	bond	2,4-diF-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
49b	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	allyl
50b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	allyl
51b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
52b	CHMe	Ph	bond	H	bond	4-F-Ph	vinyl
53b	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂
54b	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	Ph	HOCH ₂ CH ₂
55b	bond	2,6-pyridyl	bond	2-Cl-4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
56b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
57b	CHMe	c-hex	bond	H	bond	4-F-Ph	allyl

58b	CHMe	c-hex	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
59b	CHMe	1,4-C ₆ H ₄	bond	c-Pr	bond	4-F-Ph	allyl
60b	CHMe	4-MeO ₂ C-Ph	bond	H	bond	4-F-Ph	allyl
61b	CHMe	1,3-C ₆ H ₄	bond	c-Pr	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
62b	CHMe	4-MeO ₂ C-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
63b	CH ₂ Et	4-Br-Ph	bond	H	bond	4-F-Ph	allyl
64b	bond	2,6-(5-Cl)-pyridyl	bond	4-F-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
65b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NCH ₂ CH ₂
66b	bond	2,6-(5-Cl)-pyridyl	bond	2,4-diF-Ph	bond	2-F-Ph	HOCH ₂ CH ₂
67b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
68b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeCH(OH)CH ₂
69b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeC(=O)CH ₂
70b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOC(Me) ₂ CH ₂
71b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeOCH ₂ CH ₂
72b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHC(=O)NHCH ₂ CH ₂
73b	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂
74b	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH(OH)CH ₂
75b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
76b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHC(=O)CH ₂ CH ₂
77b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeCONHCH ₂ CH ₂
78b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHC(=O)OCH ₂ CH ₂
79b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NSO ₂ NHCH ₂ CH ₂
80b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NSO ₂ OCH ₂ CH ₂
81b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	(HO) ₂ P(=O)OCH ₂ CH ₂
82b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NCH ₂ C(=O)NHCH ₂ CH ₂
83b	CHMe	4-HOCH ₂ -Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
84b	CHMe	4-HOC(Me) ₂ -Ph	bond	H	bond	4-F-Ph	allyl
85b	CHMe	4-Br-Ph	bond	H	bond	2-thienyl	allyl
86b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂
87b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-thienyl	allyl
88b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
89b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂

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90b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	2-thienyl	allyl
91b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-thienyl	HOCH ₂ CH ₂ CH ₂
92b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-thienyl	MeCH(OH)CH ₂
93b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH(OH)CH ₂
94b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
95b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	MeCH(OH)CH ₂
96b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	2-thienyl	HOCH ₂ CH ₂ CH ₂
97b	CHMe	Ph	bond	2,4-diF-Ph	bond	4-F-Ph	NCCH ₂ CH ₂
98b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH(OH)CH ₂
99b	CHEt	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
100b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOC(=O)CH ₂ CH ₂
101b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ NHCH ₂ CH ₂
102b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ C(=O)NHCH ₂ CH ₂
103b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeOC(=O)NHCH ₂ CH ₂
104b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	2-(4-morpholino)ethyl
105b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	EtNHCONHCH ₂ CH ₂
106b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHC(=NCN)NHCH ₂ CH ₂
107b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH ₂ CH ₂
108b	CHMe	4-Cl-Ph	bond	H	bond	i-Pr	HOCH ₂ CH ₂ CH ₂
109b	CHMe	4-Me-Ph	bond	H	bond	4-F-Ph	allyl
110b	CHMe	4-MeO-Ph	bond	H	bond	Ph	HOCH ₂ CH ₂
111b	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	allyl
112b	CHMe	4-HOCH ₂ -Ph	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
113b	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂
114b	CHMe	4-Cl-Ph	bond	H	bond	4-F-Ph	allyl
115b	CHMe	c-hex	bond	H	bond	Ph	HOCH ₂ CH(OH)CH ₂
116b	CHMe	4-HOCH ₂ CH ₂ -Ph	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
117b	CHMe	4-MeOCH ₂ -Ph	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
118b	CHMe	4-Br-Ph	bond	H	bond	i-Pr	HOCH ₂ CH ₂ CH ₂
119b	CHMe	4-Cl-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
120b	CHMe	4-Cl-Ph	bond	H	bond	4-F-Ph	MeCH(OH)CH ₂
121b	CHMe	4-Br-Ph	bond	H	bond	Ph	allyl

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122b	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	Ph	HOCH ₂ CH ₂
123b	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH(OH)CH ₂
124b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	i-Pr	HOCH ₂ CH ₂
125b	bond	1-(<i>t</i> -BuOC(=O))pyrrolidin-3-yl	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
126b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH ₂
127b	CHMe	1,4-C ₆ H ₄	bond	4-pyridyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
128b	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
129b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	i-Pr	HOCH ₂ CH ₂ CH ₂
130b	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂
131b	CHMe	1,4-C ₆ H ₄	bond	2-thienyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
132b	CHMe	1,4-C ₆ H ₄	bond	4-morpholinyl	bond	4-F-Ph	allyl
133b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-thienyl	HOCH ₂ CH ₂
134b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	NCCH ₂ CH ₂
135b	CH ₂ Et	4-Br-Ph	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
136b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
137b	CHMe	1,4-C ₆ H ₄	bond	1-oxo-3-pyridyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
138b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	i-Pr	HOCH ₂ CH(OH)CH ₂
139b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	MeCH(OH)CH ₂
140b	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
141b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	Pr
142b	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
143b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeSO ₂ CH ₂ CH ₂
144b	CHMe	1,4-C ₆ H ₄	bond	5-Me-1,3,4-thiadiazol-2-yl	bond	4-F-Ph	allyl
145b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-thienyl	HOCH ₂ CH ₂ CH ₂
146b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	2-thienyl	HOCH ₂ CH ₂
147b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	H ₂ NCOCH ₂ CH ₂
148b	CHMe	1,4-C ₆ H ₄	bond	2-MeO-5-pyridyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
149b	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
150b	CH ₂ Et	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
151b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOC(Me) ₂ CH ₂
152b	CH ₂ Et	4-Br-Ph	bond	H	bond	Ph	HOCH ₂ CH(OH)CH ₂

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153b	CHMe	4-Br-Ph	bond	H	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
154b	CHEt	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
155b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	NCCH ₂
156b	CHMe	1,4-C ₆ H ₄	bond	2,4-diMe-5-thiazolyl	bond	4-F-Ph	allyl
157b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
158b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	2-F-Ph	HOCH ₂ CH ₂ CH ₂
159b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	3-F-Ph	HOCH ₂ CH ₂ CH ₂
160b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOC(Me) ₂ CH ₂ CH ₂
161b	CHMe	1,4-C ₆ H ₄	bond	5-MeCO-2-thienyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
162b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	H ₂ NCOCH ₂ CH ₂
163b	CHMe	1,4-C ₆ H ₄	bond	5-(H ₂ NCHMe)-2-thienyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
164b	CHEt	1,4-C ₆ H ₄	bond	4-F-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
165b	CHEt	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
166b	CHMe	1,4-C ₆ H ₄	bond	5-(HOCHMe)-2-thienyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
167b	CHEt	4-Br-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH(OH)CH ₂
168b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NCH ₂ CH ₂ CH ₂
169b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHCH ₂ CH ₂
170b	CHMe	1,4-C ₆ H ₄	bond	3-(CF ₃)-1-pyrazolyl	bond	4-F-Ph	allyl
171b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	Ph	HOC(Me) ₂ CH ₂ CH ₂
172b	CHEt	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
173b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeSCH ₂ CH ₂
174b	CHMe	Ph	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)NHCH ₂ CH ₂
175b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)OCH ₂ CH ₂
176b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂ OCH ₂ CH ₂
177b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	2-(1-imidazolyl)ethyl
178b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeCONMeCH ₂ CH ₂
179b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	MeSO ₂ NHCH ₂ CH ₂ CH ₂
180b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)NHCH ₂ CH ₂ CH ₂
181b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)OCH ₂ CH ₂ CH ₂
182b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	2-(1-aminoimidazol-1-yl)ethyl
183b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	MeNHC(=O)NHCH ₂ CH ₂ CH ₂
184b	CHMe	1,4-C ₆ H ₄	bond	2,4-diF-Ph	bond	4-F-Ph	H ₂ NC(=O)NHCH ₂ CH(OH)CH ₂

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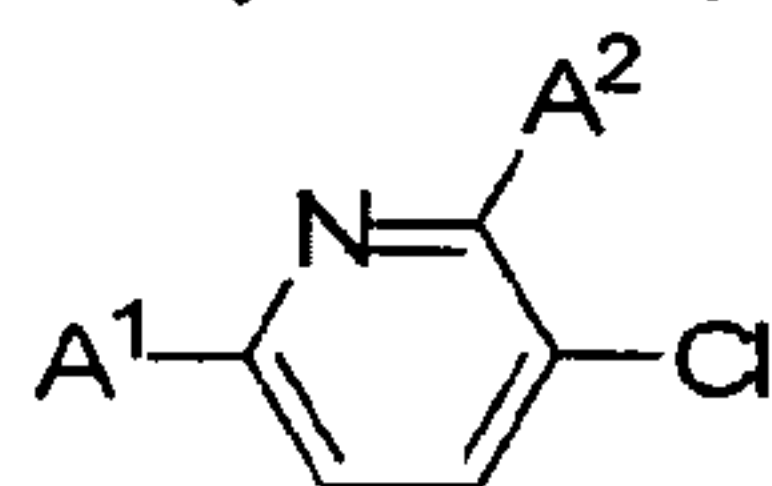
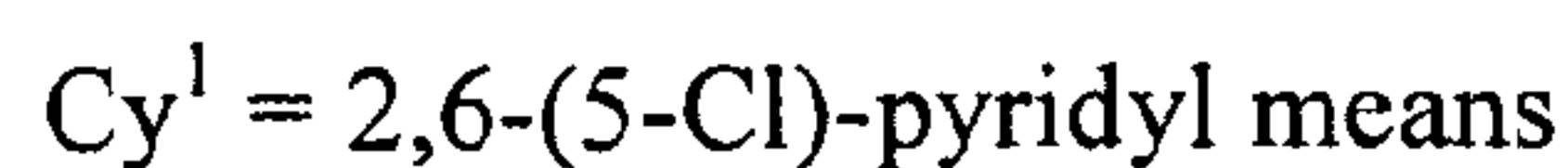
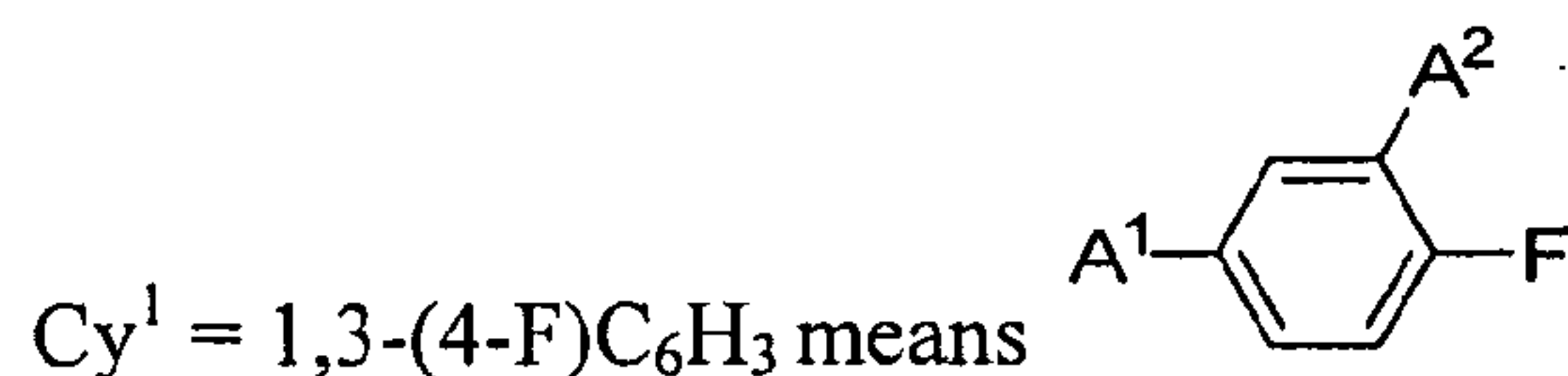
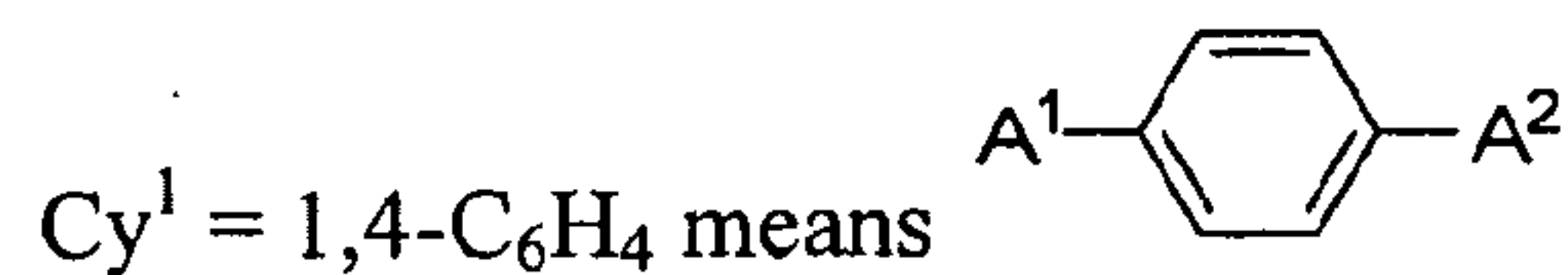
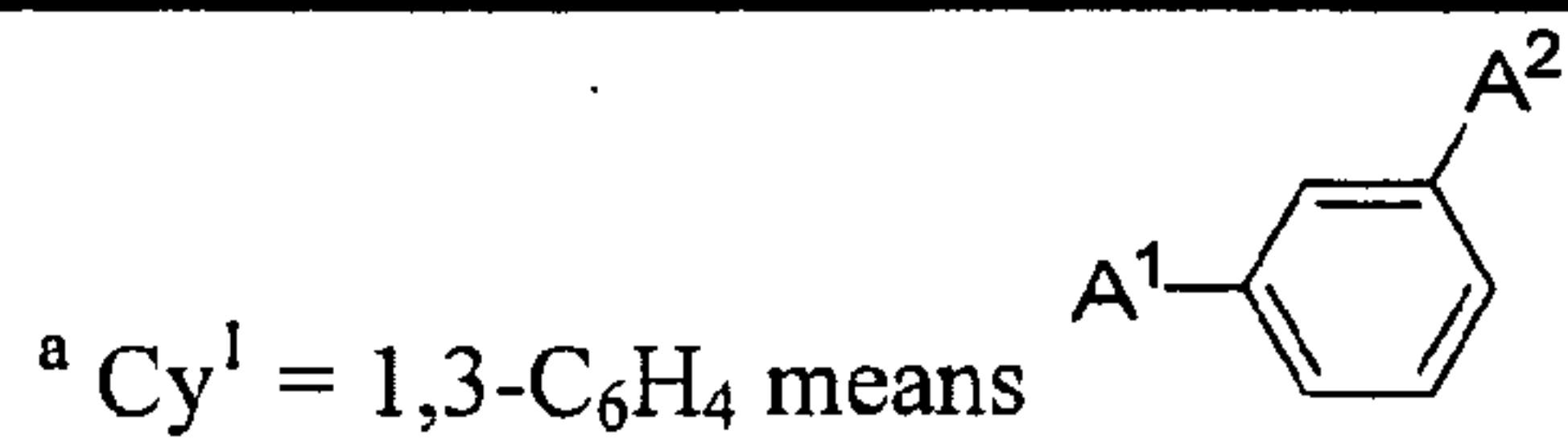
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185b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH(OH)CH ₂
186b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	4-F-Ph	MeSO ₂ NMeCH ₂ CH(OH)CH ₂
187b	CHMe	1,4-C ₆ H ₄	bond	6-CF ₃ -3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
188b	CHMe	4-MeO-Ph	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
189b	CHMe	3-F-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
190b	CHMe	2-F-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
191b	CHMe	4-F-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
192b	CHMe	4-MeO-Ph	bond	H	bond	Ph	HOCH ₂ CH(OH)CH ₂
193b	CHMe	4-Cl-Ph	bond	H	bond	Ph	H ₂ NCOCH ₂ CH ₂
194b	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
195b	CHMe	4-F ₂ HCO-Ph	bond	H	bond	4-F-Ph	allyl
196b	CHMe	Ph	bond	3-pyrazolyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
197b	CHMe	1,4-C ₆ H ₄	bond	5-F-3-pyridyl	bond	Ph	allyl
198b	CHMe	3-CF ₃ -Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
199b	CHMe	4-CF ₃ -Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
200b	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	Ph	H ₂ NCOCH ₂ CH ₂
201b	CHMe	1,4-C ₆ H ₄	bond	4-pyridyl	bond	Ph	H ₂ NCOCH ₂ CH ₂
202b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	HOCH ₂ CH ₂ CH ₂
203b	CHMe	1,4-C ₆ H ₄	bond	5-F-3-pyridyl	bond	Ph	HOCH ₂ CH ₂ CH ₂
204b	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH ₂
205b	CHMe	1,4-C ₆ H ₄	bond	5-F-3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
206b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	NCC(Me) ₂ CH ₂
207b	CHMe	1,4-C ₆ H ₄	bond	6-MeO-3-pyridyl	bond	Ph	H ₂ NCOCH ₂ CH ₂
208b	CHMe	1,4-C ₆ H ₄	bond	5-MeO-3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
209b	CHMe	1,4-C ₆ H ₄	bond	5-Cl-3-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
210b	CHMe	1,4-C ₆ H ₄	bond	3-pyridyl	bond	Ph	MeSO ₂ NHCH ₂ CH ₂
211b	CHMe	4-F ₂ HCO-Ph	bond	H	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
212b	CHMe	1,4-C ₆ H ₄	bond	4-F-Ph	bond	Ph	(HO) ₂ P(=O)OCH ₂ CH ₂ CH ₂
213b	CHMe	1,4-C ₆ H ₄	bond	2-Me-4-pyridyl	bond	4-F-Ph	HOCH ₂ CH ₂ CH ₂
214b	CHMe	1,4-C ₆ H ₄	bond	H	bond	Ph	HOCH ₂ CH ₂ CH ₂
215b	CHMe	1,4-C ₆ H ₄	bond	1-Me-6-oxo-3-(1,6-dihydropyridyl)	bond	Ph	HOCH ₂ CH ₂ CH ₂
216b	CHMe	4-MeO-Ph	bond	H	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH ₂ CH ₂

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217b	CHMe	4-MeO-Ph	bond	H	bond	Ph	H ₂ NCOCH ₂ CH ₂
218b	CHMe	4-F-Ph	bond	H	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
219b	CHMe	c-hex	bond	H	bond	4-F-Ph	H ₂ NCOCH ₂ CH ₂
220b	bond	1,3-(4-F)C ₆ H ₃	bond	2,4-diF-Ph	bond	4-F-Ph	HOCH ₂ CH ₂
221b	CHMe	c-hex	bond	H	bond	4-F-Ph	MeSO ₂ NHCH ₂ CH ₂ CH ₂



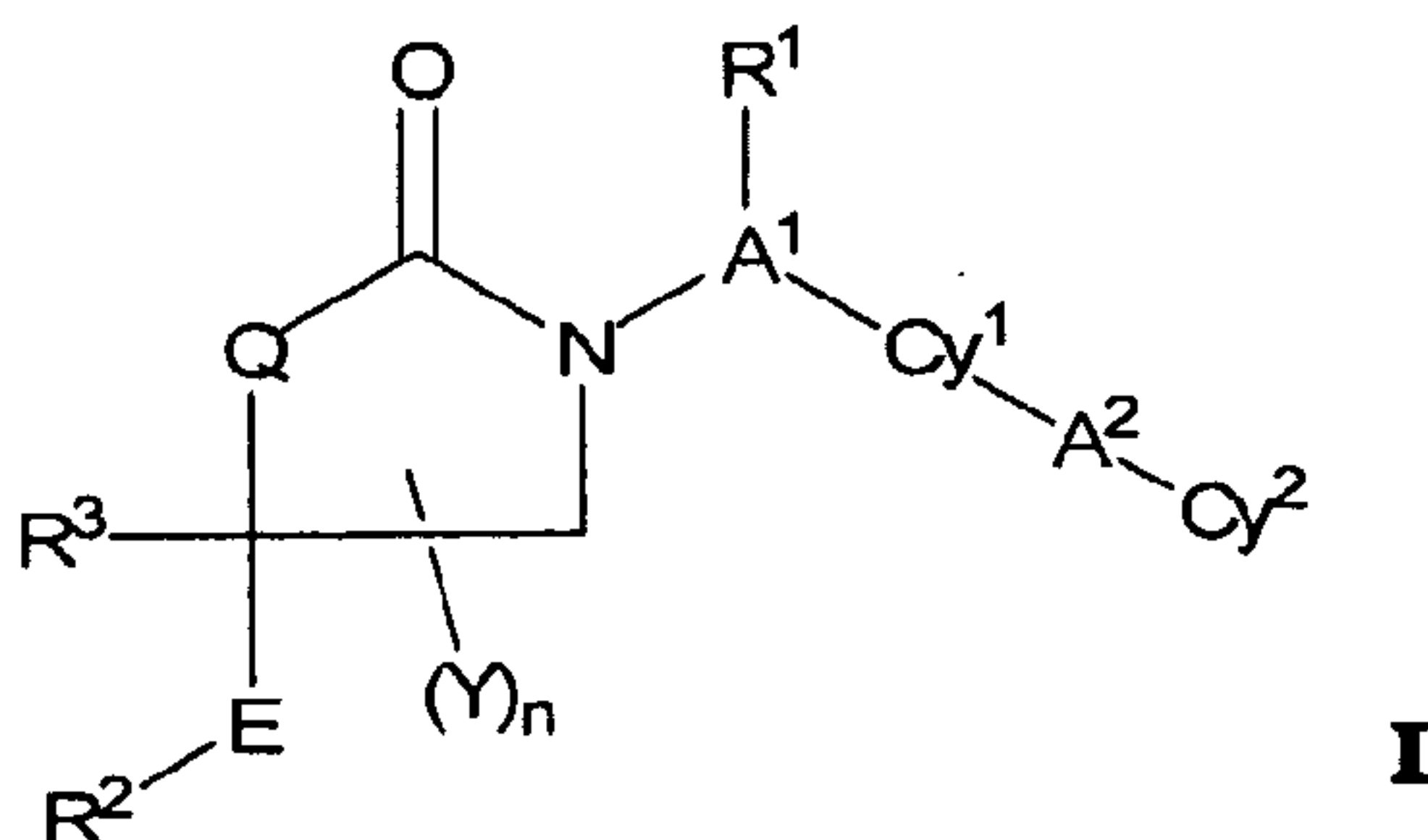
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All publications, patents and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually designated as having 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.

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What is claimed is:

1. A compound of Formula (I):



5 wherein:

- R^1 is (a) absent or (b) selected from (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl and (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;

- 20 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, $(C_1-$

C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-
 C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio,
 (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-
 C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-
 5 C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-
 C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl,
 (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-
 C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cyclo-
 alkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-
 10 C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO,
 H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-
 C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-
 C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkyl-
 carbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-
 15 C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-
 C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl oxo, amino(C₁-C₆)alkyl, (C₁-
 C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-
 C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl,
 (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl} {(C₁-
 20 C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl,
 {(C₃-C₆)cycloalkyl} {(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-
 C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-
 C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-
 C₆)cycloalkyl} {(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-
 25 C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;

A² is (a) a bond, O, S or NR⁴; or (b) (C₁-C₃)alkylene or (C₁-C₂)alkyleneoxy, each of
 which is optionally substituted with 1 to 4 groups independently selected from methyl,
 ethyl, trifluoromethyl or oxo;

30

Cy² 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, (C₁-C₆)alkyl, hydroxy(C₁-
 C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-
 35 C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-

C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;

Y is (C₁-C₆)alkyl or halo(C₁-C₆)alkyl;

30

n is 0, 1 or 2;

E is (a) a bond or (b) (C₁-C₃)alkylene or (C₁-C₂)alkylenyloxy, wherein the O is attached to R², each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo;

35

R^2 is (C₁-C₆)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, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl,

5 (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio,

10 (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl,

15 (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy,

20 di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl} {(C₁-C₆)alkyl} aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl} {(C₁-C₆)alkyl} aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl,

25 aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl} {(C₁-C₆)alkyl} aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;

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- R^3 is selected from (C₂-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl and (C₁-C₃)alkoxy(C₁-C₃)alkyl, wherein the (C₂-C₆)alkyl is substituted with, and each of the (C₂-C₆)alkenyl, (C₂-C₆)alkynyl and (C₁-C₃)alkoxy(C₁-C₃)alkyl is optionally substituted with, up to four groups independently selected from fluorine, cyano, oxo, halo(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, R^4O- , $(R^4)_2N-$, R^4O_2C- , R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=N)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, heterocyclyl (which in turn may be optionally substituted with alkyl, haloalkyl or oxo), heteroaryl (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo), arylamino (which in turn may be optionally substituted with alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido) and heteroaryl amino (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); provided that if Q is NR⁵, A¹ is methylene, R¹ is absent, Cy¹ is optionally substituted phenyl, A² is a bond, Cy² is hydrogen, E is a bond and R² is optionally substituted phenyl, then R³ is not hydroxyethyl or hydroxypropyl;
- R^4 is independently selected from H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl and (C₁-C₆)alkoxy(C₁-C₆)alkyl;

Q = O, NR⁵; and

R⁵ is H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl or hydroxy(C₁-C₆)alkyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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2. The compound of Claim 1, wherein

Cy¹ 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, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl;

Cy² 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, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl; and

R² is (C₁-C₆)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, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio,

(C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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3. The compound of Claims 1 or 2, provided that:

if A¹ is optionally substituted methylene and A² is a bond, then Cy² is not ortho to the ring atom of Cy¹ that is bonded to A¹, and Cy¹ is not substituted with an optionally substituted amine or aminomethyl group at a ring atom ortho to the ring atom of Cy¹ that is bonded to A¹;

25

if Q is NR⁵ and R³ is (C₂-C₆)alkyl substituted with one to three groups independently selected from fluorine, halo(C₁-C₆)alkyl, hydroxy and hydroxy(C₁-C₆)alkyl, then (a) E is (C₁-C₂)alkylenyloxy; (b) E is a bond or (C₁-C₃)alkylene and R² is (C₁-C₆)alkyl substituted with up to 4 groups independently selected from cyano, nitro, amino, carboxy, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-

30

C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio,
 (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-
 C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-
 C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-
 5 C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl,
 (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-
 C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cyclo-
 alkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-
 C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO,
 10 H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-
 C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-
 C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-
 C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-
 C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-
 15 C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy,
 heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-
 C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy,
 di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl; (c) E is a bond and R² is
 optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclyl; or (d) E is (C₁-
 20 C₃)alkylene and R² is optionally substituted heteroaryl, cycloalkyl or heterocyclyl; and

if Q is NR⁵ and E-R² is (a) (C₁-C₆)alkyl optionally substituted with one to three groups
 independently selected from fluorine, chlorine, bromine, iodine, hydroxy, (C₁-C₆)alkyl,
 hydroxy(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or (b) benzyl, then R³ is (a) (C₂-C₆)alkyl
 25 substituted up to four groups independently selected from cyano, oxo, amino(C₁-
 C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, (C₁-
 C₆)alkoxy(C₁-C₆)alkyl, R⁴O- (except hydroxy), (R⁴)₂N-, R⁴O₂C-, R⁴S, R⁴S(=O)-,
 R⁴S(=O)₂-, R⁴C(=O)NR⁴-, (R⁴)₂NC(=O)-, (R⁴)₂NC(=O)O-, (R⁴)₂NC(=O)NR⁴-,
 R⁴OC(=O)NR⁴-, (R⁴)₂NC(=NCN)NR⁴-, (R⁴O)₂P(=O)O-, (R⁴O)₂P(=O)NR⁴-,
 30 R⁴OS(=O)₂NR⁴-, (R⁴)₂NS(=O)₂O-, (R⁴)₂NS(=O)₂NR⁴-, R⁴S(=O)₂NR⁴-,
 R⁴S(=O)₂NHC(=O)-, R⁴S(=O)₂NHC(=O)O-, R⁴S(=O)₂NHC(=O)NR⁴-,
 R⁴OS(=O)₂NHC(=O)-, R⁴OS(=O)₂NHC(=O)O-, R⁴OS(=O)₂NHC(=O)NR⁴-,
 (R⁴)₂NS(=O)₂NHC(=O)-, (R⁴)₂NS(=O)₂NHC(=O)O-, (R⁴)₂NS(=O)₂NHC(=O)NR⁴-,
 R⁴C(=O)NHS(=O)₂-, R⁴C(=O)NHS(=O)₂O-, R⁴C(=O)NHS(=O)₂NR⁴-,

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$R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$,
 $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$,
 heterocyclyl (which in turn may be optionally substituted with alkyl, haloalkyl or oxo),
 heteroaryl (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy,
 5 alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H ,
 $CONH_2$, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo), aryl-
 amino (which in turn may be optionally substituted with alkyl, alkoxy, alkylthio,
 alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H , $CONH_2$, N-
 monoalkyl-substituted amido and N,N-dialkyl-substituted amido) and heteroaryl amino
 10 (which in turn may be optionally substituted with 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); or (b) optionally
 substituted (C_2-C_6) alkenyl, (C_2-C_6) alkynyl or (C_1-C_3) alkoxy (C_1-C_3) alkyl.

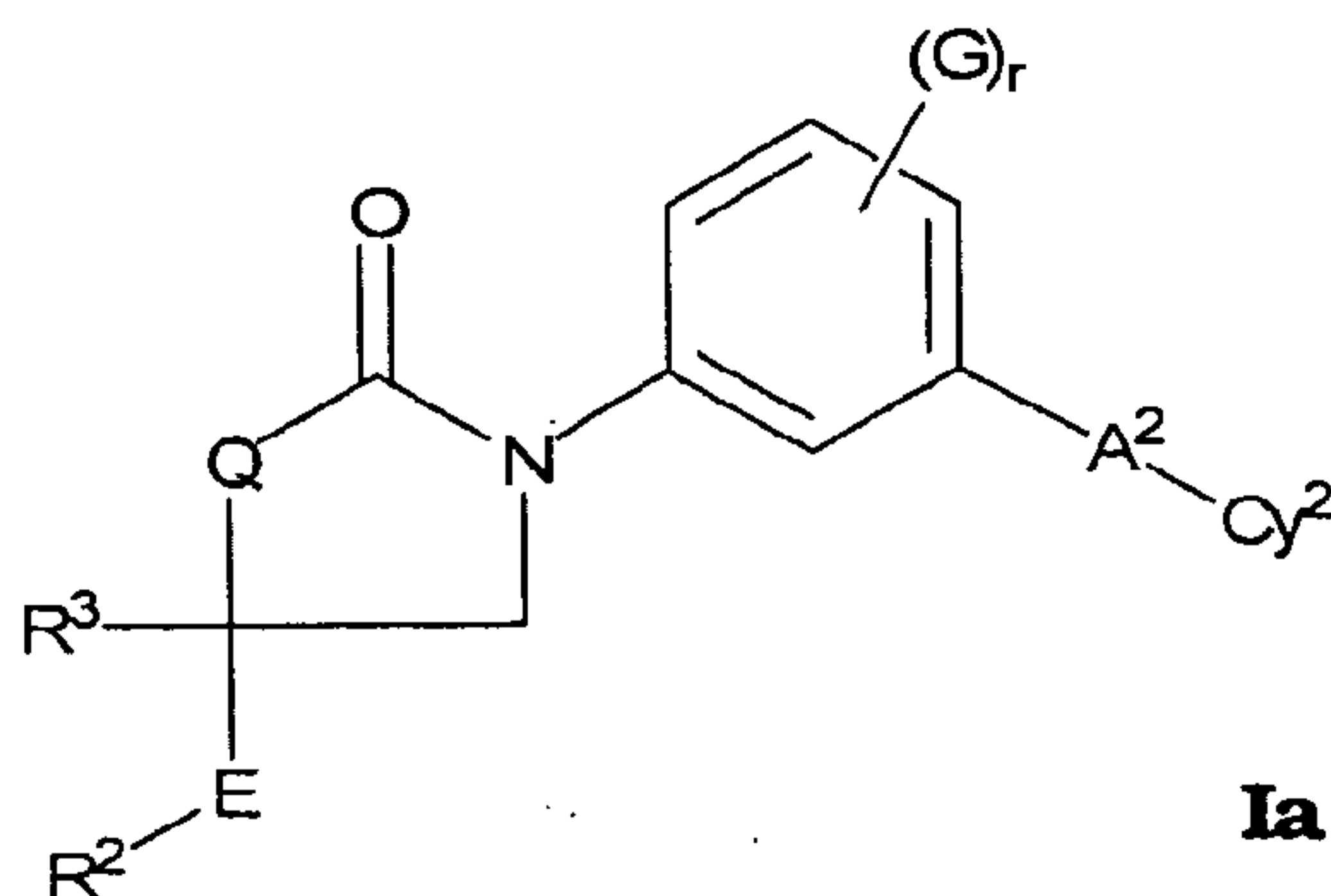
15 4. The compound of Claim 3, wherein E is (C_1-C_3) alkylene or (C_1-C_2) alkylenyloxy.

5. The compound of Claim 3, provided that if E is a bond, then R^2 is optionally substituted (C_1-C_6) alkyl.

20 6. The compound of Claim 3, provided that if E is a bond, and R^2 is optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclyl, then the optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclyl represented by R^2 is not substituted with heteroaryl, amine or aminomethyl at a ring atom ortho to the ring atom of R^2 that is bonded to E.

25

7. The compound of Claims 1 or 2, wherein the compound is of Formula (Ia):



wherein:

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkane-sulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclsulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxyl or (C₁-C₆)alkylcarbonyl; and

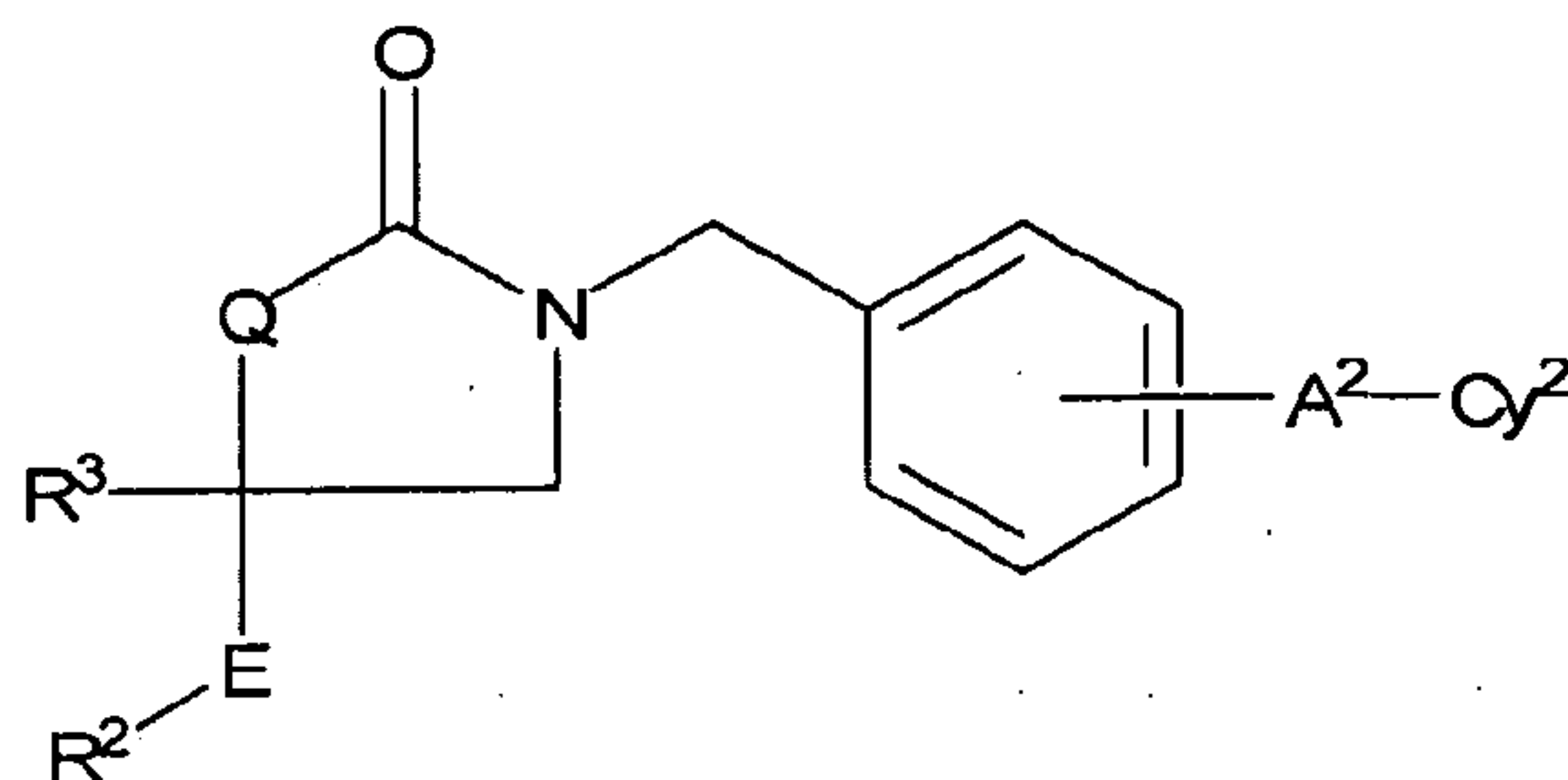
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r is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

30 8. The compound of Claims 1 or 2, wherein the compound is of Formula (Ib):

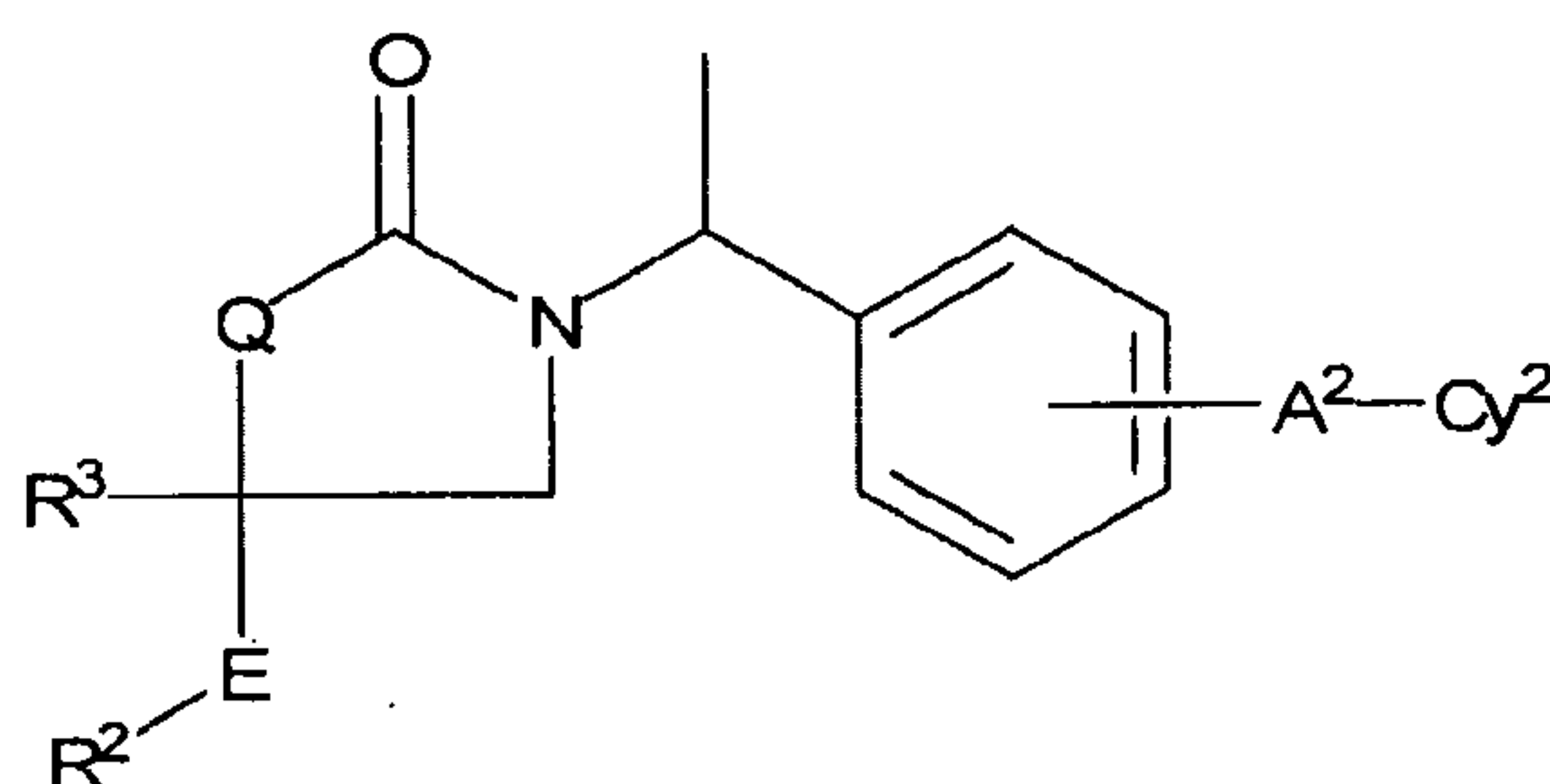
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**Ib**

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

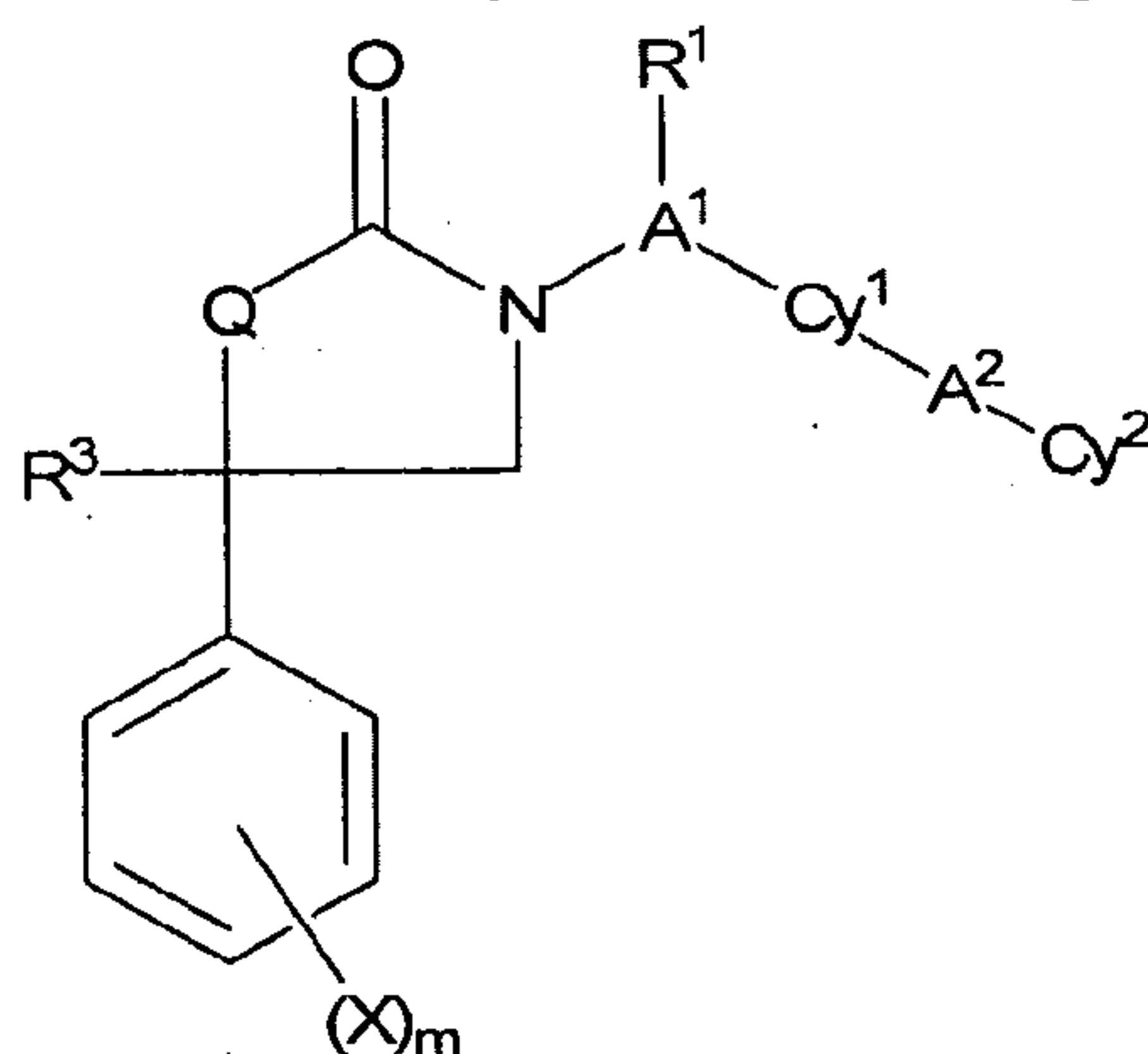
9. The compound of Claims 1 or 2, wherein the compound is of Formula (Ic):

5

**Ic**

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

10. The compound of Claims 1 or 2, wherein the compound is of Formula (Id):

**Id**

10

wherein:

X is fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-

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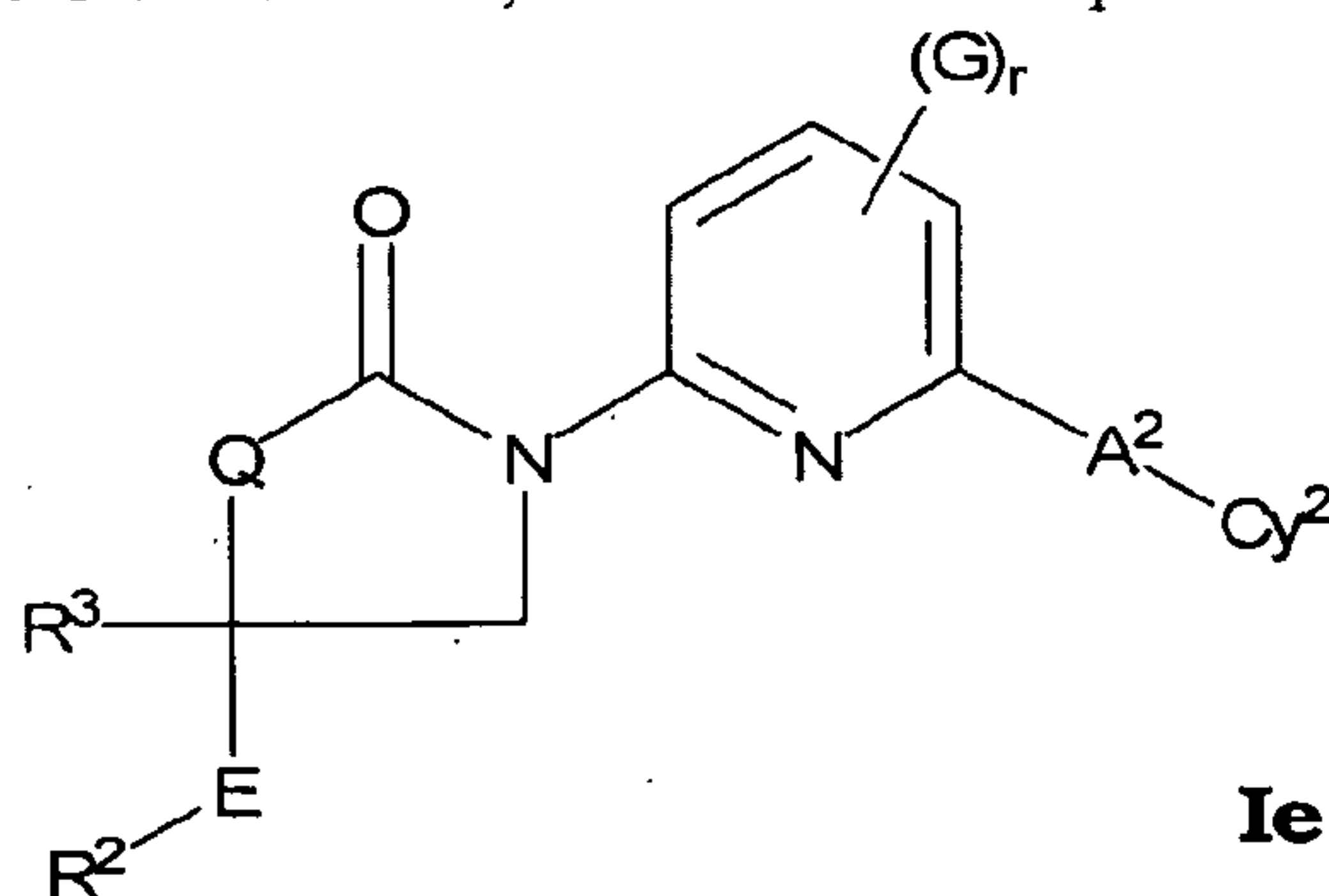
C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-
 C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-
 C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkane-sulfinyl, halo(C₃-
 C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl,
 5 (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-
 C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cyclo-
 alkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-
 C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO,
 H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-
 10 C₃)alkylaminocarbonyl, heterocyclcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-
 C₆)alkylaminosulfonyl, heterocyclsulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-
 C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-
 C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-
 C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy,
 15 heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-
 C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-
 C₆)alkylamino(C₂-C₆)alkoxyl and (C₁-C₆)alkylcarbonyl; and

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

20

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

11. The compound of Claims 1 or 2, wherein the compound is of Formula (Ie):



25 wherein:

G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro,
 amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl,
 hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkynyl, (C₃-
 30 C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-

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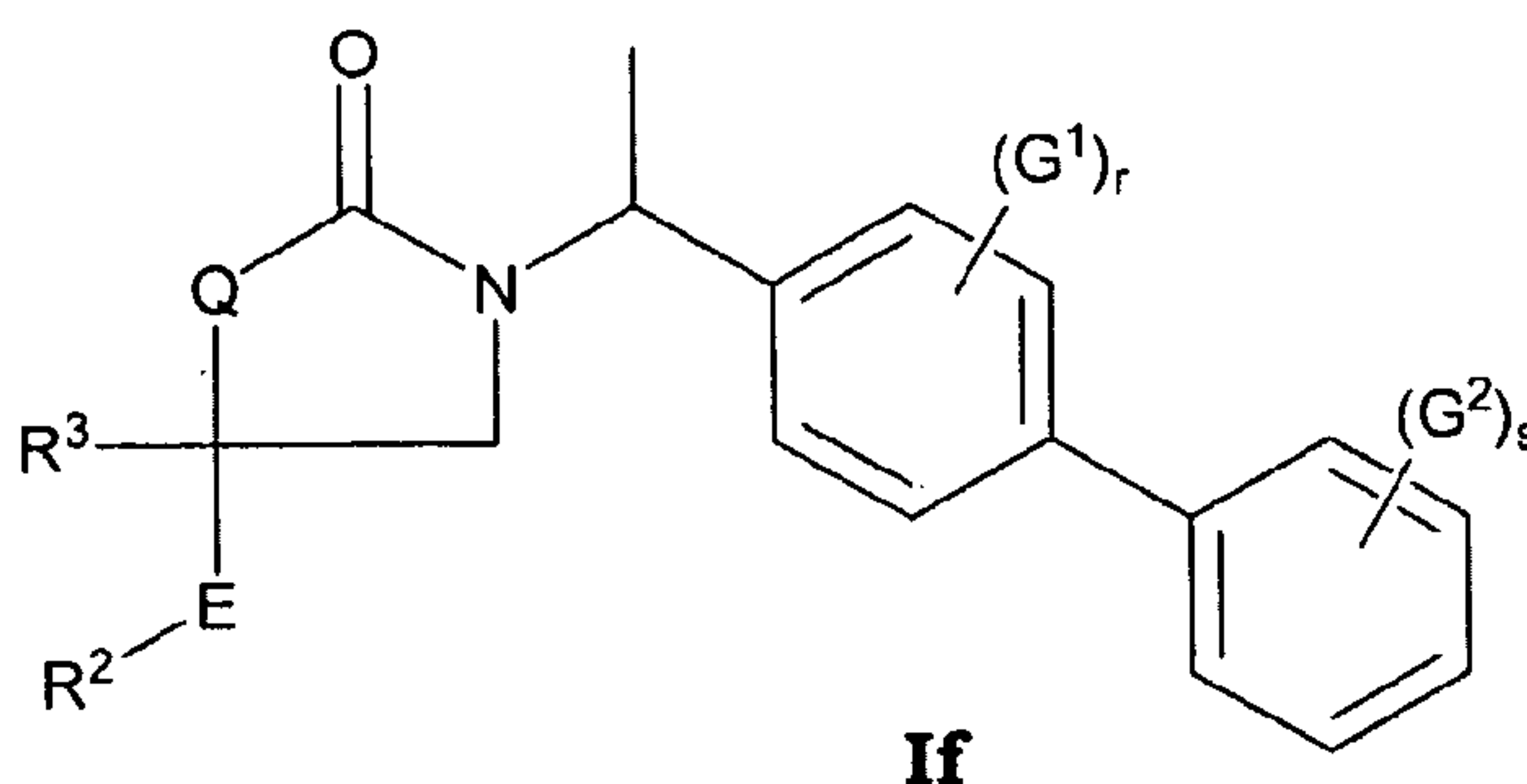
C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy,
 halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy,
 (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-
 C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-
 5 C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl,
 halo(C₁-C₆)alkane-sulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-
 C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-
 C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-
 C₆)cycloalkanesulfonyl, halo(C₄-C₇)cyclo-alkylalkanesulfonyl, (C₁-C₆)alkylamino,
 10 di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy,
 (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-
 C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl,
 heterocyclcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl,
 heterocyclsulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl,
 15 (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-
 C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-
 C₆)alkyl,, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-
 C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-
 C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxyl and (C₁-
 20 C₆)alkylcarbonyl; and

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

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

25

12. The compound of Claims 1 or 2, wherein the compound is of Formula (If):



wherein:

30

G^1 and G^2 are each independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkane-sulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclsulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxyl or (C₁-C₆)alkylcarbonyl;

R^5 is H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, or hydroxy(C₁-C₆)alkyl; and

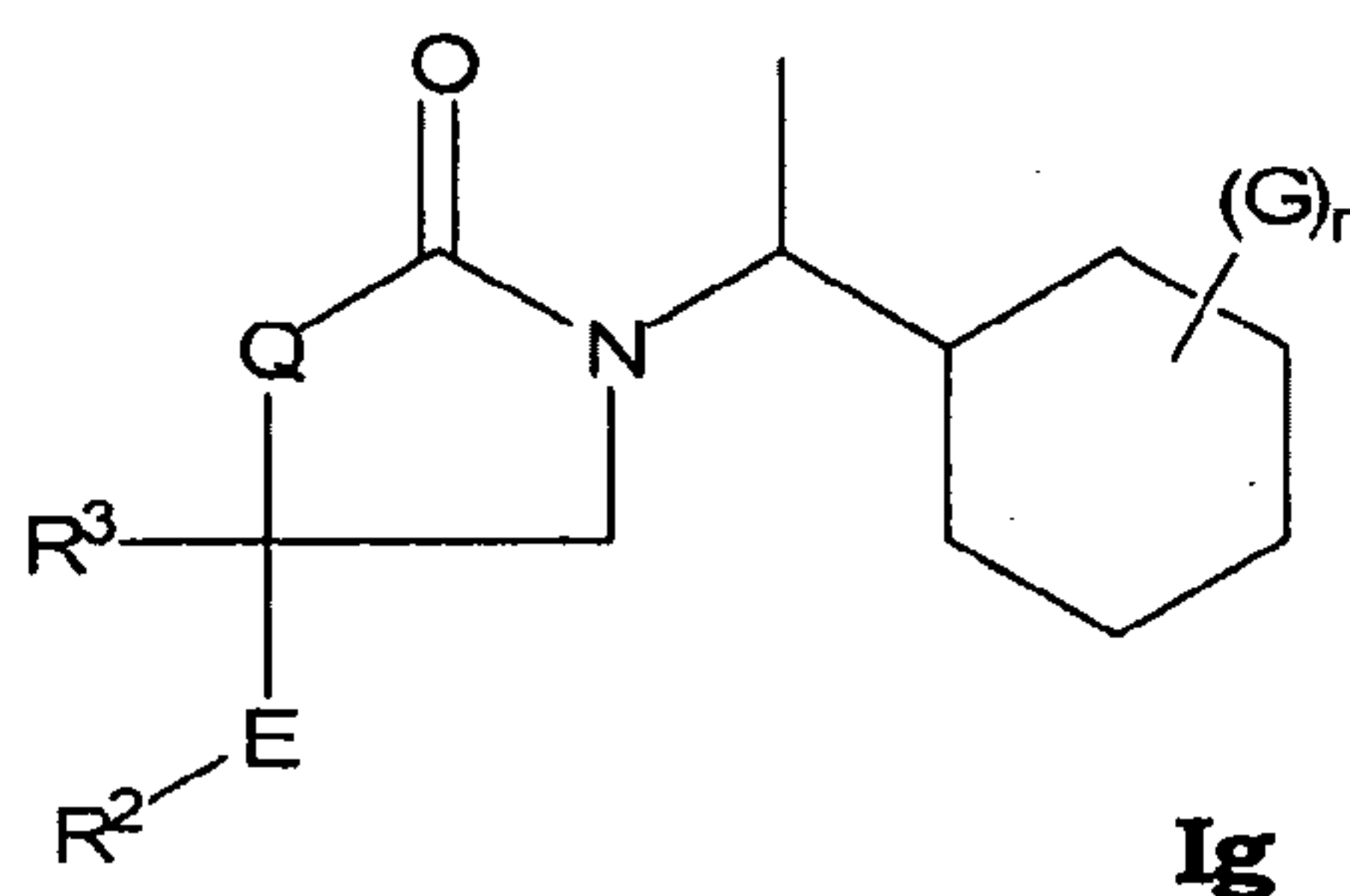
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r and s are independently 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

30 13. The compound of Claim 1 or 2, wherein the compound is of Formula (Ig):

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wherein:

- G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclsulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxyl and (C₁-C₆)alkylcarbonyl; and

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

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

14. The compound of any one of Claims 1-13, wherein Q is O.
- 5 15. The compound of any one of Claims 1-13, wherein Q is NR⁵.
16. The compound of Claim 15, wherein Q is NH.
17. The compound of any one of Claims 1-16, wherein E is a bond or alkylene.
- 10 18. The compound of Claim 17, wherein E is a bond.
19. The compound of any one of Claims 17 or 18, wherein R² is optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclyl; or R² is (C₁-C₆)alkyl substituted
 15 with up to 4 groups independently selected from fluorine, cyano, nitro, amino, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-
 20 C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-
 25 C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO,
 30 H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-
 35 C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy,

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heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl.

- 5 20. The compound of any one of Claims 17-19, wherein R² is optionally substituted (C₁-C₆)alkyl; or R² is aryl, heteroaryl, cycloalkyl or heterocyclyl substituted with up to 4 groups independently selected from fluorine, bromine, iodine, cyano, amino, hydroxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl.

21. The compound of any one of Claims 1-20, wherein R² is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl or optionally substituted heterocyclyl.

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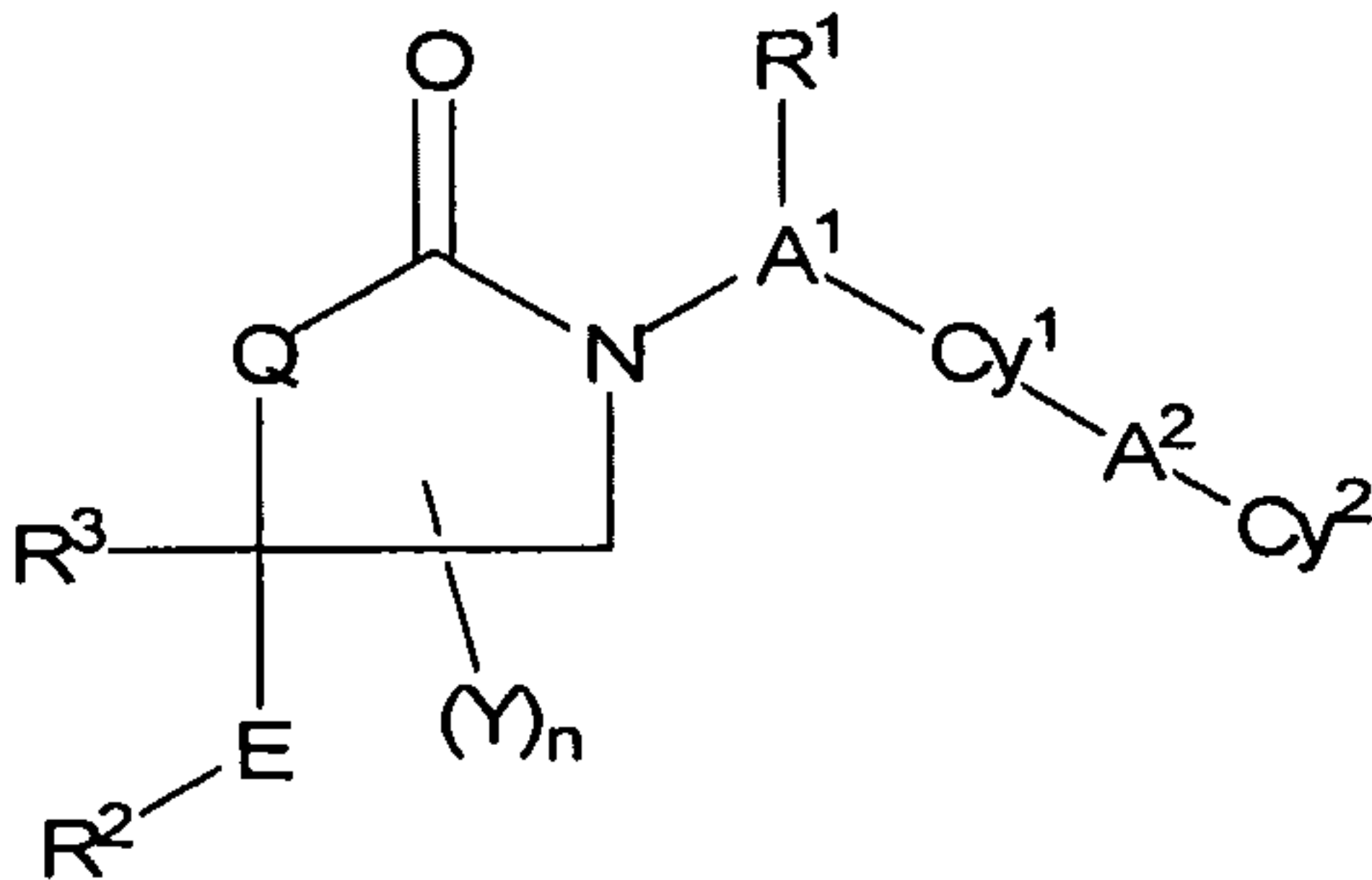
22. The compound of any one of Claims 1-20, wherein R^2 is (a) isopropyl or (b) selected from optionally substituted phenyl, optionally substituted pyridyl and optionally substituted thienyl.
- 5 23. The compound of Claim 22, wherein R^2 is optionally substituted phenyl.
24. The compound of Claim 23, wherein R^2 is fluorophenyl.
25. The compound of any one of Claims 1-24, wherein R^3 is substituted (C₂-C₆)alkyl.
- 10 26. The compound of Claim 25, wherein R^3 is hydroxy(C₂-C₅)alkyl.
27. The compound of Claim 25, wherein R^3 is dihydroxy(C₃-C₅)alkyl.
- 15 28. The compound of Claim 25, wherein R^3 is ω -H₂NCO(C₁-C₃)alkyl.
29. The compound of Claim 25, wherein R^3 is (C₁-C₂)alkoxy(C₁-C₃)alkyl.
30. The compound of Claim 25, wherein R^3 is H₂NSO₂O(C₂-C₄)alkyl.
- 20 31. The compound of Claim 25, wherein R^3 is H₂NSO₂NH(C₂-C₄)alkyl.
32. The compound of Claim 25, wherein R^3 is oxo(C₂-C₄)alkyl.
- 25 33. The compound of Claim 25, wherein R^3 is MeC(=O)NH(C₂-C₄)alkyl.
34. The compound of Claim 25, wherein R^3 is 2-hydroxy-2-methylpropyl.
35. The compound of Claim 25, wherein R^3 is 2-(4-morpholino)ethyl.
- 30 36. The compound of Claim 25, wherein R^3 is MeSO₂NH(C₂-C₄)alkyl.
37. The compound of Claim 36, wherein R^3 is MeSO₂NHCH₂CH₂CH₂-.

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38. The compound of any one of Claims 1-37, wherein A¹ is a bond.
39. The compound of any one of Claims 1-37, wherein A¹ is (C₁-C₃)alkylene.
40. The compound of Claim 39, wherein A¹ is methylene.
41. The compound of any one of Claims 1-40, wherein R¹ is absent.
- 5 42. The compound of any one of Claims 1-40, wherein R¹ is unsubstituted or substituted (C₁-C₆)alkyl.
43. The compound of Claim 42, wherein R¹ is unsubstituted or substituted methyl or ethyl.
44. The compound of Claim 43, wherein R¹ is unsubstituted methyl or ethyl.
- 10 45. The compound of any one of Claims 1-44, wherein Cy¹ is optionally substituted aryl or optionally substituted heteroaryl.
46. The compound of any one of Claims 1-44, wherein Cy¹ is optionally substituted phenyl or optionally substituted pyridyl.
- 15 47. The compound of Claim 46, wherein Cy¹ is optionally substituted phenyl.
48. The compound of any one of Claims 1-44, wherein Cy¹ is optionally substituted monocyclic cycloalkyl.
- 20 49. The compound of Claim 48, wherein Cy¹ is optionally substituted cyclohexyl.
50. The compound of any one of Claims 45-49, wherein Cy¹ is substituted with fluorine, chlorine, bromine, methoxy, difluoromethoxy, methoxycarbonyl, carboxy, 25 methyl, or trifluoromethyl.
51. The compound of any one of Claims 1-50, wherein A² is a bond.
52. The compound of any one of Claims 1-51, wherein Cy² is hydrogen.

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53. The compound of any one of Claims 1-51, wherein Cy² is optionally substituted aryl or heteroaryl.
54. The compound of any one of Claims 1-51, wherein Cy² is optionally substituted
5 cycloalkyl or heterocyclyl.
55. The compound of Claim 53, wherein Cy² is optionally substituted phenyl or pyridyl.
- 10 56. The compound of any one of Claims 53-55, wherein Cy² is substituted with 1 to 4 groups independently selected from chlorine or fluorine.
57. The compound of Claim 55, wherein Cy² is difluorophenyl or monofluorophenyl.
- 15 58. The compound of Claim 54, wherein Cy² is 1,2-dihydro-2-oxopyridyl or 1,2-dihydro-1-methyl-2-oxopyridyl.
59. The compound of Claim 54, wherein Cy² is cyclopropyl.
- 20 60. A pharmaceutical composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) the compound in any one of claims 1-59; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.
61. A method of inhibiting 11 β -HSD1 activity comprising the step of administering
25 to a mammal in need of such treatment an effective amount of a compound of any one of claims 1-59.
62. A method of treating a disease or disorder associated with activity or expression of 11 β -HSD1, comprising administering to a mammal in need thereof an effective
30 amount of a compound of any one of claims 1-59.



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