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(54) Titre : INHIBITEURS CYCLIQUES DE LA 11 β -HYDROXYSTEROIDE DESHYDROGENASE 1
(54) Title: CYCLIC INHIBITORS OF 11 β -HYDROXYSTERIOD DEHYDROGENASE 1

(57) **Abrégé/Abstract:**

This invention relates to novel compounds of the Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih); (Ii); (Ij), (Ik), (Il) pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, which are useful for the therapeutic treatment of diseases associated with the modulation or inhibition of 11 β -HSD1 in mammals. The invention further relates to pharmaceutical compositions of the novel compounds and methods for their use in the reduction or control of the production of cortisol in a cell or the inhibition of the conversion of cortisone to cortisol in a cell.



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(54) Title: CYCLIC INHIBITORS OF 11 β -HYDROXYSTERIOD DEHYDROGENASE 1

(57) Abstract: This invention relates to novel compounds of the Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih); (Ii); (Ij), (Ik), (II) pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, which are useful for the therapeutic treatment of diseases associated with the modulation or inhibition of 11 β -HSD1 in mammals. The invention further relates to pharmaceutical compositions of the novel compounds and methods for their use in the reduction or control of the production of cortisol in a cell or the inhibition of the conversion of cortisone to cortisol in a cell.

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
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THIS IS VOLUME __1__ OF __3__

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CYCLIC INHIBITORS OF 11 β -HYDROXYSTEROID DEHYDROGENASE 1**RELATED APPLICATIONS**

5 This application claims the benefit of U.S. Provisional Application No. 60/962,058, filed on July 26, 2007, U.S. Provisional Application No. 61/001,253, filed October 31, 2007 and U.S. Provisional Application No. 61/049,650, filed May 1, 2008. The entire teachings of the above applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

10 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
15 effects on development, neurobiology, inflammation, blood pressure, metabolism, and programmed cell death. Cortisol and other corticosteroids bind both the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), which are members of the nuclear hormone receptor superfamily and have been shown to mediate cortisol function in vivo. These receptors directly modulate transcription via
20 DNA-binding zinc finger domains and transcriptional activation domains.

Until recently, the major determinants of glucocorticoid action were attributed to three primary factors: (1) circulating levels of glucocorticoid (driven primarily by the hypothalamic-pituitary-adrenal (HPA) axis); (2) protein binding of glucocorticoids in circulation; and (3) intracellular receptor density inside target tissues. Recently, a
25 fourth determinant of glucocorticoid function has been identified: tissue-specific pre-receptor metabolism by glucocorticoid-activating and -inactivating enzymes. These 11 β -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:
30 11 β -HSD1 (also known as 11-beta-HSD type 1, 11betaHSD1, HSD11B1, HDL, 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.

35 The two isoforms are expressed in a distinct tissue-specific fashion, consistent with the differences in their physiological roles. 11 β -HSD1 is widely

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distributed in rat and human tissues; expression of the enzyme and corresponding mRNA have been detected in human liver, adipose tissue, lung, testis, bone and ciliary epithelium. In adipose tissue, increased cortisol concentrations stimulate adipocyte differentiation and may play a role in promoting visceral obesity. In the eye, 11 β -HSD1 may regulate intraocular pressure and may contribute to glaucoma; some data suggest that inhibition of 11 β -HSD1 may cause a drop in intraocular pressure in patients with intraocular hypertension (Kotelevstev et al. (1997), Proc. Natl. Acad. Sci. USA 94(26):14924-9). Although 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 inert cortisone (Low et al. (1994) J. Mol. Endocrin. 13: 167-174). In contradistinction, 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: 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 cortisol-inactivation activity and, as a result, present with a syndrome of apparent mineralocorticoid excess (also referred to as 'SAME') characterized by hypertension, hypokalemia, and sodium retention (Edwards et al. (1988) Lancet 2: 986-989; Wilson et al. (1998) Proc. Natl. Acad. Sci. 95: 10200-10205). Similarly, mutations in 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); these individuals present with ACTH-mediated androgen excess (hirsutism, menstrual irregularity, hyperandrogenism), a phenotype resembling polycystic ovary syndrome (PCOS) (Draper et al. (2003) Nat. Genet. 34: 434-439).

Notably, disruption of homeostasis in the HPA axis by either deficient or excess secretion or action results in Cushing's syndrome or Addison's disease, respectively (Miller and Chrousos (2001) Endocrinology and Metabolism, eds. Felig and Frohman (McGraw-Hill, New York), 4th Ed.: 387-524). Patients with Cushing's syndrome or receiving glucocorticoid therapy develop reversible visceral fat obesity.

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The phenotype of Cushing's syndrome patients closely resembles that of Reaven's metabolic syndrome (also known as Syndrome X or insulin resistance syndrome), the symptoms of which include visceral obesity, glucose intolerance, insulin resistance, hypertension, type 2 diabetes and hyperlipidemia (Reaven (1993) *Ann. Rev. Med.* 44: 121-131). Although the role of glucocorticoids in human obesity is not fully characterized, there is mounting evidence that 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. (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 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 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. Natl. Acad. Sci.* 94: 14924-14929; Morton et al. (2001) *J. Biol. Chem.* 276: 41293-41300; Morton et al. (2004) *Diabetes* 53: 931-938).

The published data supports the hypothesis that increased expression of 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 aspects of the metabolic syndrome cluster, including glucose intolerance, insulin

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resistance, hyperglycemia, hypertension, and/or hyperlipidemia (Kotelevstev et al. (1997) *Proc. Natl. Acad. Sci.* 94: 14924-14929; Morton et al. (2001) *J. Biol. Chem.* 276: 41293-41300; Morton et al. (2004) *Diabetes* 53: 931-938). In addition, inhibition of 11 β -HSD1 activity may have beneficial effects on the pancreas, including the
5 enhancement of glucose-stimulated insulin release (Billaudel and Sutter (1979) *Horm. Metab. Res.* 11: 555-560; Ogawa et al. (1992) *J. Clin. Invest.* 90: 497-504; Davani et al. (2000) *J. Biol. Chem.* 275: 34841-34844).

Furthermore, given that inter-individual differences in general cognitive function have been linked to variability in the long-term exposure to glucocorticoids
10 (Lupien et al. (1998) *Nat. Neurosci.* 1: 69-73) and dysregulation of the HPA axis resulting in chronic exposure to glucocorticoid excess in certain brain subregions has been theorized to contribute to the decline of cognitive function (McEwen and Sapolsky (1995) *Curr. Opin. Neurobiol.* 5: 205-216), one might predict that inhibition of 11 β -HSD1 could reduce exposure to glucocorticoids in the brain and thereby
15 protect against deleterious glucocorticoid effects on neuronal function, including cognitive impairment, dementia, and/or depression. Notably, it is known that stress and glucocorticoids influence cognitive function (de Quervain et al. (1998) *Nature* 394: 787-790); and it has been shown that 11 β -HSD1, through its control of glucocorticoid action in the brain, may have effects on neurotoxicity (Rajan et al.
20 (1996) *Neuroscience* 16: 65-70; Seckl (2000) *Neuroendocrinol.* 18:49-99).

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
25 eventually blindness. Thus, inhibition of 11 β -HSD1 in the eye could reduce local glucocorticoid concentrations and IOP, and 11 β -HSD1 hence could potentially be used to treat glaucoma and other visual disorders.

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

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expected to attenuate secretion of plasminogen activator inhibitor 1 (PAI-1), which is an independent cardiovascular risk factor (Halleux et al. (1999) J. Clin. Endocrinol. Metab. 84: 4097-4105).

Glucocorticoids can have adverse effects on skeletal tissues; and prolonged exposure to even moderate glucocorticoid doses can result in osteoporosis (Cannalis (1996) J. Clin. Endocrinol. Metab. 81: 3441-3447). In addition, 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.

11 β -HSD1 inhibitors may also be useful for immunomodulation. Although glucocorticoids are perceived to suppress the immune system, in actuality, there is a complex, dynamic interaction between the HPA axis and the immune system (Rook (1999) Baillier's Clin. Endocrinol. Metab. 13: 576-581). Glucocorticoids play a role in modulating the balance between cell-mediated and humoral immune response, with high glucocorticoid activity normally associated with a humoral response. Inhibition of 11 β -HSD1 therefore can be used as a means of shifting the immune response towards a cell-mediated response. Certain disease states, such as tuberculosis, leprosy (Hansen's disease) and psoriasis, trigger immune responses that are biased towards a humoral response whereas the more effective immune response may be a cell-mediated response. Hence, 11 β -HSD1 inhibitors may be useful for treating such diseases.

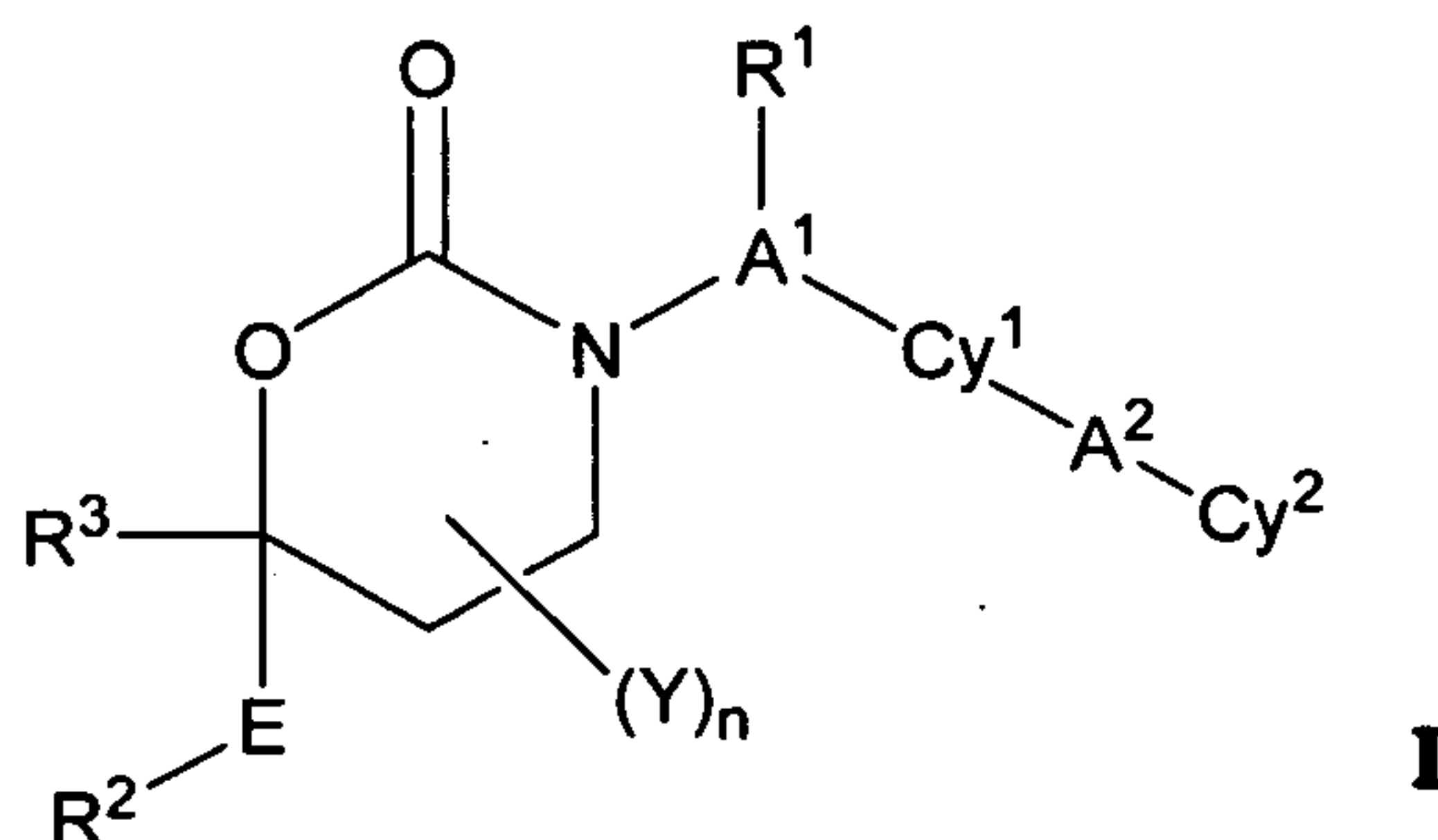
It has been reported that glucocorticoids inhibit wound healing, especially in diabetic patients with ulcers (Bitar et al. (1999) J. Surg. Res. 82: 234-243; Bitar et al. (1999) Surgery 125: 594-601; Bitar (2000) Surgery 127: 687-695; Bitar (1998) Am. J. Pathol. 152: 547-554). Patients that exhibit impaired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

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

SUMMARY OF THE INVENTION

5 It has now been found that compounds of Formula I or pharmaceutically acceptable salts or prodrugs thereof, are effective inhibitors of 11 β -HSD1. The invention is a compound represented by Formula I:



10 In a first embodiment of the invention, Formula I and its constituent members are defined herein as follows:

R^1 is (a) absent or (b) is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and 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)NR⁴-, $R^4OC(=O)NR^4$ -, (R^4)₂NC(=N)NR⁴-, (R^4O)₂P(=O)O-, (R^4O)₂P(=O)NR⁴-, $R^4OS(=O)_2NR^4$ -, (R^4)₂NS(=O)₂O-, (R^4)₂NS(=O)₂NR⁴-, $R^4S(=O)_2NR^4$ -, $R^4S(=O)_2NHC(=O)$ -, $R^4S(=O)_2NHC(=O)O$ -, $R^4S(=O)_2NHC(=O)NR^4$ -, $R^4OS(=O)_2NHC(=O)$ -, $R^4OS(=O)_2NHC(=O)O$ -, $R^4OS(=O)_2NHC(=O)NR^4$ -, (R^4)₂NS(=O)₂NHC(=O)-, (R^4)₂NS(=O)₂NHC(=O)O-, (R^4)₂NS(=O)₂NHC(=O)NR⁴-, $R^4C(=O)NHS(=O)_2$ -, $R^4C(=O)NHS(=O)_2O$ -, $R^4C(=O)NHS(=O)_2NR^4$ -, $R^4OC(=O)NHS(=O)_2$ -, $R^4OC(=O)NHS(=O)_2O$ -, $R^4OC(=O)NHS(=O)_2NR^4$ -, (R^4)₂NC(=O)NHS(=O)₂-, (R^4)₂NC(=O)NHS(=O)₂O-, (R^4)₂NC(=O)NHS(=O)₂NR⁴-, heterocyclyl, heteroaryl, arylamino and heteroarylamino;

A^1 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;

25 Cy¹ is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl and 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-

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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;

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;

Cy² is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl or heterocyclyl and 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,

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halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkyl-
 alkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkyl-
 alkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-
 C₇)cyclo-alkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-
 5 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-
 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. In one aspect, the heterocyclyl
 15 represented by Cy² is other than optionally substituted thiazolidine-2,4-dionyl;
 Y is (C₁-C₆)alkyl, halo(C₁-C₆)alkyl or oxo;
 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
 20 independently selected from methyl, ethyl, trifluoromethyl or oxo;
 R² is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl and 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-
 25 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-
 30 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)cycloalkyl-
 alkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkyl-
 alkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-
 35 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,

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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;

10

R³ is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₅)cycloalkyl(C₁-C₄)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R⁴, R⁴O-, (R⁴)₂N-, R⁴O₂C-, R⁴C(=O)O-, 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-, spirocycloalkyl; heterocyclyl (which in turn may be optionally substituted with alkyl, haloalkyl, halogen 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, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); and

30

- 10 -

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;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

5

In a second embodiment, Formula I and its constituent members are defined herein as follows:

R^1 is (a) absent or (b) is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and 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 , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, heterocyclyl, heteroaryl, arylamino and heteroarylamino; A^1 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; Cy¹ is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl and 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,

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(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;

15 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;

Cy² is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl or heterocyclyl and 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,

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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;

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

10

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;

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R² is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl and 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,

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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;

R^3 is selected from (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, (C_1 - C_3)alkoxy(C_1 - C_3)alkoxy or (C_1 - C_3)alkoxy(C_1 - C_3)alkyl and 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 , $R^4S(=O)$ -, $R^4S(=O)_2$ -, $R^4C(=O)NR^4$ -, $(R^4)_2NC(=O)$ -, $(R^4)_2NC(=O)O$ -, $(R^4)_2NC(=O)NR^4$ -, $R^4OC(=O)NR^4$ -, $(R^4)_2NC(=N)NR^4$ -, $(R^4O)_2P(=O)O$ -, $(R^4O)_2P(=O)NR^4$ -, $R^4OS(=O)_2NR^4$ -, $(R^4)_2NS(=O)_2O$ -, $(R^4)_2NS(=O)_2NR^4$ -, $R^4S(=O)_2NR^4$ -, $R^4S(=O)_2NHC(=O)$ -, $R^4S(=O)_2NHC(=O)O$ -, $R^4S(=O)_2NHC(=O)NR^4$ -, $R^4OS(=O)_2NHC(=O)$ -, $R^4OS(=O)_2NHC(=O)O$ -, $R^4OS(=O)_2NHC(=O)NR^4$ -, $(R^4)_2NS(=O)_2NHC(=O)$ -, $(R^4)_2NS(=O)_2NHC(=O)O$ -, $(R^4)_2NS(=O)_2NHC(=O)NR^4$ -, $R^4C(=O)NHS(=O)_2$ -, $R^4C(=O)NHS(=O)_2O$ -, $R^4C(=O)NHS(=O)_2NR^4$ -, $R^4OC(=O)NHS(=O)_2$ -, $R^4OC(=O)NHS(=O)_2O$ -, $R^4OC(=O)NHS(=O)_2NR^4$ -, $(R^4)_2NC(=O)NHS(=O)_2$ -, $(R^4)_2NC(=O)NHS(=O)_2O$ -, $(R^4)_2NC(=O)NHS(=O)_2NR^4$ -, 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, 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 (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); and

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

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In a third embodiment, Formula I and its constituent members are defined herein as follows:

R^1 is absent or is selected from (C_1-C_6) alkyl or (C_2-C_6) alkenyl, (C_2-C_6) alkynyl or (C_1-C_3) alkoxy (C_1-C_3) alkoxy and 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 , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, 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 ;

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Cy^1 is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl each 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) alkynyl, (C_3-C_6) cycloalkyl (C_2-C_4) alkynyl, halo (C_1-C_6) alkyl, halo (C_3-C_6) cycloalkyl, halo (C_4-C_7) cycloalkylalkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkoxy, (C_4-C_7) cycloalkylalkoxy, halo (C_1-C_6) alkoxy, halo (C_3-C_6) cycloalkoxy, halo (C_4-C_7) cycloalkylalkoxy, (C_1-C_6) alkylthio, (C_3-C_6) 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-C_7) cycloalkylalkanesulfinyl, halo (C_1-C_6) alkanesulfinyl, halo (C_3-C_6) cycloalkanesulfinyl, halo (C_4-C_7) cycloalkylalkanesulfinyl, (C_1-C_6) alkanesulfonyl, (C_3-C_6) cycloalkanesulfonyl, (C_4-C_7) cycloalkylalkanesulfonyl, halo (C_1-C_6) alkanesulfonyl, halo (C_3-C_6) cycloalkanesulfonyl, halo (C_4-C_7) cycloalkylalkanesulfonyl, (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, (C_1-C_6) alkoxy (C_1-C_6) alkoxy, halo (C_1-C_6) alkoxy (C_1-C_6) alkoxy, (C_1-C_6) alkoxycarbonyl, H_2NCO ,

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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 and oxo;

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

Cy² is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl or heterocyclyl each 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)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 and oxo;

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

n is 0, 1 or 2;

- 5 E is (a) a bond or (b) (C₁-C₃)alkylene, (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 and 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)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 or oxo;

R³ is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₃)alkoxy(C₁-C₃)alkoxy and 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-,

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- $(R^4)_2NC(=NCN)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$,
 $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$,
 $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$,
 $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$,
5 $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$,
 $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$,
 $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$,
 $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, heterocyclyl (which in turn
may be optionally substituted with alkyl, haloalkyl or oxo), heteroaryl which in turn
10 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), arylamino (which in turn
may be optionally substituted with alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen,
trifluoromethyl, dialkylamino, nitro, cyano, CO_2H , $CONH_2$, N-monoalkyl-substituted
15 amido and N,N-dialkyl-substituted amido) and heteroarylamino (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); and
- 20 R^4 is independently selected from H, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, amino $(C_1-$
 $C_6)$ alkyl, (C_1-C_6) alkylamino (C_1-C_6) alkyl, di (C_1-C_6) alkylamino (C_1-C_6) alkyl, hydroxy $(C_1-$
 $C_6)$ alkyl and (C_1-C_6) alkoxy (C_1-C_6) alkyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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In a fourth embodiment,

- R^1 is (a) absent or (b) is selected from (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl,
 (C_1-C_3) alkoxy (C_1-C_3) alkoxy, or (C_1-C_3) alkoxy (C_1-C_3) alkyl and is optionally substituted
with up to four groups independently selected from fluorine, cyano, oxo, R^4 , R^4O- ,
30 $(R^4)_2N-$, R^4O_2C- , R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$,
 $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$,
 $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$,
 $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$,
 $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$,
35 $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$,
 $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$,

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$R^4C(=O)NHS(=O)_2NR^4$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$,
 $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$,
 $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, heterocyclyl, heteroaryl, arylamino and heteroarylamino;

- 5 A^1 is (a) a bond, or (b) (C_1) 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 monocyclic heterocyclyl, each optionally substituted with 1 to 4 groups independently selected from nitro, amino,
 10 hydroxy, carboxy, (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, 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_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,
 15 (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-C_7) cycloalkylalkanesulfinyl, halo (C_1-C_6) alkanesulfinyl, halo (C_3-C_6) cycloalkanesulfinyl, halo (C_4-C_7) cycloalkylalkanesulfinyl, (C_1-C_6) alkanesulfonyl, (C_3-C_6) cycloalkanesulfonyl, (C_4-C_7) cycloalkylalkanesulfonyl, halo (C_1-C_6) alkanesulfonyl, halo (C_3-C_6) cycloalkanesulfonyl, halo (C_4-C_7) cycloalkylalkanesulfonyl, (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, (C_1-C_6) alkoxy (C_1-C_6) alkoxy, halo (C_1-C_6) alkoxy (C_1-C_6) alkoxy, (C_1-C_6) alkoxycarbonyl, H_2NCO , H_2NSO_2 , (C_1-C_6) alkylaminocarbonyl, di (C_1-C_6) alkylaminocarbonyl, (C_1-C_3) alkoxy (C_1-C_3) alkylaminocarbonyl,
 25 heterocyclylcarbonyl, (C_1-C_6) alkylaminosulfonyl, di (C_1-C_6) alkylaminosulfonyl, heterocyclosulfonyl, (C_1-C_6) alkylcarbonylamino, (C_1-C_6) alkylcarbonylamino (C_1-C_6) alkyl, (C_1-C_6) alkylsulfonylamino, (C_1-C_6) alkylsulfonylamino (C_1-C_6) alkyl, (C_1-C_6) alkoxycarbonyl (C_1-C_6) alkoxy, (C_1-C_6) alkoxy (C_1-C_6) alkyl, halo (C_1-C_6) alkoxy (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkoxy, oxo, amino (C_1-C_6) alkyl, (C_1-C_6) alkylamino (C_1-C_6) alkyl, di (C_1-C_6) alkylamino (C_1-C_6) alkyl amino (C_2-C_6) alkoxy, (C_1-C_6) alkylamino (C_2-C_6) alkoxy, di (C_1-C_6) alkylamino (C_2-C_6) alkoxy and (C_1-C_6) alkylcarbonyl; or if the substitution is either meta or para to A^1 , the substituents may also include optionally substituted cycloalkyl, optionally substituted halo cycloalkyl or optionally substituted heteroaryl.

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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 *meta* or *para* to A₁ and is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl, 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,
- 10 tetrahydropyran, tetrahydrothiophene, tetrahydrothiopyran, isoxazolidine, 1,3-dioxolane, 1,3-dithiolane, 1,3-dioxane, 1,4-dioxane, 1,3-dithiane, 1,4-dithiane, oxazolidin-2-one, imidazolidin-2-one, imidazolidine-2,4-dione, tetrahydropyrimidin-2(1H)-one, morpholine, N-methylmorpholine, morpholin-3-one, 1,3-oxazinan-2-one, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-1,2,5-thiaoxazole 1,1-dioxide,
- 15 tetrahydro-2H-1,2-thiazine 1,1-dioxide, hexahydro-1,2,6-thiadiazine 1,1-dioxide, tetrahydro-1,2,5-thiadiazole 1,1-dioxide, isothiazolidine 1,1-dioxide, 6-oxo-1,6-dihydropyridazin-3-yl, 6-oxo-1,6-dihydropyridazin-4-yl, 5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl and 5-oxo-4,5-dihydro-1H-imidazol-2-yl optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano,
- 20 nitro, 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-
- 25 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,
- 30 (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, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-
- 35 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;

10 **n is 0, 1 or 2;**

15

R² is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl and 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)alkanefsulfinyl, (C₃-C₆)cycloalkanefsulfinyl, (C₄-C₇)cycloalkylalkanefsulfinyl, halo(C₁-C₆)alkanefsulfinyl, halo(C₃-C₆)cycloalkanefsulfinyl, halo(C₄-C₇)cycloalkylalkanefsulfinyl, (C₁-C₆)alkanefsulfonyl, (C₃-C₆)cycloalkanefsulfonyl, (C₄-C₇)cycloalkylalkanefsulfonyl, halo(C₁-C₆)alkanefsulfonyl, halo(C₃-C₆)cycloalkanefsulfonyl, halo(C₄-C₇)cyclo-alkylalkanefsulfonyl, (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-

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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;

5

R³ is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₅)cycloalkyl(C₁-C₄)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R⁴, R⁴O-, (R⁴)₂N-, R⁴O₂C-, R⁴C(=O)O-, R⁴S, R⁴S(=O)-, R⁴S(=O)₂-, R⁴C(=O)NR⁴,
 10 (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)-, 15 (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-, spirocycloalkyl; heterocyclyl (which in turn may be optionally substituted with alkyl, haloalkyl, halogen or oxo),
 20 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, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); and

25

30

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;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof; and the remainder of the variables are as defined as for the first, second or third
 35 embodiments.

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In a fifth embodiment,

n is 0;

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

Cy¹ is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl, each optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl,
10 hydroxy(C₁-C₆)alkyl, 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(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-
20 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, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-
30 C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl; or if the substitution is either meta or para to A¹, the substituents may also include optionally substituted cycloalkyl, optionally substituted halo cycloalkyl or optionally substituted heteroaryl.

35 Cy² is *meta* or *para* to A₁ and is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl pyrrolidine, pyrrolidin-2-one, 1-methylpyrrolidin-2-one, piperidine, piperidin-2-one,

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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-thiaoxazole 1,1-dioxide, tetrahydro-2H-1,2-thiazine 1,1-dioxide, hexahydro-1,2,6-thiadiazine 1,1-dioxide, tetrahydro-1,2,5-thiadiazole 1,1-dioxide isothiazolidine 1,1-dioxide, 6-oxo-1,6-dihydropyridazin-3-yl, 6-oxo-1,6-dihydropyridazin-4-yl, 5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl and 5-oxo-4,5-dihydro-1H-imidazol-2-yl 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;

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or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof; and the remainder of the variables are as defined as for the first, second, third or fourth embodiments.

5 In a sixth embodiment,

R^3 is selected from (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_3) alkoxy (C_1-C_3) alkoxy or (C_1-C_3) alkoxy (C_1-C_3) alkyl and is substituted with one to four groups independently selected from cyano, oxo, R^4O- , $(R^4)_2N-$, R^4O_2C- , R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$,
 10 $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4SO_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$,
 15 $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$ and $(R^4)_2NC(=O)NHS(=O)_2NR^4-$;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof; and the remainder of the variables are as defined as for the first, second, third, fourth or fifth
 20 embodiments.

In a seventh embodiment, the variables in Formula (I) are as defined in the first or second embodiment, provided that the substituents for the aryl, heteroaryl, monocyclic cycloalkyl and monocyclic heterocyclyl group represented by Cy^1 can
 25 additionally be selected from (C_3-C_6) cycloalkylcarbonyl, (C_3-C_6) cycloalkylaminocarbonyl, $\{(C_3-C_6)$ cycloalkyl $\}(C_1-C_6)$ alkylaminocarbonyl, di (C_3-C_6) cycloalkylaminocarbonyl, (C_3-C_6) cycloalkylaminosulfonyl, $\{(C_3-C_6)$ cycloalkyl $\}(C_1-C_6)$ alkylaminosulfonyl, 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 $\}(C_1-C_6)$ alkylaminocarbonyl (C_1-C_6) alkyl and di (C_3-C_6) cycloalkylaminocarbonyl (C_1-C_6) alkyl;
 30

the substituents for the aryl, heteroaryl, cycloalkyl and heterocyclyl group represented by Cy^2 can additionally be selected from (C_3-C_6) cycloalkylcarbonyl, (C_3-C_6) cycloalkylaminocarbonyl, $\{(C_3-C_6)$ cycloalkyl $\}(C_1-C_6)$ alkylaminocarbonyl, di (C_3-C_6) cycloalkylaminocarbonyl, (C_3-C_6) cycloalkylaminosulfonyl, $\{(C_3-C_6)$ cycloalkyl $\}(C_1-C_6)$ alkylaminosulfonyl, 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 $\}(C_1-C_6)$ alkylaminocarbonyl (C_1-C_6) alkyl and di (C_3-C_6) cycloalkylaminocarbonyl (C_1-C_6) alkyl;
 35

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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; and

the substituents for the aryl, heteroaryl, cycloalkyl and heterocyclyl group represented by R² can additionally be selected from (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.

Another embodiment of the invention is a method of inhibiting 11 β -HSD1 activity comprising the step of administering to a mammal in need of such treatment an effective amount of a compound of Formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il or , Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the invention is a method of treating a subject with a disease associated with the activity or expression of 11 β -HSD1, comprising the step of administering to the subject an effective amount of a compound of Formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il , Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the invention is the use of a compound of Formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il or , Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for the manufacture of a medicament for inhibiting 11 β -HSD1 activity in a mammal in need of such treatment.

Another embodiment of the invention is the use of a compound of Formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il , Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for the manufacture of a medicament for treating a subject with a disease associated with the activity or expression of 11 β -HSD1.

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Another embodiment of the invention is a compound of Formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il, Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for use in inhibiting 11 β -HSD1 activity in a mammal in need of such treatment.

Another embodiment of the invention is a compound of Formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il, Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for use in for treating a subject with a disease associated with the activity or expression of 11 β -HSD1.

DETAILED DESCRIPTION OF THE INVENTION

In an eighth embodiment, the variables in Formula I or any one of Formulas Ia-II are as defined in the following paragraphs:

15 R¹ is (a) absent or (b) (C₁-C₆)alkyl 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)₂NS(=O)₂NR⁴- and R⁴S(=O)₂NR⁴-;

20 A¹ is (a) a bond, or (b) (C₁-C₂)alkylene;

Cy¹ is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl and 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, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, halo(C₁-C₆)alkoxy, (C₁-C₆)alkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, oxo, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl and di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl;

35 A² is a bond;

Cy² is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl or heterocyclyl and 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)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl and di(C₃-C₆)cycloalkylaminosulfonyl; In one aspect, the heterocyclyl represented by Cy² is other than optionally substituted thiazolidine-2,4-dionyl;

n is 0;

E is a bond;

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R^2 is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl and 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, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, halo(C₁-C₆)alkoxy, (C₁-C₆)alkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino and oxo;

R^3 is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₅)cycloalkyl, (C₁-C₄)alkyl, (C₁-C₃)alkoxy, (C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and 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 , $R^4S(=O)^-$, $R^4S(=O)_2^-$, $R^4C(=O)NR^4^-$, $(R^4)_2NC(=O)^-$, $(R^4)_2NC(=O)O^-$, $(R^4)_2NC(=O)NR^4^-$, $R^4OC(=O)NR^4^-$, $(R^4)_2NS(=O)_2NR^4^-$ and $R^4S(=O)_2NR^4^-$; and

R^4 is independently selected from H, (C₁-C₆)alkyl and halo(C₁-C₆)alkyl; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In a ninth embodiment, the variables in Formula I or in any one of Formulas Ia-II are defined in the following paragraphs:

R^1 (for Formulas I, Id, Ig and Ih) is absent or is methyl or ethyl;

A^1 (for Formulas I, Id, Ig and Ih) is a bond or CH₂ or CH when R^1 is present;

Cy^1 (for Formulas I, Id, Ig, Ih) is phenyl, cyclohexyl, pyridyl, N-oxo-pyridyl, thiazolyl or pyrimidinyl each optionally substituted with 1 to 4 groups independently selected from halo, methyl, trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy and 2-hydroxy-2-methylpropoxy;

A^2 (for Formulas I, Ia-e, Ig and Ih) is a bond, O or OCH₂CO;

Cy^2 (for Formulas I, Ia-e, Ig and Ih) is (a) hydrogen or (b) phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl or piperazinyl each optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl,

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dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonylaminomethyl or tetrazolyl;

n (for Formulas I, Ig and Ih) is 0;

E (for Formulas I, Ia-c and Ie-i) is a bond or CH₂;

5 R² (for Formulas I, Ia-c and Ie-i) is phenyl, thienyl or pyridyl each optionally substituted with halo, methyl, methylthio or (4-morpholino)methyl; and

R³ (for Formulas I and Ia-i) is methyl, ethyl, propyl, vinyl or allyl each optionally substituted with up to two groups independently selected from HO-, MeO-, H₂N-,

10 MeC(=O)NH-, MeS(=O)₂NH-, H₂NC(=O)-, MeNHC(=O)-, HO₂C-, (HO)₂P(=O)O-, H₂NS(=O)₂O-, H₂NS(=O)₂NH-, MeNHC(=O)NH-, MeNHC(=O)O- oxo, cyano, HO₂C-, HOCH₂CH₂NH-, 4-morpholino, HOCH₂C(=O)NH-, H₂NCH₂C(=O)NH-, EtNHC(=O)NH-, MeOC(=O)NH-, MeNHC(=NC≡N)NH-, or oxo;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

15 In a tenth embodiment, the variables in Formula I or in any one of Formulas Ia-II are as defined in the following paragraphs:

R¹ is absent or is methyl or ethyl;

A¹ is a bond, CH₂, CH₂CH₂, or CH when R¹ is present;

20 Cy¹ is phenyl, cyclopropyl, cyclohexyl, pyrrolidinyl, pyridyl, N-oxo-pyridyl, thiazolyl or pyrimidinyl each optionally substituted with 1 to 4 groups independently selected from halo, methyl, trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy, 2-hydroxy-2-methylpropoxy, cyano, difluoromethoxy, t-butoxycarbonyl, hydroxy, hydroxymethyl, 2-hydroxyethyl, 2-hydroxy-2-propyl, methoxymethyl, methylsulfonyl and methylsulfonylamino;

25 A² is a bond, O, OCH₂CO or C=O;

30 Cy² is (a) hydrogen or (b) phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl, piperazinyl, morpholinyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, S,S-dioxothiazinyl, 2-oxo-1,2-dihydropyridyl each optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonylaminomethyl, tetrazolyl, methyl, trifluoromethyl, acetyl, 2-hydroxyethyl and 1-aminoethyl;

35 n is 0;

E is a bond or CH₂;

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R^2 is phenyl, thienyl, pyridyl or isopropyl each optionally substituted with halo, methyl, methylthio or (4-morpholino)methyl; and

R^3 is methyl, ethyl, propyl, butyl, vinyl, allyl or ethoxyethyl each optionally substituted with up to two groups independently selected from Methyl, HO-, MeO-, H_2N -,

- 5 MeC(=O)NH-, MeS(=O)₂NH-, $H_2NC(=O)$ -, MeNHC(=O)-, HO₂C-, (HO)₂P(=O)O-, $H_2NS(=O)_2O$ -, $H_2NS(=O)_2NH$ -, MeNHC(=O)NH-, MeNHC(=O)O-, oxo, cyano, HO₂C-, HOCH₂CH₂NH-, 4-morpholino, HOCH₂C(=O)NH-, $H_2NCH_2C(=O)NH$ -, EtNHC(=O)NH-, MeOC(=O)NH-, MeNHC(=NC≡N)NH-, Me-, MeS-, MeSO₂-, MeSO₂N(Me)-, MeS(=O)₂NHC(=O)-, imidazolylamino-, imidazolyl, tetrazolyl, H_2NCONH -, H_2NCO_2 -,
 10 HOCH₂CH₂O-, MeNH-, Me₂N- and MeCONMe;
 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In an eleventh embodiment, the variables in Formula I or any one of Formulas Ia-II are as defined in the following paragraphs:

- 15 R^1 (for Formulas I, Id, Ig and Ih) is absent or is methyl or ethyl;
 R^{1a} (for Formulas Ij and Ik) is methyl or ethyl;
 A^1 (for Formulas I, Id, Ig and Ih) is a bond, CH₂ or CH₂CH₂ or CH when R^1 is present;
 Cy¹ (for Formulas I, Id, Ig, Ih) is phenyl, cyclopropyl, cyclohexyl, pyrrolidinyl, pyridyl, N-oxo-pyridyl, thiazolyl, piperidinyl or pyrimidinyl each optionally substituted with 1 to
 20 4 groups independently selected from halo, methyl, trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy, 2-hydroxy-2-methylpropoxy, cyano, difluoromethoxy, t-butoxycarbonyl, hydroxy, hydroxymethyl, 2-hydroxyethyl, 2-hydroxy-2-propyl, methoxymethyl, methylsulfonyl, methylsulfonylamino and benzyloxycarbonyl;
 25 A^2 (for Formulas I, Ia-e, Ig and Ih) is a bond, CH₂, O, OCH₂CO or C=O;
 Cy² (for Formulas I, Ia-e, Ig, Ih, Ik and II) is (a) hydrogen or (b) phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl, piperazinyl, morpholinyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, S,S-dioxothiazinyl, 2-oxo-1,2-dihydropyridyl each optionally substituted by 1 to 4 groups independently selected from halo, hydroxy,
 30 methoxy, hydroxymethyl, methoxycarbonyl, amino, aminomethyl, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonylaminomethyl, tetrazolyl, methyl, trifluoromethyl, acetyl, 2-hydroxyethyl
 35 and 1-aminoethyl;
 n (for Formulas I, Ig and Ih) is 0;

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E (for Formulas I, Ia-c and Ie-i) is a bond or CH₂;

R² (for Formulas I, Ia-c and Ie-l) is phenyl, thienyl, pyridyl, t-butyl or isopropyl each optionally substituted with halo, methyl, methylthio, hydroxymethyl or (4-morpholino)methyl; and

5 R³ (for Formulas I and Ia-l) is methyl, ethyl, propyl, butyl, vinyl, allyl or ethoxyethyl each optionally substituted with up to two groups independently selected from methyl, HO-, MeO-, H₂N-, MeC(=O)NH-, MeS(=O)₂NH-, H₂NC(=O)-, MeNHC(=O)-, HO₂C-, (HO)₂P(=O)O-, H₂NS(=O)₂O-, H₂NS(=O)₂NH-, MeNHC(=O)NH-, MeNHC(=O)O-, oxo, cyano, HO₂C-, HOCH₂CH₂NH-, 4-morpholino, HOCH₂C(=O)NH-
 10 , H₂NCH₂C(=O)NH-, EtNHC(=O)NH-, MeOC(=O)NH-, MeNHC(=NC≡N)NH-, Me-, MeS-, MeSO₂-, MeSO₂N(Me)-, MeS(=O)₂NHC(=O)-, imidazolylamino-, imidazolyl, tetrazolyl, spirocyclopropyl, FCH₂CH₂NH-, 1-pyrrolidinyl, 3-fluoro-1-pyrrolidinyl, 3-oxo-1-piperazinyl, 1-azetidyl, 1,1-dioxo-2-isothiazolidinyl, 2-oxo-1-pyrrolidinyl, H₂NCONH-, H₂NCO₂-, HOCH₂CH₂O-, MeNH-, Me₂N- and MeCONMe;

15 G (for Formulas Ia, Ie, Ii and Ij) is alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido;

r (for Formulas Ia, Ie, Ii and Ij) is 0, 1 or 2;

G¹ and G² (for Formula If) are independently alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido;

r (for Formulas Ia, Ie, If, Ii and Ij) is 0, 1 or 2;

s (for Formula If) is 0, 1 or 2;

t (for Formula II) is 1 or 2;

25 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In a twelfth embodiment, the variables in formula I or in any one or Formulas Ia-II are as defined in the following paragraphs:

30 R¹ is absent or is methyl or ethyl;

A¹ is a bond, CH₂, CH₂CH₂, or CH when R¹ is present;

Cy¹ is phenyl, cyclopropyl, cyclohexyl, pyrrolidinyl, pyridyl, N-oxo-pyridyl, thiazolyl, pyrimidinyl, piperidinyl, each optionally substituted with 1 to 4 groups independently selected from halo, methyl, trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy, 2-hydroxy-2-methylpropoxy, cyano, difluoromethoxy, t-butoxycarbonyl, hydroxy, hydroxymethyl, 2-hydroxyethyl, 2-

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hydroxy-2-propyl, methoxymethyl, methylsulfonyl, methylsulfonylamino, trifluoromethoxy, 2,2,2-trifluoroethoxy and benzyloxycarbonyl;

A² is a bond, O, OCH₂CO, C=O or CH₂;

Cy² is (a) hydrogen or (b) phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl, piperazinyl, morpholinyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, S,S-dioxothiazinyl, 2-oxo-1,2-dihydropyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 3-oxo-2,3-dihydropyridazinyl, 4-oxo-3,4-dihydropyrimidinyl or 2-oxo-1,2-dihydropyrimidinyl each optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonylaminomethyl, tetrazolyl, methyl, trifluoromethyl, acetyl, 2-hydroxyethyl, 1-aminoethyl, ethyl, isopropyl, 2,2,2-trifluoroethyl, cyano, ethoxy, cyclopropylcarbamoyl and t-butylcarbamoyl;

n is 0;

E is a bond or CH₂;

R² is phenyl, thienyl, pyridyl or isopropyl, t-butyl each optionally substituted with halo, methyl, methylthio or (4-morpholino)methyl; and

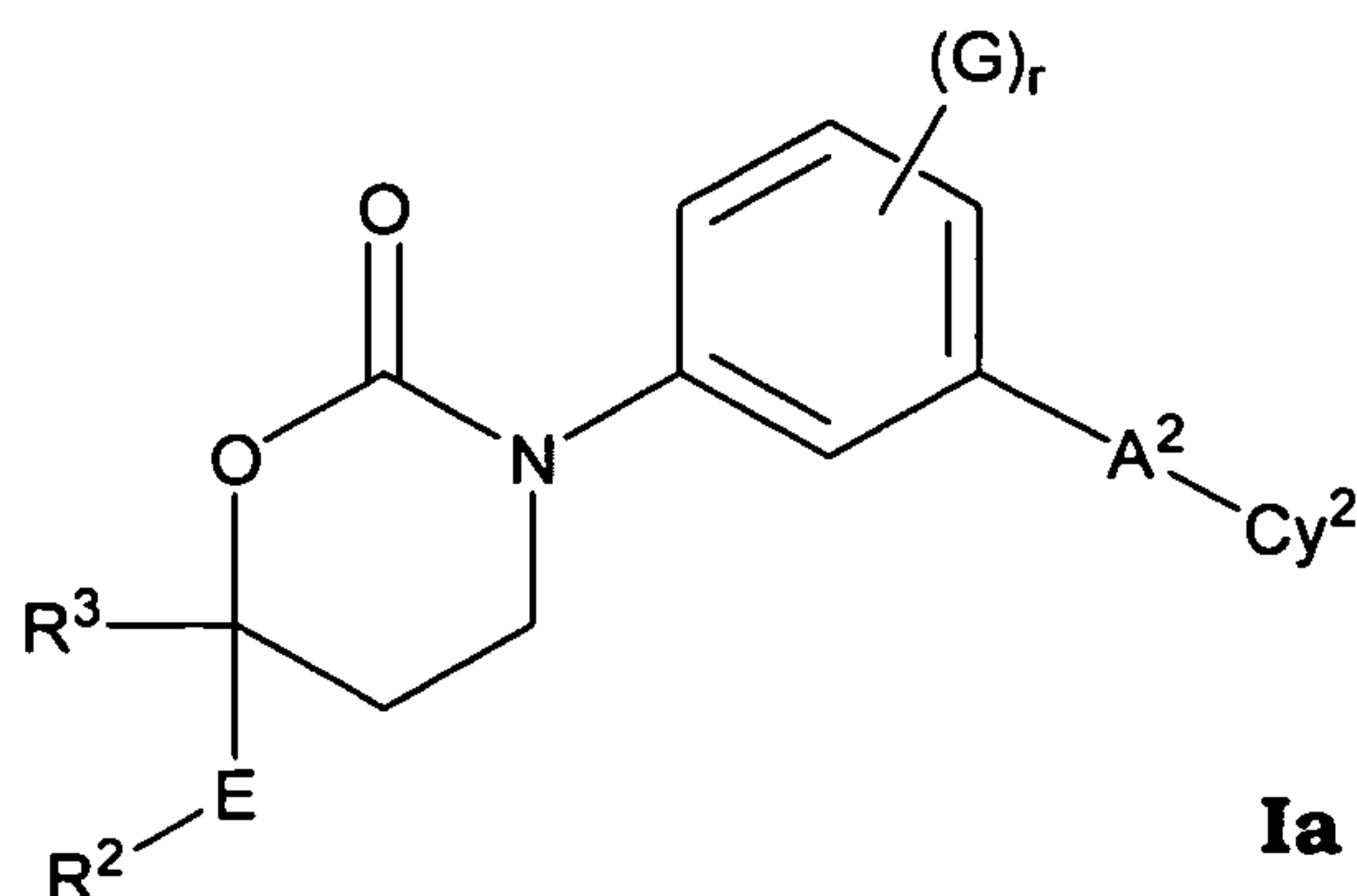
R³ is methyl, ethyl, propyl, butyl, vinyl, allyl or ethoxyethyl each optionally substituted with up to two groups independently selected from methyl, HO-, MeO-, H₂N-, MeC(=O)NH-, MeS(=O)₂NH-, H₂NC(=O)-, MeNHC(=O)-, HO₂C-, (HO)₂P(=O)O-, H₂NS(=O)₂O-, H₂NS(=O)₂NH-, MeNHC(=O)NH-, MeNHC(=O)O-, oxo, cyano, HO₂C-, HOCH₂CH₂NH-, 4-morpholino, HOCH₂C(=O)NH-, H₂NCH₂C(=O)NH-, EtNHC(=O)NH-, MeOC(=O)NH-, MeNHC(=NC≡N)NH-, Me-, MeS-, MeSO₂-, MeSO₂N(Me)-, MeS(=O)₂NHC(=O)-, imidazolylamino-, imidazolyl, tetrazolyl, H₂NCONH-, H₂NCO₂-, HOCH₂CH₂O-, MeNH-, Me₂N-, MeCON(Me)-, 2-fluoroethylamino, azetidiny, pyrrolidinyl, 3-fluoropyrrolidinyl, 3-oxopiperazinyl, 1,1-dioxoisothiazolidin-2-yl, 5-methyl-1H-imidazol-2-yl, 5-methyl-1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl, EtOC(=O)NH-, and fluoro;

alternatively R³ is (1-hydroxycyclopropyl)methyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a compound of Formula Ia:

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wherein A², Cy², E, R², and R³ are as defined for the first embodiment described for Formula I above, r is 0, 1, 2, 3 or 4 and substituents G are 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.

Alternatively for Formula Ia, A², Cy², E, R², and R³ are as defined for the second embodiment described for Formula I above, and r is 0, 1, 2, 3 or 4 and substituents G are 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 and oxo;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

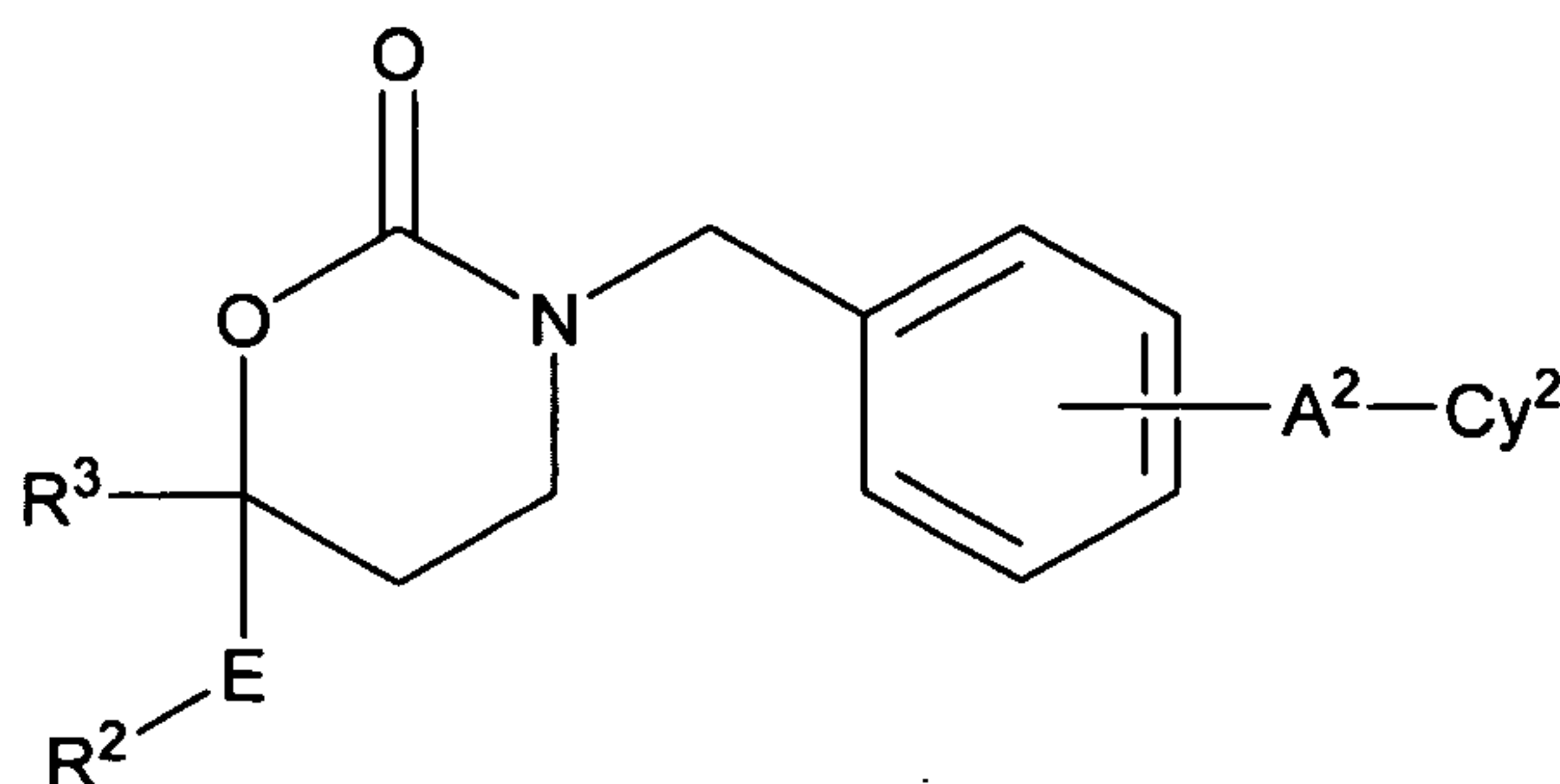
In another alternative for Formulas Ia, A², Cy², E, R², and R³ are as defined for the second embodiment described for Formula I above, and r is 0, 1, 2, 3 or 4 and substituents G are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, 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,

- 35 -

(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, 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; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

25

Another embodiment is a compound of Formula Ib:

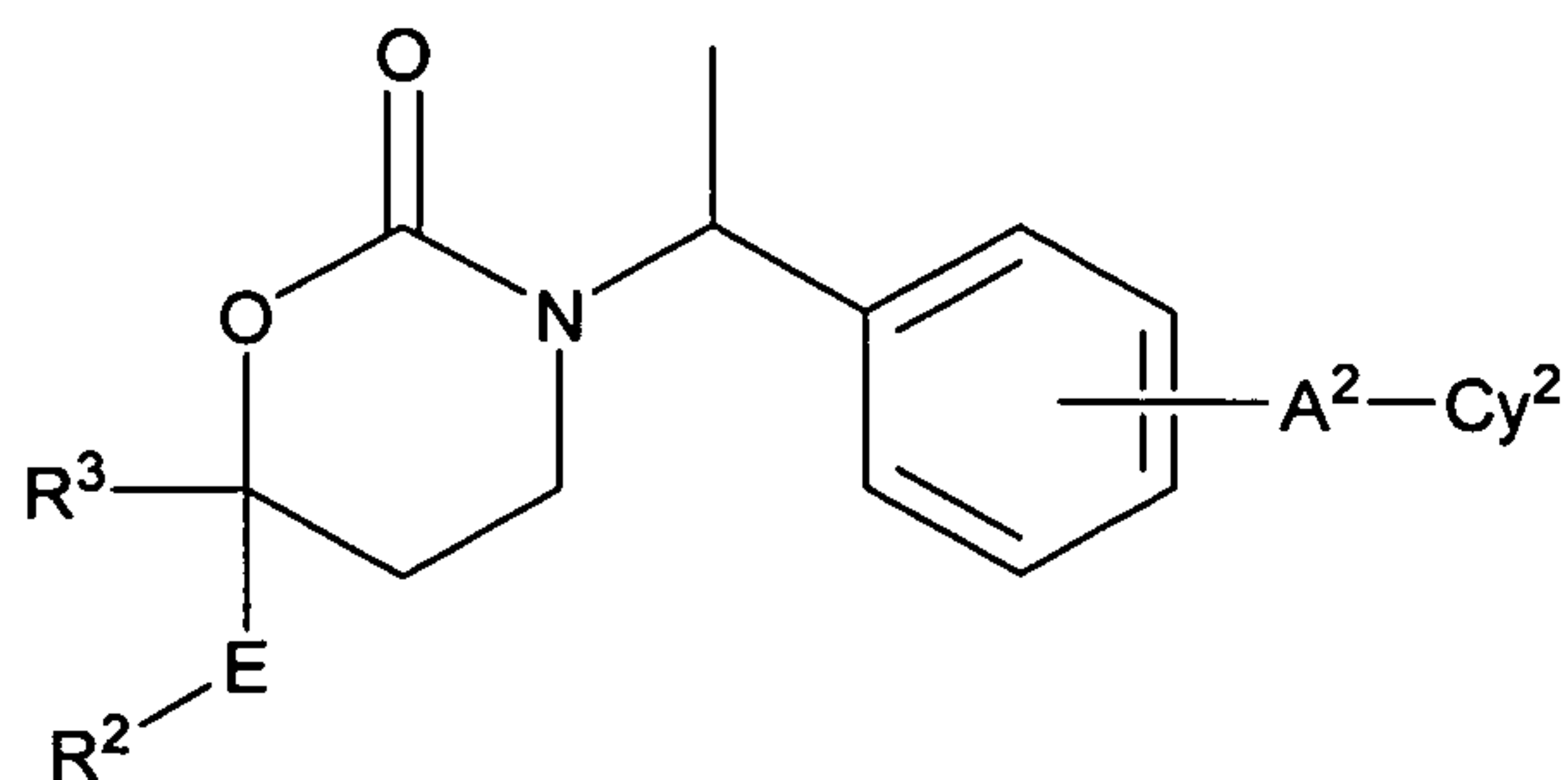
**Ib**

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wherein A^2 , Cy^2 , E , R^2 , and R^3 are as defined for the first or second embodiments described for Formula I above;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

5 Another embodiment is a compound of Formula Ic:

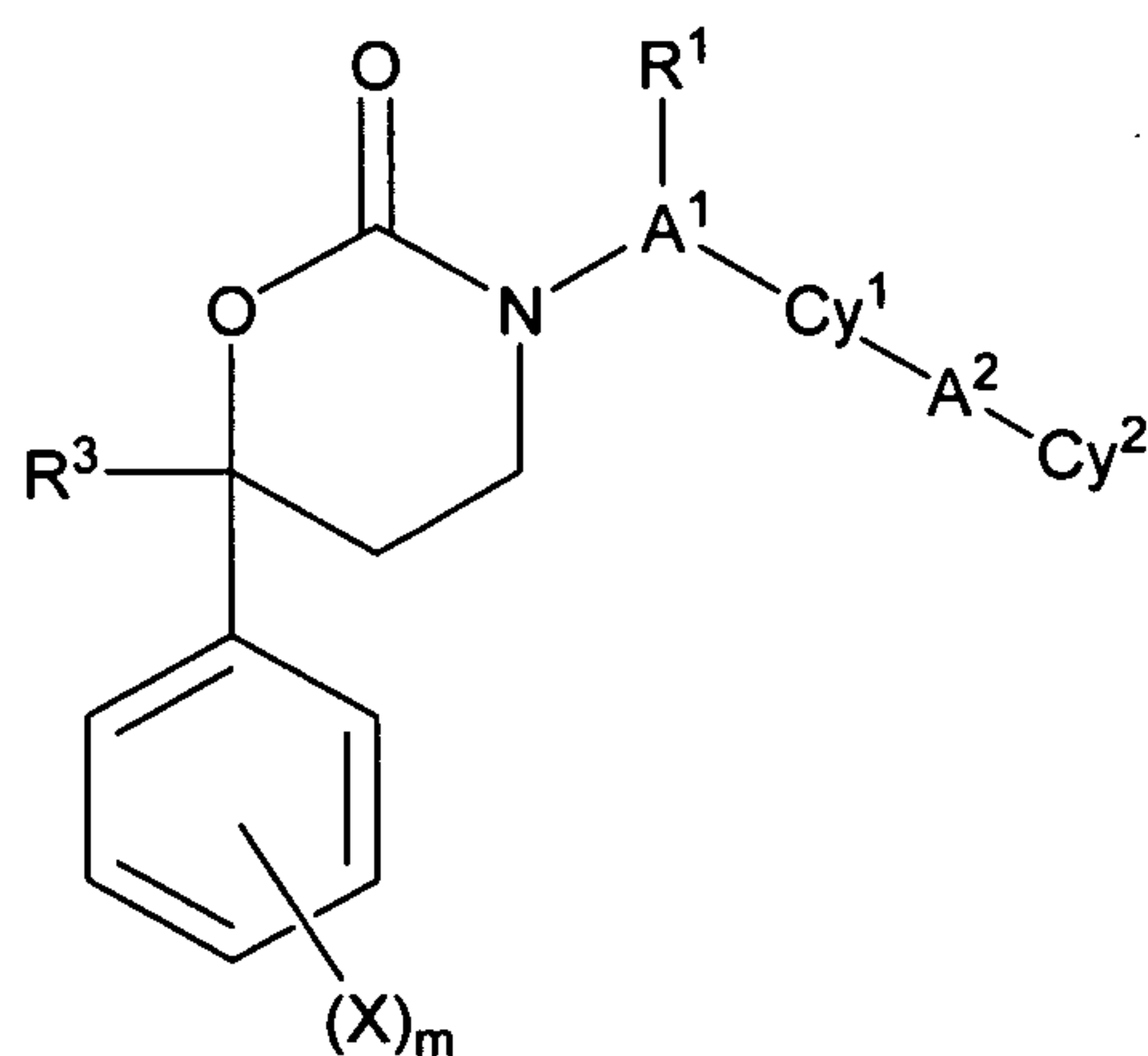
**Ic**

wherein A^2 , Cy^2 , E , R^2 , and R^3 are as defined for the first or second embodiments described for Formula I above;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

10

Another embodiment is a compound of Formula Id:

**Id**

wherein, Cy^1 , A^1 , R^1 , A^2 , Cy^2 , and R^3 are as defined for the first embodiment described for Formula I above, m is 0, 1, 2, 3 or 4 and substituents X are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, hydroxy (C_3-C_6) cycloalkyl, (C_4-C_7) cycloalkylalkyl, (C_2-C_6) alkenyl, halo (C_2-C_6) alkenyl, hydroxy (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_3-C_6) cycloalkyl (C_2-C_4) alkynyl, halo (C_1-C_6) alkyl, halo (C_3-C_6) cycloalkyl, halo (C_4-C_7) cycloalkylalkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkoxy, (C_4-C_7) cycloalkylalkoxy, halo (C_1-C_6) alkoxy, halo (C_3-C_6) cycloalkoxy, halo (C_4-C_7) cycloalkylalkoxy, (C_1-C_6) alkylthio, (C_3-C_6) cycloalkylthio, (C_4-C_7) cycloalkylalkylthio, halo (C_1-C_6) alkylthio, halo (C_3-C_6) cycloalkylthio, halo (C_4-C_7) cycloalkylalkylthio, $(C_1-$

15

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C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl,
 halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkyl-
 alkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkyl-
 alkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-
 5 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, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl,
 di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-
 10 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-
 15 C₆)alkoxy and (C₁-C₆)alkylcarbonyl;
 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

20 Alternatively for Formula Id, Cy¹, A¹, R¹, A², Cy², and R³ are as defined for the
 second embodiment described for Formula I above, m is 0, 1, 2, 3 or 4 and
 substituents X are 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,
 25 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-
 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-
 35 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,

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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 and heteroaryl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

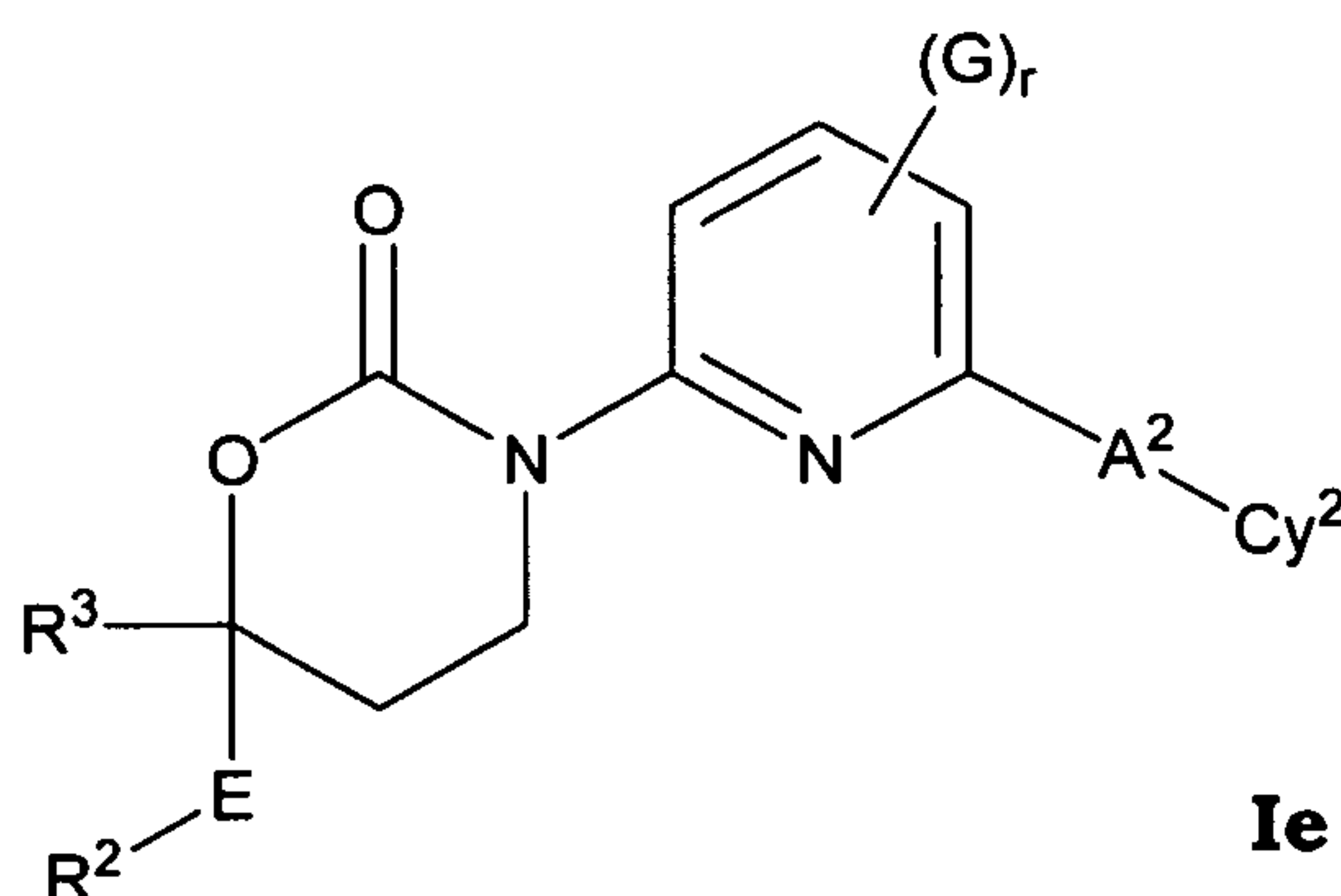
10

In another alternative for Formula Id, Cy¹, A¹, R¹, A², Cy², and R³ are as defined for the second embodiment described for Formula I above, m is 0, 1, 2, 3 or 4 and substituents X are 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, 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-

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C_6)cycloalkyl} $\{(C_1-C_6)alkyl\}$ aminocarbonyl, di(C_3-C_6)cycloalkylaminocarbonyl, (C_3-C_6)cycloalkylaminosulfonyl, $\{(C_3-C_6)cycloalkyl\}\{(C_1-C_6)alkyl\}$ aminosulfonyl, di(C_3-C_6)cycloalkylaminosulfonyl, cyano(C_1-C_6)alkyl, aminocarbonyl(C_1-C_6)alkyl, (C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, di(C_1-C_6)alkylaminocarbonyl(C_1-C_6)alkyl, (C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl, $\{(C_3-C_6)cycloalkyl\}\{(C_1-C_6)alkyl\}$ aminocarbonyl(C_1-C_6)alkyl and di(C_3-C_6)cycloalkylaminocarbonyl(C_1-C_6)alkyl; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

10 Another embodiment is a compound of Formula Ie:



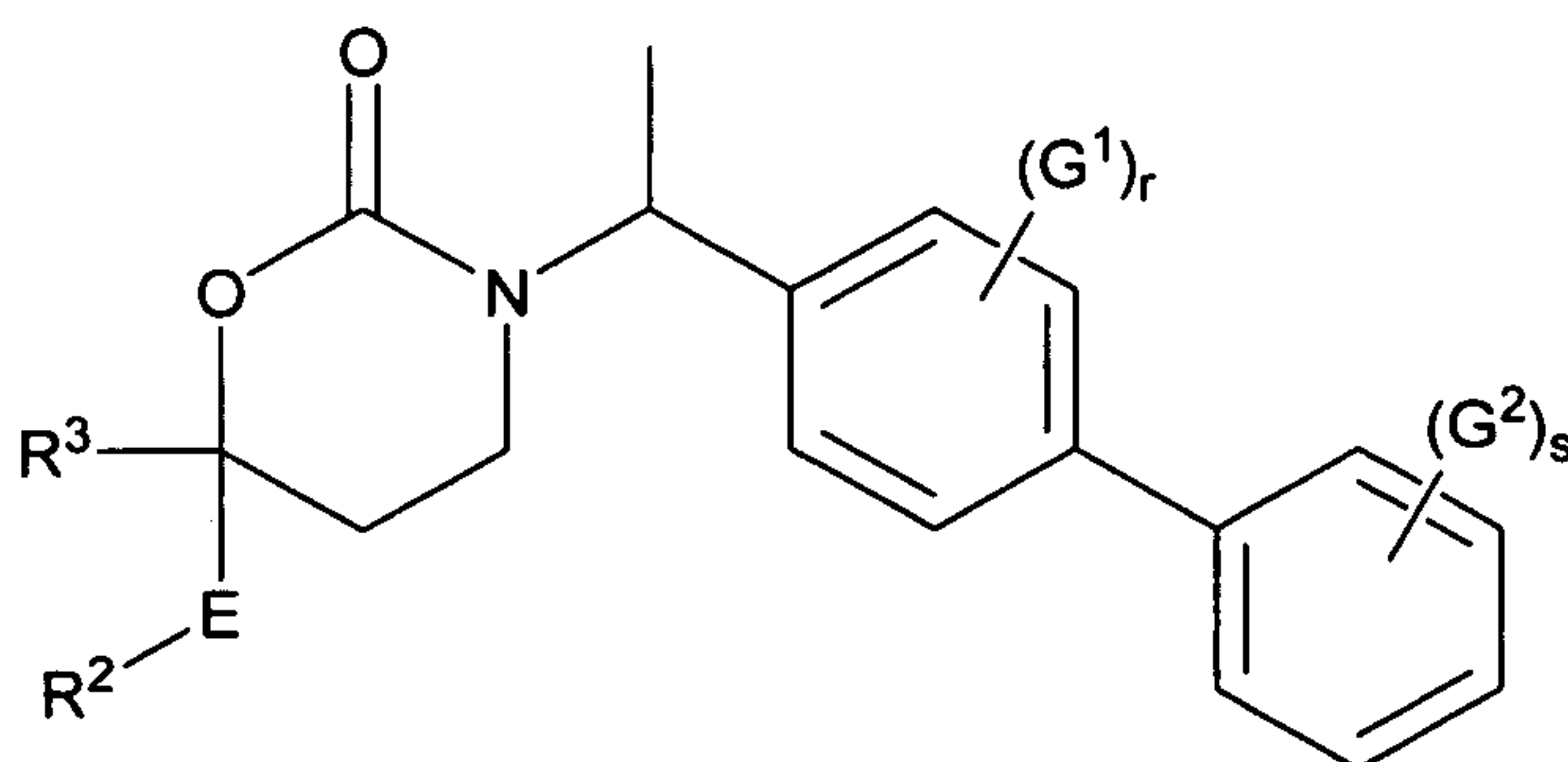
wherein A^2 , Cy^2 , E, R^2 , and R^3 are as defined for the first embodiment described for Formula I above; r is 0, 1, 2, 3 or 4 and substituents G are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_4-C_7)cycloalkylalkyl, (C_2-C_6)alkenyl, halo(C_2-C_6)alkenyl, hydroxy(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_6)cycloalkyl(C_2-C_4)alkynyl, halo(C_1-C_6)alkyl, halo(C_3-C_6)cycloalkyl, halo(C_4-C_7)cycloalkylalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, (C_4-C_7)cycloalkylalkoxy, halo(C_1-C_6)alkoxy, halo(C_3-C_6)cycloalkoxy, halo(C_4-C_7)cycloalkylalkoxy, (C_1-C_6)alkylthio, (C_3-C_6)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-C_7)cycloalkylalkanesulfinyl, halo(C_1-C_6)alkanesulfinyl, halo(C_3-C_6)cycloalkanesulfinyl, halo(C_4-C_7)cycloalkylalkanesulfinyl, (C_1-C_6)alkanesulfonyl, (C_3-C_6)cycloalkanesulfonyl, (C_4-C_7)cycloalkylalkanesulfonyl, halo(C_1-C_6)alkanesulfonyl, halo(C_3-C_6)cycloalkanesulfonyl, halo(C_4-C_7)cycloalkylalkanesulfonyl, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, (C_1-C_6)alkoxy(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy(C_1-C_6)alkoxy, (C_1-C_6)alkoxycarbonyl, H_2NCO , H_2NSO_2 , (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_3)alkoxy(C_1-C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6)alkylaminosulfonyl, di(C_1-C_6)alkylaminosulfonyl, heterocyclosulfonyl, (C_1-C_6)alkylcarbonylamino, (C_1-

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

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a compound of Formula If:



If

10 wherein E, R^2 , and R^3 are as defined for the first embodiment described for Formula I above; r and s are independently 0, 1, 2, 3 or 4, and G^1 and G^2 are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1 - C_6)alkyl, hydroxy(C_1 - C_6)alkyl, (C_3 - C_6)cycloalkyl, hydroxy(C_3 - C_6)cycloalkyl, (C_4 - C_7)cycloalkylalkyl, (C_2 - C_6)alkenyl, halo(C_2 - C_6)alkenyl, hydroxy(C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, (C_3 - C_6)cycloalkyl(C_2 - C_4)alkynyl, halo(C_1 - C_6)alkyl, halo(C_3 - C_6)cycloalkyl, halo(C_4 - C_7)cycloalkylalkyl, (C_1 - C_6)alkoxy, (C_3 - C_6)cycloalkoxy, (C_4 - C_7)cycloalkylalkoxy, halo(C_1 - C_6)alkoxy, halo(C_3 - C_6)cycloalkoxy, halo(C_4 - C_7)cycloalkylalkoxy, (C_1 - C_6)alkylthio, (C_3 - C_6)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 - C_7)cycloalkylalkanesulfinyl, halo(C_1 - C_6)alkanesulfinyl, halo(C_3 - C_6)cycloalkanesulfinyl, halo(C_4 - C_7)cycloalkylalkanesulfinyl, (C_1 - C_6)alkanesulfonyl, (C_3 - C_6)cycloalkanesulfonyl, (C_4 - C_7)cycloalkylalkanesulfonyl, halo(C_1 - C_6)alkanesulfonyl, halo(C_3 - C_6)cycloalkanesulfonyl, halo(C_4 - C_7)cyclo-alkylalkanesulfonyl, (C_1 - C_6)alkylamino, di(C_1 - C_6)alkylamino, (C_1 - C_6)alkoxy(C_1 - C_6)alkoxy, halo(C_1 - C_6)alkoxy(C_1 - C_6)alkoxy, (C_1 - C_6)alkoxycarbonyl, H_2NCO , H_2NSO_2 , (C_1 - C_6)alkylaminocarbonyl, di(C_1 - C_6)alkylaminocarbonyl, (C_1 - C_3)alkoxy(C_1 - C_3)alkylaminocarbonyl, heterocyclylcarbonyl, (C_1 - C_6)alkylaminosulfonyl, di(C_1 - C_6)alkylaminosulfonyl, heterocyclosulfonyl, (C_1 - C_6)alkylcarbonylamino, (C_1 - C_6)alkylcarbonylamino(C_1 - C_6)alkyl, (C_1 - C_6)alkylsulfonylamino, (C_1 -

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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)alkoxy and (C₁-C₆)alkylcarbonyl;

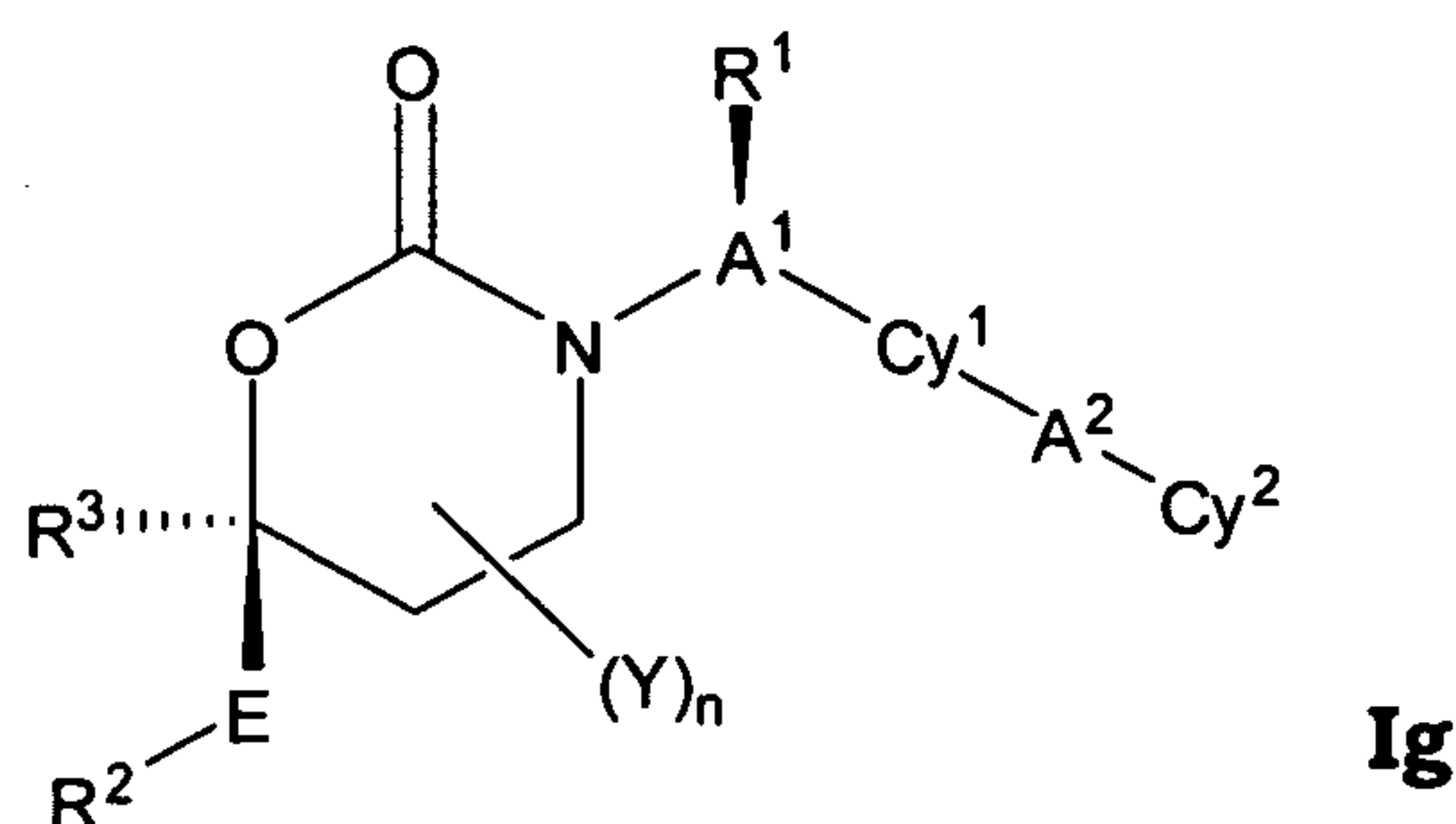
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In one alternative for Formula If E, R², and R³ are as defined for the first embodiment described for Formula I above; r and s are independently 0, 1, 2, 3 or 4, and G¹ and G² are 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, 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-

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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;
 5 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

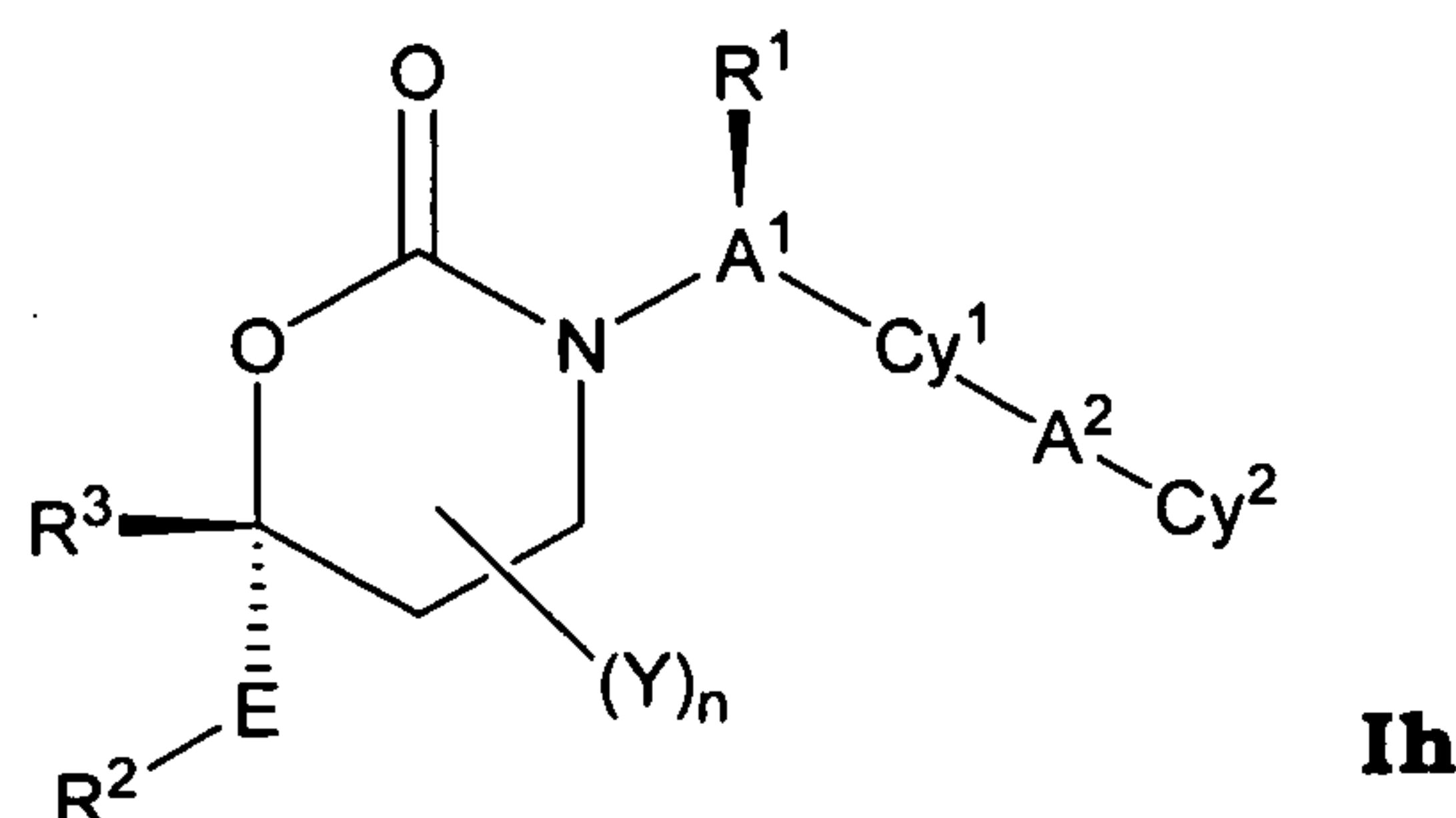
Another embodiment is a compound of Formula Ig:



10 wherein, Cy¹, A¹, R¹, A², Cy², R², E, R³, Y, and n are as defined for the first or second embodiments described for Formula I above and at least one and preferably both stereocenters are in the configuration depicted. Pharmaceutically acceptable salts, enantiomers or diastereomers thereof are also included.

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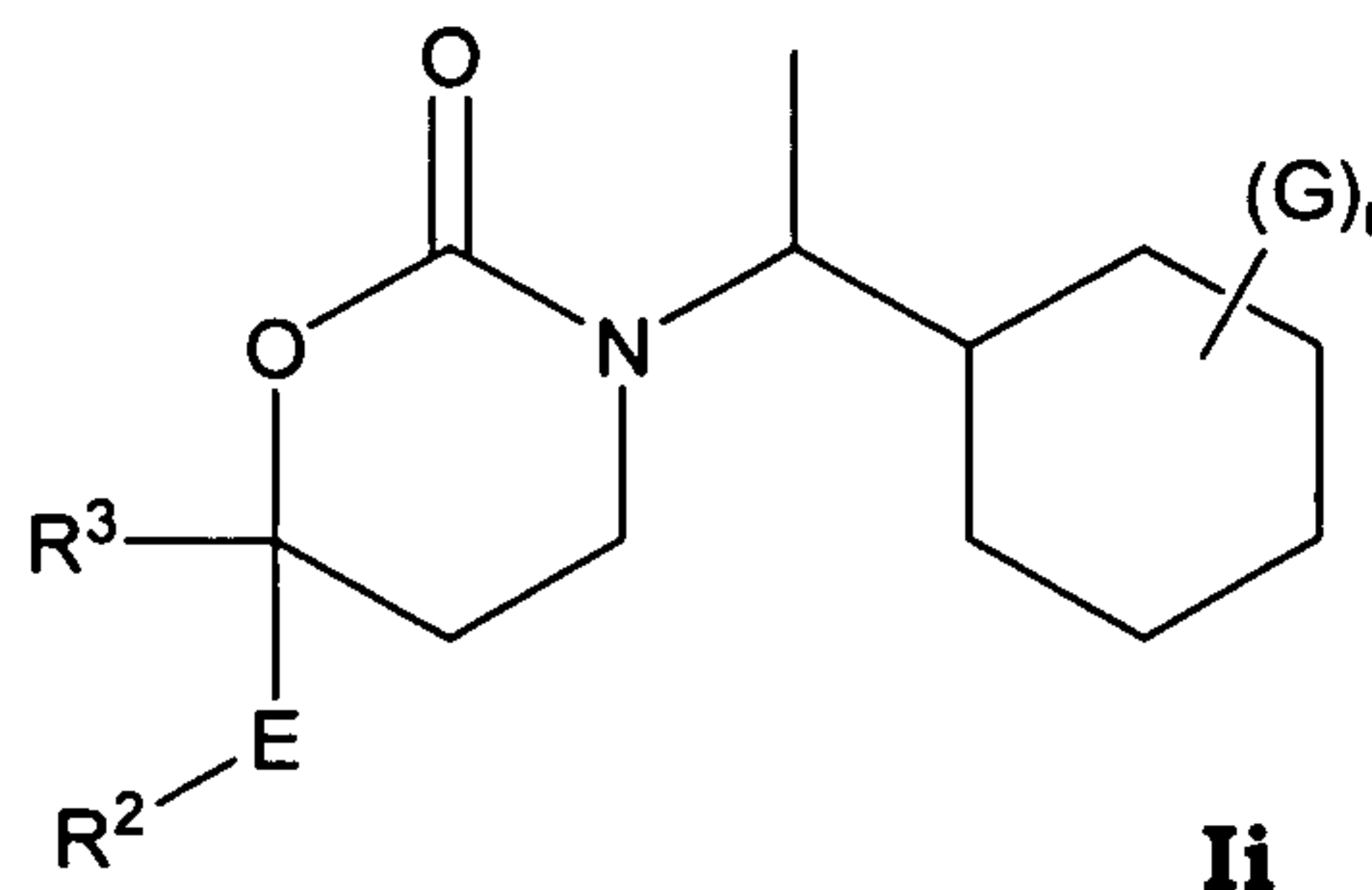
Another embodiment is a compound of Formula Ih:



wherein, Cy¹, A¹, R¹, A², Cy², R², E, R³, Y, and n are as defined for the first or second
 20 embodiments described for Formula I above and at least one and preferably both stereocenters are in the configuration depicted. Pharmaceutically acceptable salts, enantiomers or diastereomers thereof are also included.

Another embodiment is a compound of Formula Ii:

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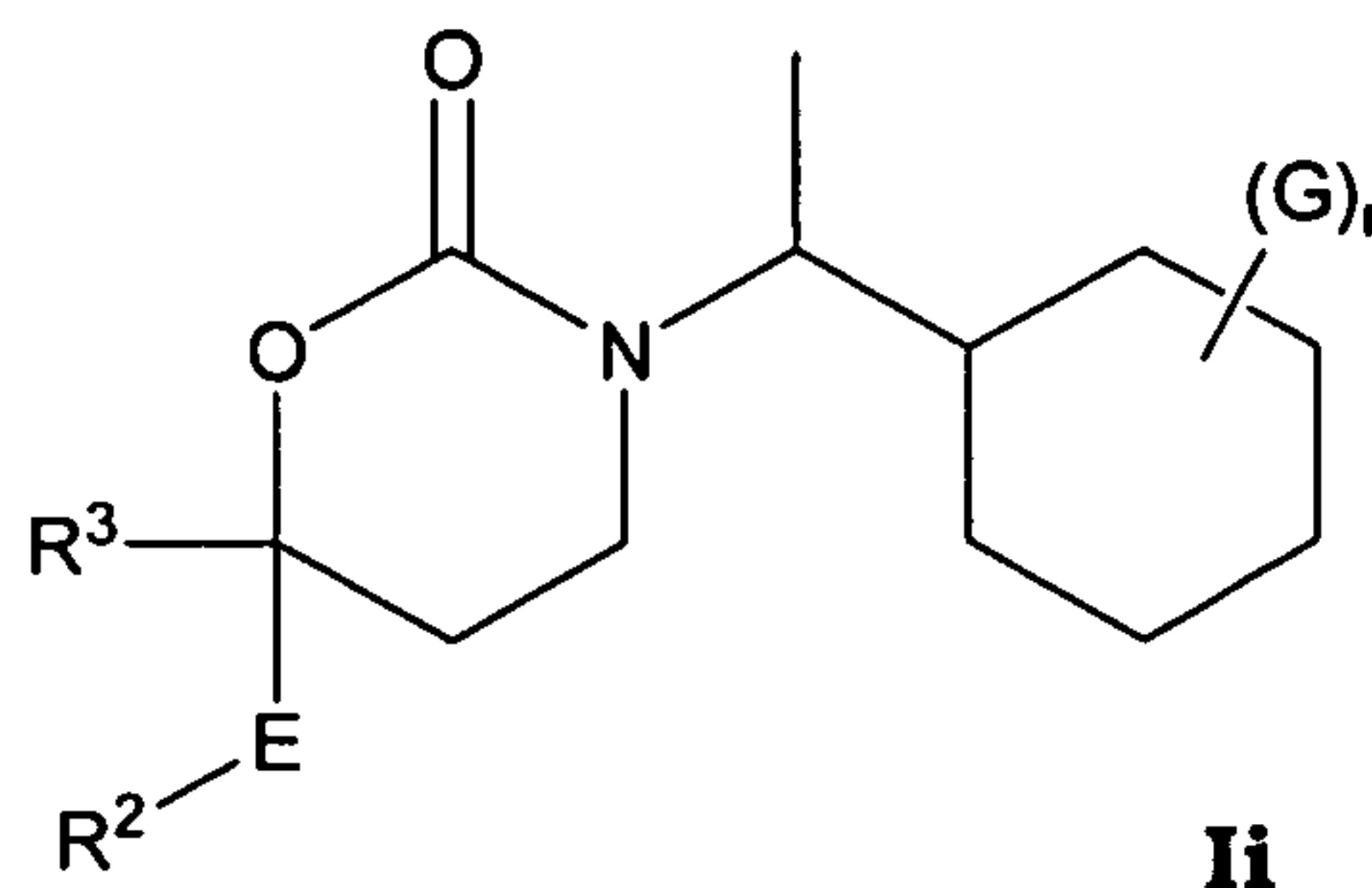


wherein E, R² and R³ are as defined for the first or second embodiments described for Formula I above, r is 0, 1, 2, 3 or 4, and substituents G are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 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, 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.

Alternatively, for Formula II:

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E, R² and R³ are as defined for the first or second embodiments described for Formula I above, r is 0, 1, 2, 3 or 4, and substituents G are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy,

5 (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,

10 (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,

15 (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-C₆)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, 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-

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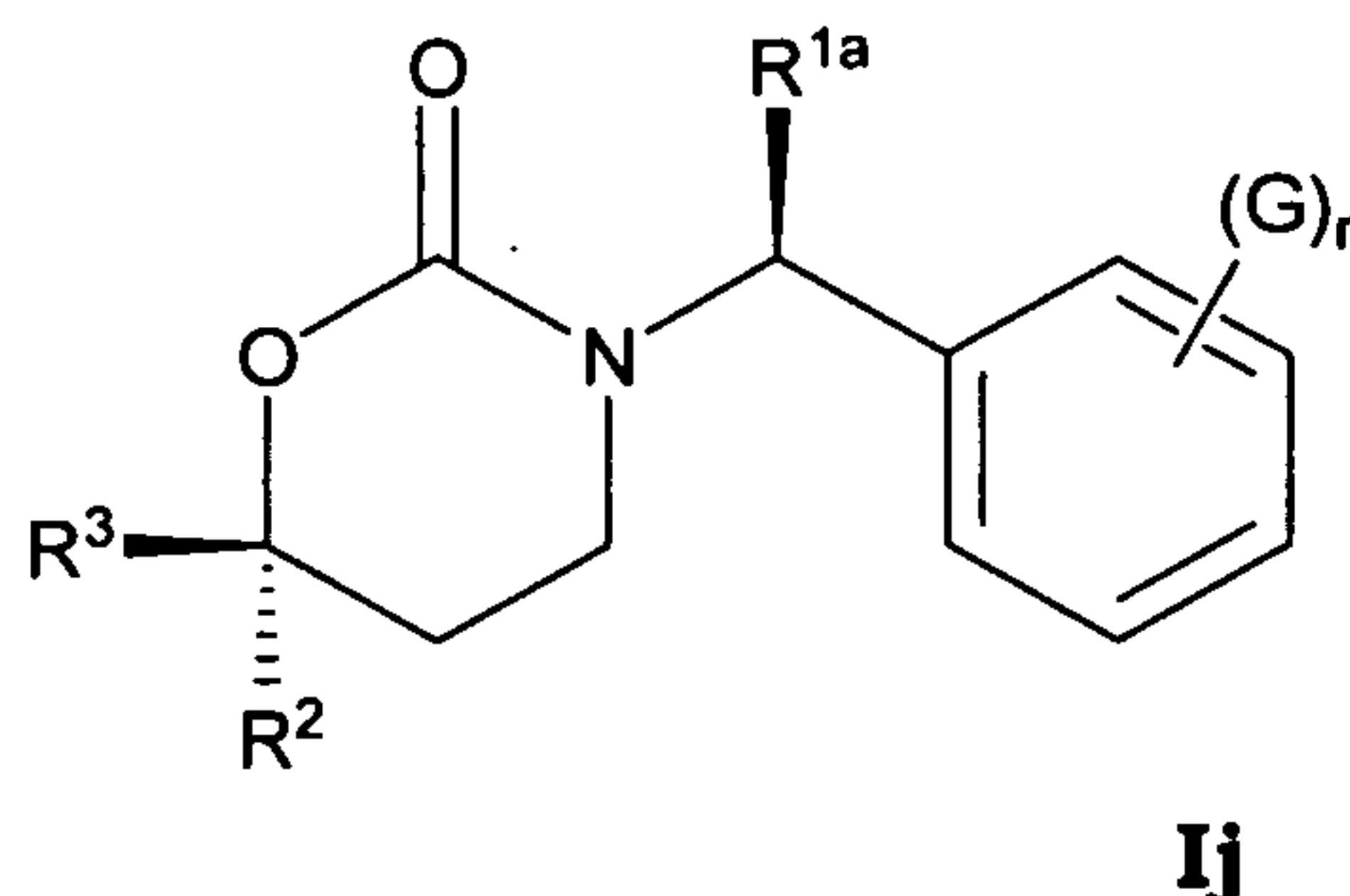
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C₆cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

5

Another embodiment is a compound of Formula Ij:



wherein R² and R³ are as defined for the first or second embodiments described for
 10 Formula I above, R^{1a} is methyl or ethyl, r is 0, 1, 2, 3 or 4, and substituents G are
 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,
 15 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,
 20 halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkyl-
 alkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkyl-
 alkanesulfonyl, 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,
 25 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-
 30 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-

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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.

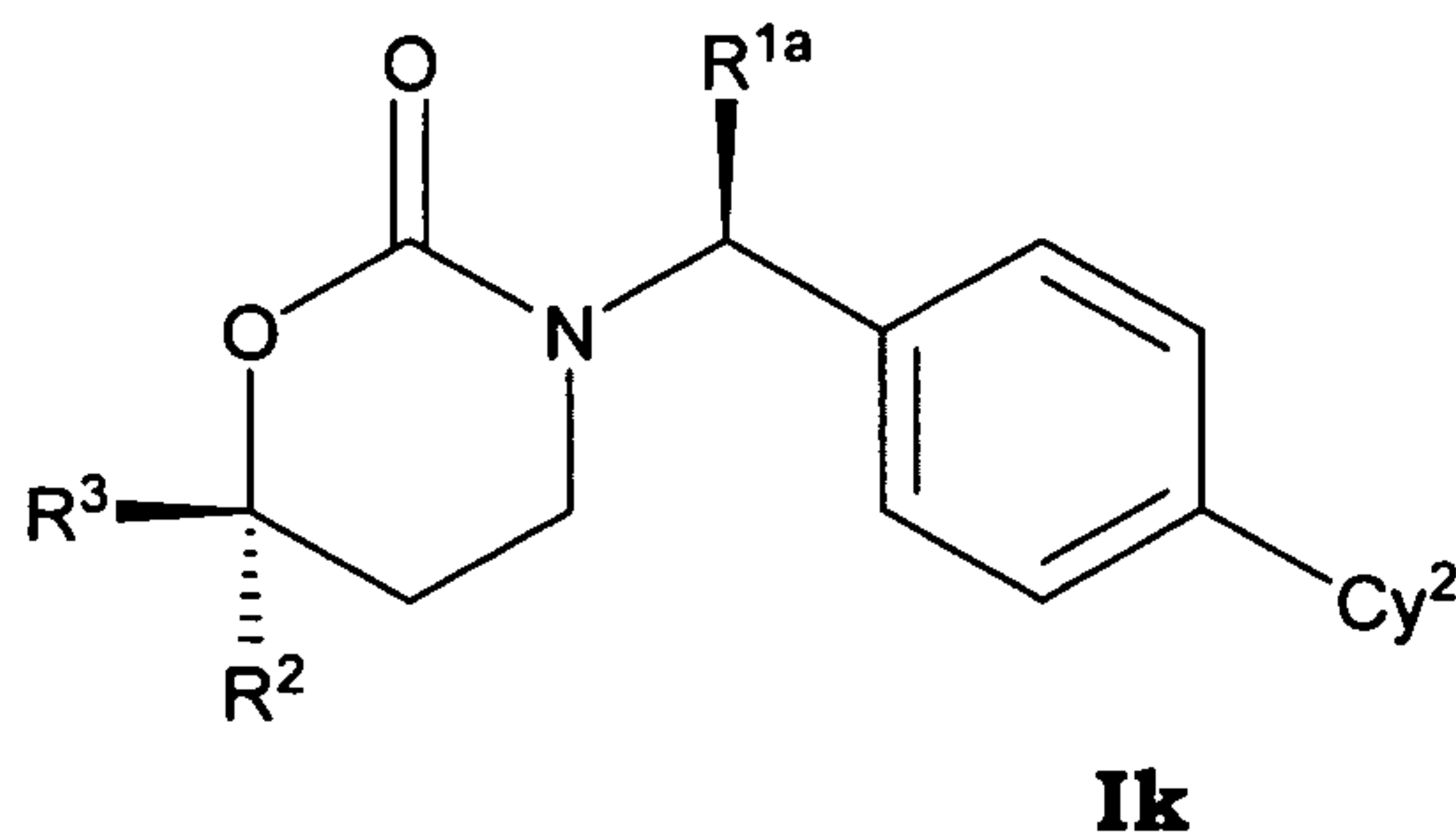
5 Alternatively for Formula Ij:

R² and R³ are as defined for the first or second embodiments described for Formula I above, R^{1a} is methyl or ethyl, r is 0, 1, 2, 3 or 4, and substituents G are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro,
 10 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,
 15 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,
 20 (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, 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-

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C_6)cycloalkylaminocarbonyl(C_1 - C_6)alkyl, $\{(C_3$ - C_6)cycloalkyl\}(C_1 - C_6)alkyl}aminocarbonyl(C_1 - C_6)alkyl and di(C_3 - C_6)cycloalkylaminocarbonyl(C_1 - C_6)alkyl; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

5 Another embodiment is a compound of Formula Ik:



wherein Cy^2 , R^2 and R^3 are as defined for the first or second embodiments described for Formula I above, and R^{1a} is methyl or ethyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

10 Another embodiment is a compound of Formula Ik wherein R^{1a} is methyl or ethyl, R^2 is phenyl optionally substituted with up to 2 groups selected from halogen, methyl, trifluoromethyl and cyano, R^3 is $MeSO_2NHCH_2CH_2CH_2$, $H_2NC(=O)CH_2CH_2$, $H_2NC(=O)CMe_2CH_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl and Cy^2 is heterocyclyl optionally substituted with up to 3 groups independently selected from those described for G^2 in Formula If and oxo;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a compound of Formula Ik wherein R^{1a} is methyl or ethyl, R^2 is phenyl optionally substituted with up to 2 groups selected from halogen, methyl, trifluoromethyl and cyano, R^3 is $MeSO_2NHCH_2CH_2CH_2$, $H_2NC(=O)CH_2CH_2$, $H_2NC(=O)CMe_2CH_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl and Cy^2 is 5-oxo-4,5-dihydro-1H-pyrazolyl, 3-oxo-2,3-dihydro-1H-pyrazolyl, 5-oxo-4,5-dihydro-1H-imidazolyl, 2-oxo-2,3-dihydro-1H-imidazolyl, 5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl, 5-oxo-4,5-dihydro-1,3,4-thiadiazolyl, 1,2-dihydro-2-oxopyridyl, 2,3-dihydro-3-oxopyridazinyl, 1,2-dihydro-2-oxopyrimidinyl, 3,4-dihydro-4-oxopyrimidinyl or 1,2-dihydro-2-oxopyrazinyl optionally substituted with up to 3 groups independently selected from fluorine, chlorine, cyano, hydroxy, amino, (C_1 - C_4)alkyl, (C_3 - C_4)cycloalkyl, (C_3 - C_4)cycloalkyl(C_1 - C_2)alkyl, halo(C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)haloalkoxy, $CONH_2$, (C_1 - C_4)alkylaminocarbonyl, di(C_1 - C_4)alkylaminocarbonyl, and (C_1 - C_4)alkylcarbonylamino; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof. In one

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alternative, the embodiments described in this paragraph exclude the compound exemplified in Examples 221 or 313 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

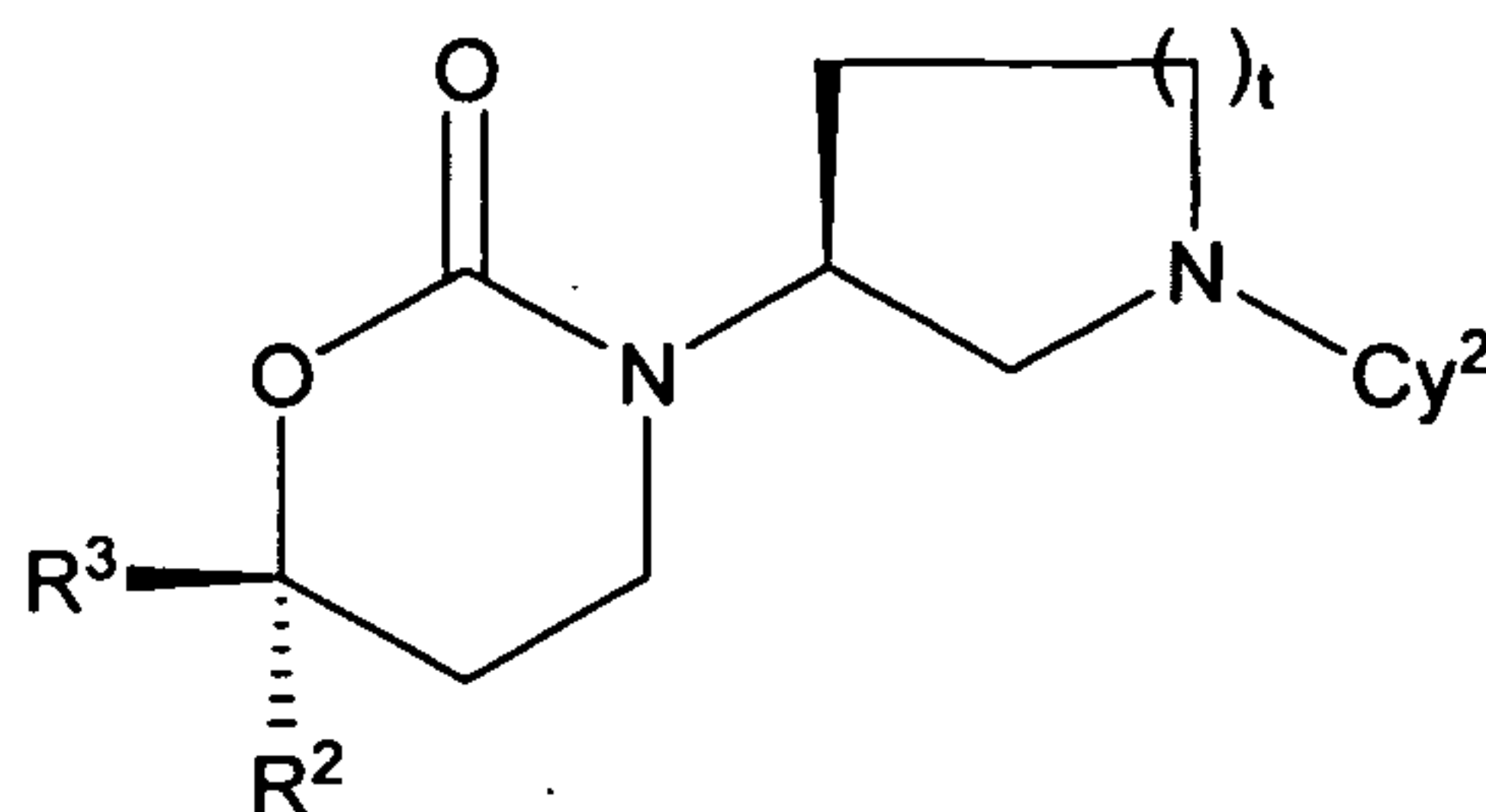
Another embodiment is a compound of Formula Ik wherein R^{1a} is methyl or ethyl, R² is phenyl optionally substituted with up to 2 groups selected from halogen, methyl, trifluoromethyl and cyano, R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl and Cy² is 1,2-dihydro-2-oxopyridyl, 2,3-dihydro-3-oxopyridazinyl, 1,2-dihydro-2-oxopyrimidinyl, 3,4-dihydro-4-oxopyrimidinyl or 1,2-dihydro-2-oxopyrazinyl optionally substituted with up to 2 groups independently selected from (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, halo(C₁-C₄)alkyl and halogen;
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a compound of Formula Ik wherein R^{1a} is methyl or ethyl, R² is phenyl optionally substituted with up to 2 groups selected from halogen, methyl, trifluoromethyl and cyano, R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl and Cy² is heteroaryl optionally substituted with up to 2 groups selected from (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, halogen, cyano, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl and (C₃-C₅)cycloalkylaminocarbonyl or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof. In another embodiment, Cy² is heteroaryl optionally substituted with one group selected from (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, halogen, cyano, CONHMe and CONMe₂; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof. In an alternative embodiment CONH₂ is excluded as a permissible substituent when Cy² is pyridine or thiazole. In yet another embodiment, Cy² is heteroaryl optionally substituted with one group selected from (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, halogen, cyano;
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment is a compound of Formula Ik wherein R^{1a} is methyl or ethyl, R² is phenyl or fluorophenyl, R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl and Cy² is pyridine, pyridine N-oxide, pyridazine, pyrimidine, pyrazine, thiazole, pyrazole or thiadiazole optionally substituted with methyl, fluorine, chlorine, cyano, CONH₂, CONHMe, CONMe₂, CONHt-Bu or CONHc-Pr;
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof. In an alternative embodiment CONH₂ is excluded as a permissible substituent when Cy² is pyridine or thiazole.

Another embodiment is a compound of Formula II:

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**II**

wherein Cy^2 , R^2 and R^3 are as defined for the first or second embodiments described for Formula I above, and t is 1, 2 or 3;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

- 5 Another embodiment is a compound of Formula II wherein t is 1, 2 or 3; R^2 is phenyl or fluorophenyl, R^3 is $MeSO_2NHCH_2CH_2CH_2$, $H_2NC(=O)CH_2CH_2$, $H_2NC(=O)CMe_2CH_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl and Cy^2 is heterocyclyl optionally substituted with up to 3 groups independently selected from oxo, fluorine, chlorine, cyano, hydroxy, amino, (C_1-C_4) alkyl, (C_3-C_4) cycloalkyl, (C_3-C_4) cycloalkyl (C_1-C_2) alkyl, halo (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, $CONH_2$, (C_1-C_4) alkylaminocarbonyl, di (C_1-C_4) alkylaminocarbonyl and (C_1-C_4) alkylcarbonylamino; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

- 15 Another embodiment is a compound of Formula II wherein t is 1, 2 or 3; R^2 is phenyl or fluorophenyl, R^3 is $MeSO_2NHCH_2CH_2CH_2$, $H_2NC(=O)CH_2CH_2$, $H_2NC(=O)CMe_2CH_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl and Cy^2 is heteroaryl optionally substituted with up to 3 groups independently selected from oxo, fluorine, chlorine, cyano, hydroxy, amino, (C_1-C_4) alkyl, (C_3-C_4) cycloalkyl, (C_3-C_4) cycloalkyl (C_1-C_2) alkyl, halo (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, $CONH_2$, (C_1-C_4) alkylaminocarbonyl, di (C_1-C_4) alkylaminocarbonyl and (C_1-C_4) alkylcarbonylamino; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

- 25 Another embodiment is a compound of Formula II wherein t is 1, 2 or 3; R^2 is phenyl or fluorophenyl, R^3 is $MeSO_2NHCH_2CH_2CH_2$, $H_2NC(=O)CH_2CH_2$, $H_2NC(=O)CMe_2CH_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl and Cy^2 is pyridine, pyridazine, pyrimidine, pyrazine, thiadiazole, pyrazole or thiazole optionally substituted with up to 2 groups independently selected from methyl, fluorine, chlorine, cyano, CF_3 , $CONH_2$, $CONHMe$ or $CONMe_2$; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.
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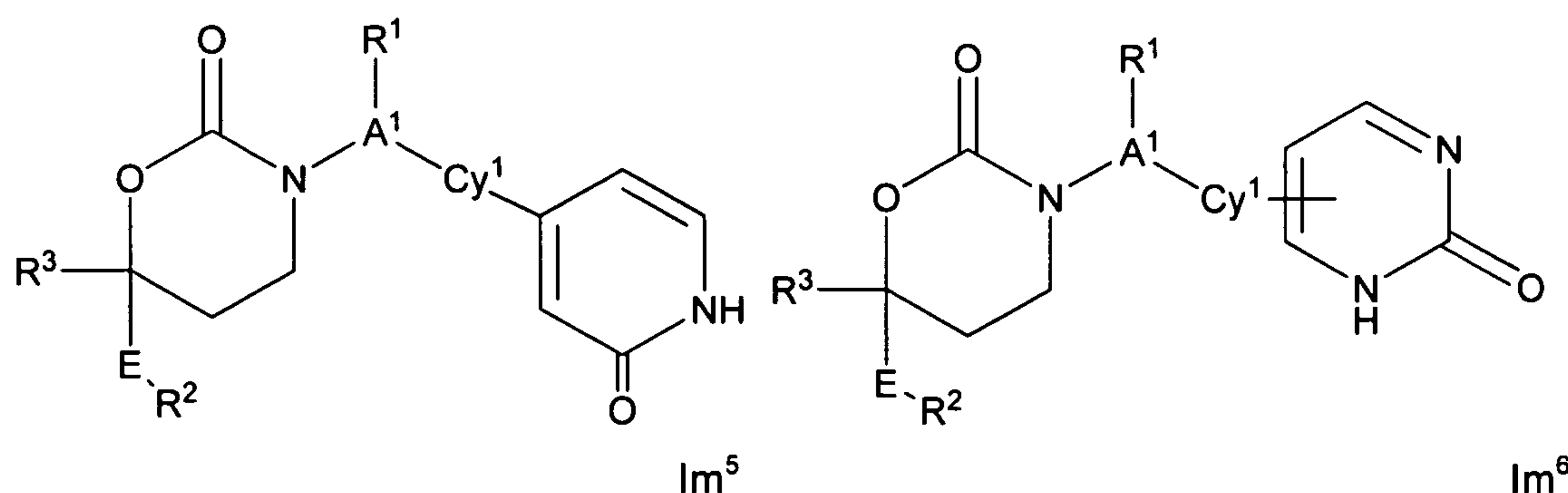
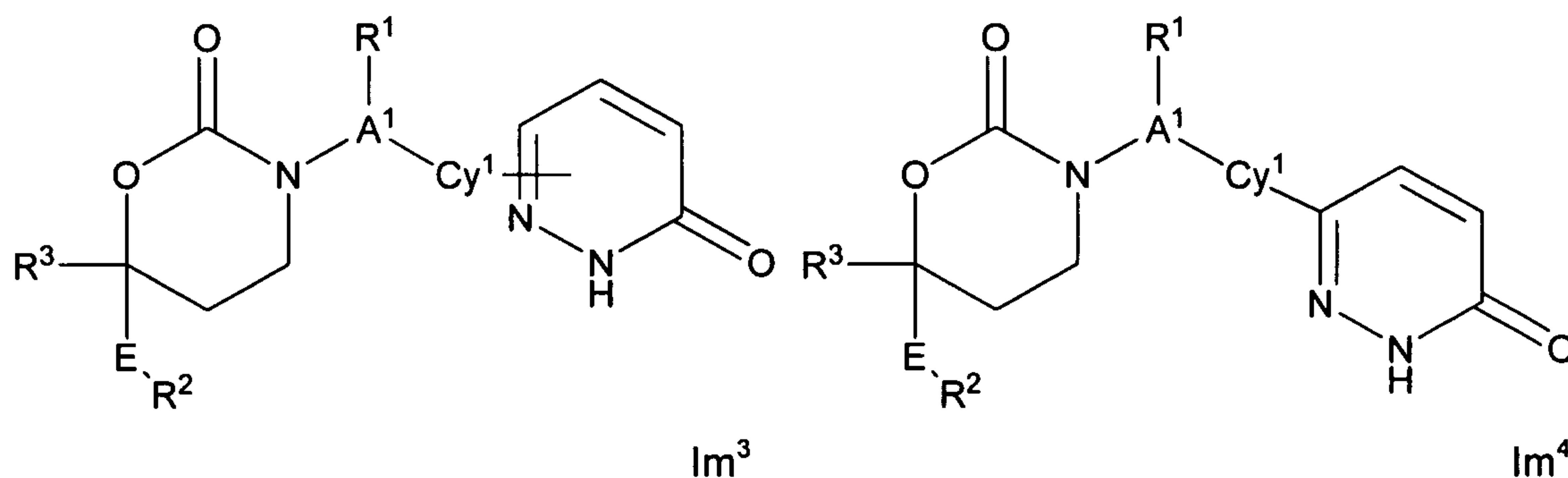
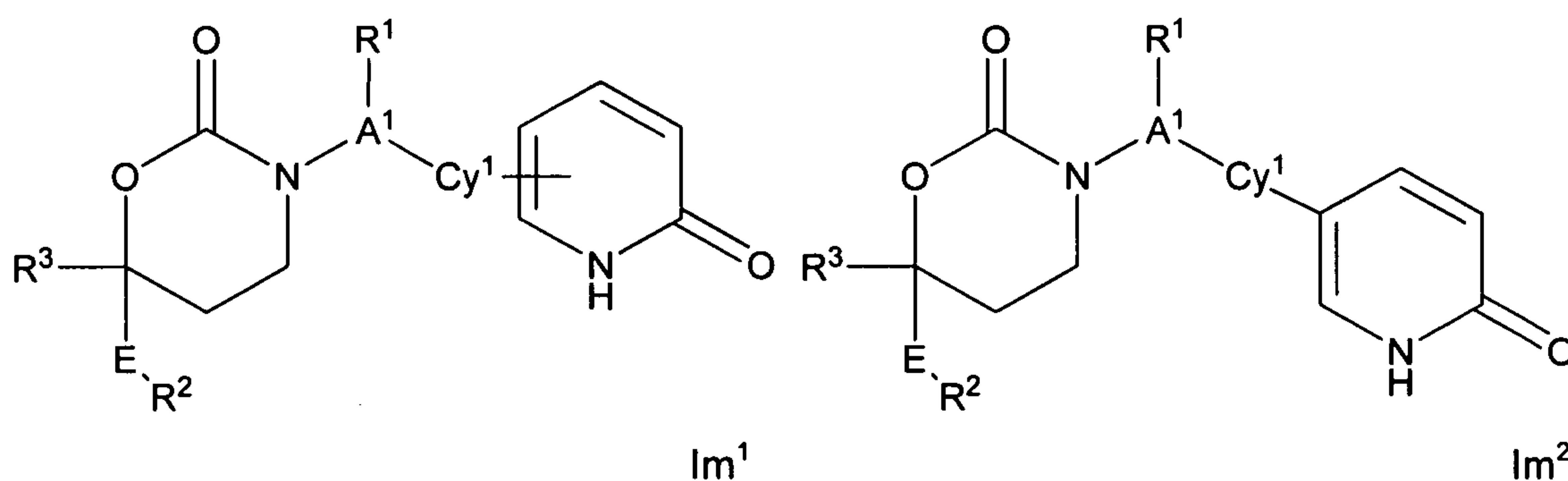
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Another embodiment is a compound of Formula II wherein R^2 is phenyl or fluorophenyl, R^3 is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl and Cy^2 is pyridine, pyridazine, pyrimidine, pyrazine, thiadiazole, pyrazole or thiazole optionally substituted with up to 2 groups independently selected from methyl, fluorine, chlorine, cyano, CF_3 , $CONH_2$, $CONHMe$ or $CONMe_2$;

5 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

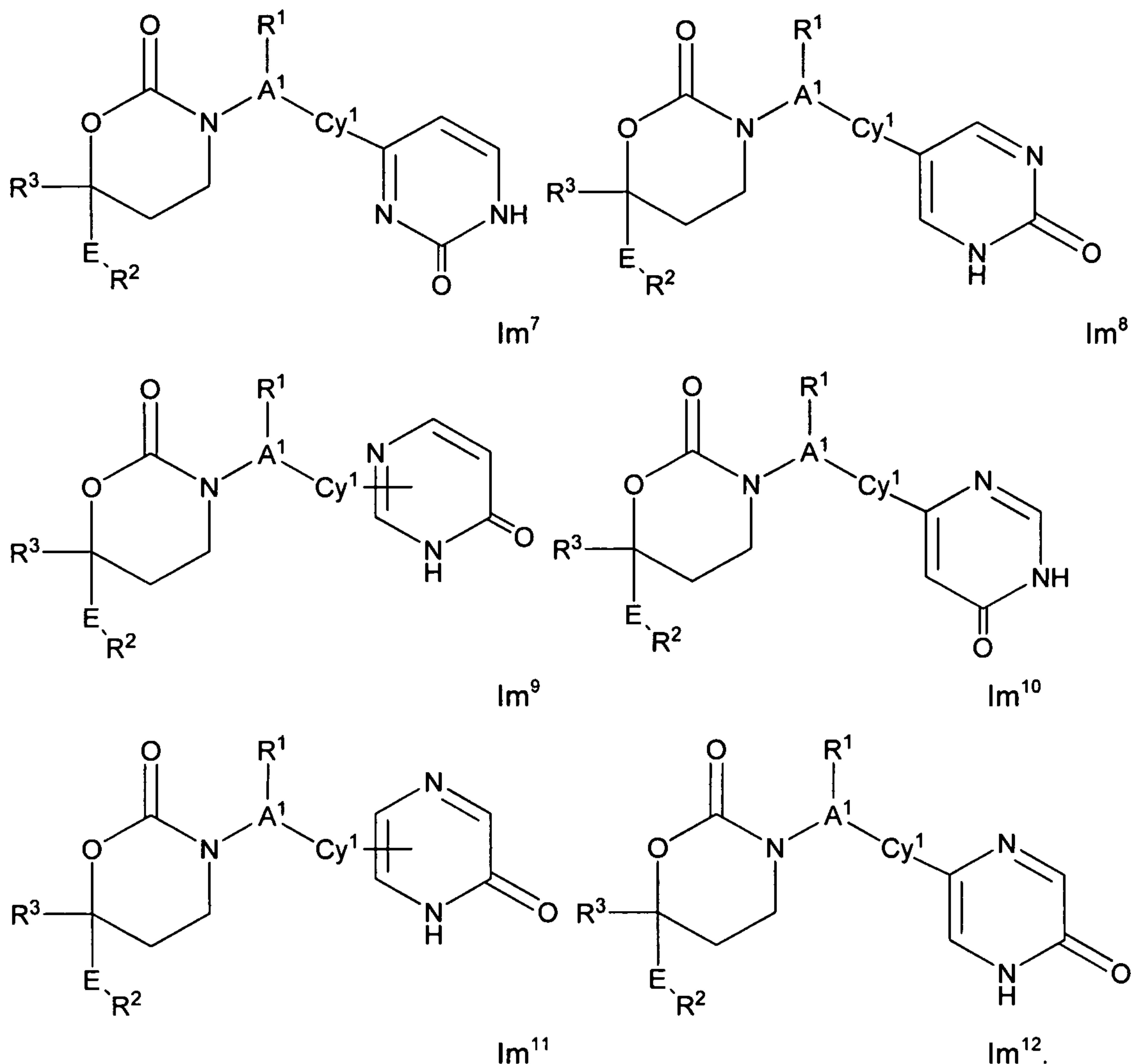
Another embodiment of the invention is a compound of any one of Formulas

10 Im^{1-12} or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof:



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In Formulas Im^{1-12} , the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas Im^{1-12} are optionally substituted (substitution at ring carbons bonded to hydrogen and ring nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a "substitutable ring nitrogen atom") with up to four substituents as described above for Cy^2 . Suitable substituents for Cy^2 and suitable values for R^1 , R^2 , R^3 , A^1 , Cy^1 and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, suitable substituents for Cy^1 and the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas Im^{1-12} are as described for G^1 and G^2 , respectively, in Formula If, and values for R^1 , R^2 , R^3 , A^1 , Cy^1 and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, suitable substituents for Cy^1 include $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkoxy, $(\text{C}_1\text{-C}_4)$ haloalkyl, $(\text{C}_1\text{-C}_4)$ haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom in the

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oxodihydropyridyl, oxodihydropyridaziny, oxodihydropyrimidinyl and oxodihydropyraziny rings in Formulas Im¹⁻¹² include (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₄)haloalkyl; suitable substituents for a ring carbon atom in the oxodihydropyridyl, oxodihydropyridaziny, oxodihydropyrimidinyl and oxodihydropyraziny rings in Formulas Im¹⁻¹² include fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl and (C₁-C₄)alkylcarbonylamino; and suitable values for R¹, R², R³, A¹, Cy¹ and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. In another alternative, the embodiments in this paragraph exclude the compound exemplified in Example 221 and Example 313 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

For each of the embodiments described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹⁻¹², R¹ is preferably methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹⁻¹², R¹ is preferably methyl or ethyl; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

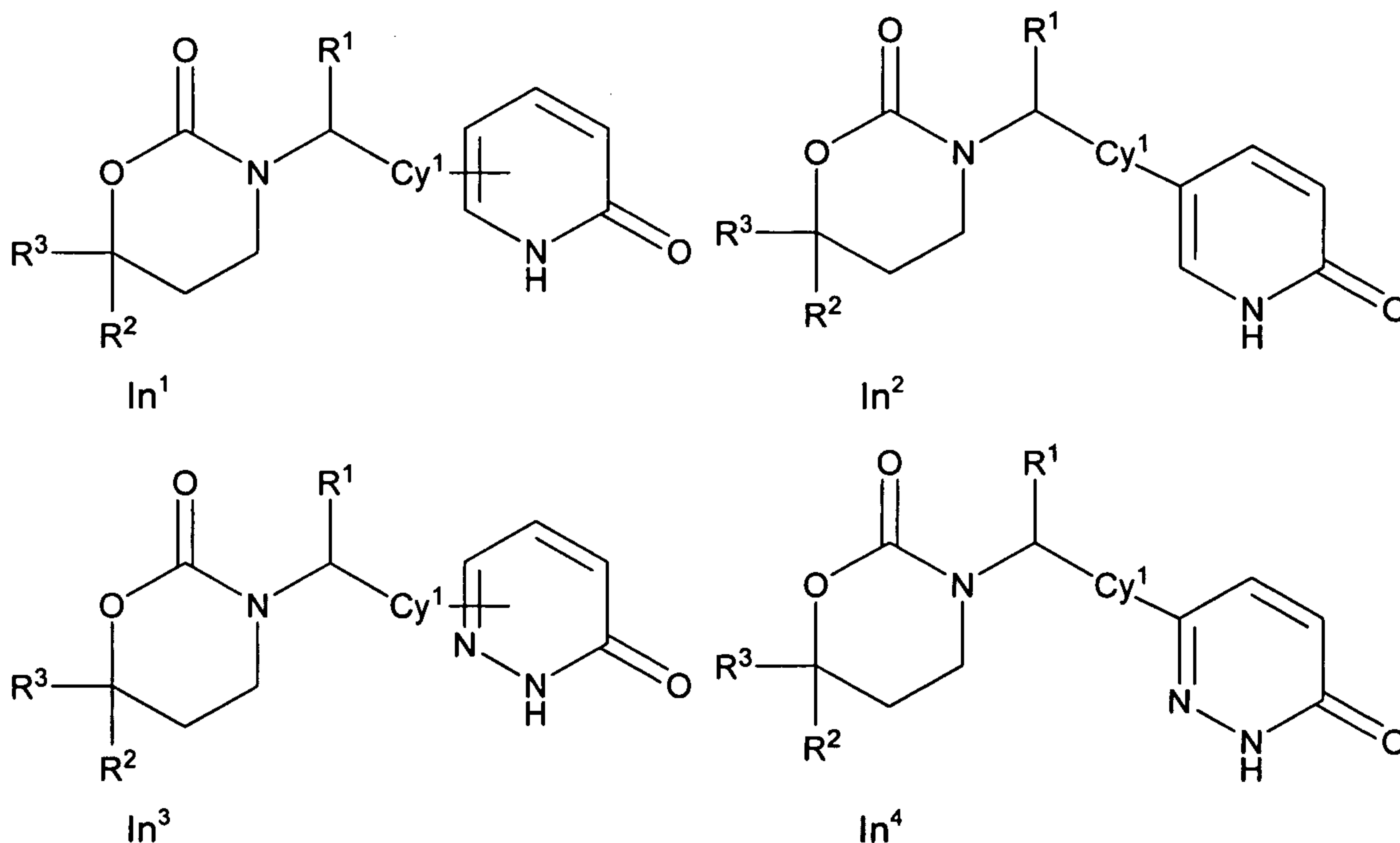
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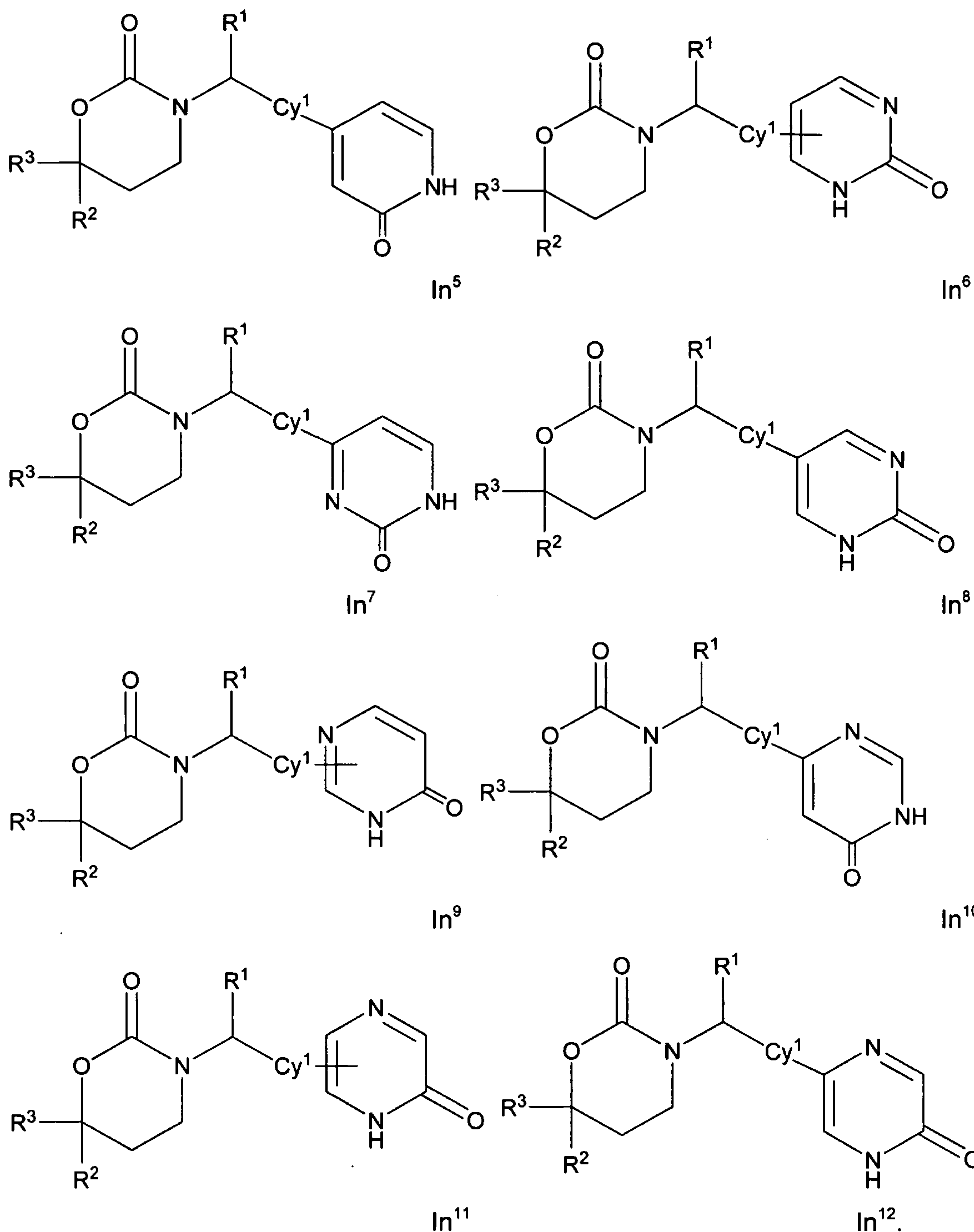
For each of the embodiments described in the paragraph immediately following Formulas Im¹⁻¹², R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent on the substitutable ring nitrogen atom in the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas Im¹⁻¹² is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, or (C₁-C₂)haloalkyl; and one or two ring carbon atoms in the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas Im¹⁻¹² are optionally substituted with methyl or ethyl.

Another embodiment of the invention is a compound of any one of Formulas In¹⁻¹², or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof:





In Formulas In¹⁻¹², the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings are optionally substituted (substitution at ring carbons bonded to hydrogen and at nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a "substitutable ring nitrogen atom") with up to four substituents as described above for Cy². Suitable substituents for Cy² and suitable values for R¹, R², R³ and Cy¹ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, suitable substituents for Cy¹ and the oxodihydropyridyl,

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oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas In¹⁻¹² are as described for G¹ and G², respectively, in Formula If, and values for R¹, R², R³ and Cy¹ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments.

5 Alternatively, suitable substituents for Cy¹ include (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom in the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas In¹⁻¹² include (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl and (C₁-C₄)haloalkyl; suitable
 10 substituents for a ring carbon atom in the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas In¹⁻¹² include fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl and (C₁-
 15 C₄)alkylcarbonylamino; and suitable values for R¹, R², R³, and Cy¹ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. In another alternative, the embodiments described in this paragraph exclude the compound exemplified in Example 221 and Example 313 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

20 For each of the embodiments described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiments described in the paragraph immediately following Formulas In¹⁻¹², R¹ is preferably methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-
 25 hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas In¹⁻¹², R¹ is preferably methyl or ethyl; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-
 30 2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas In¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂,
 35 H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

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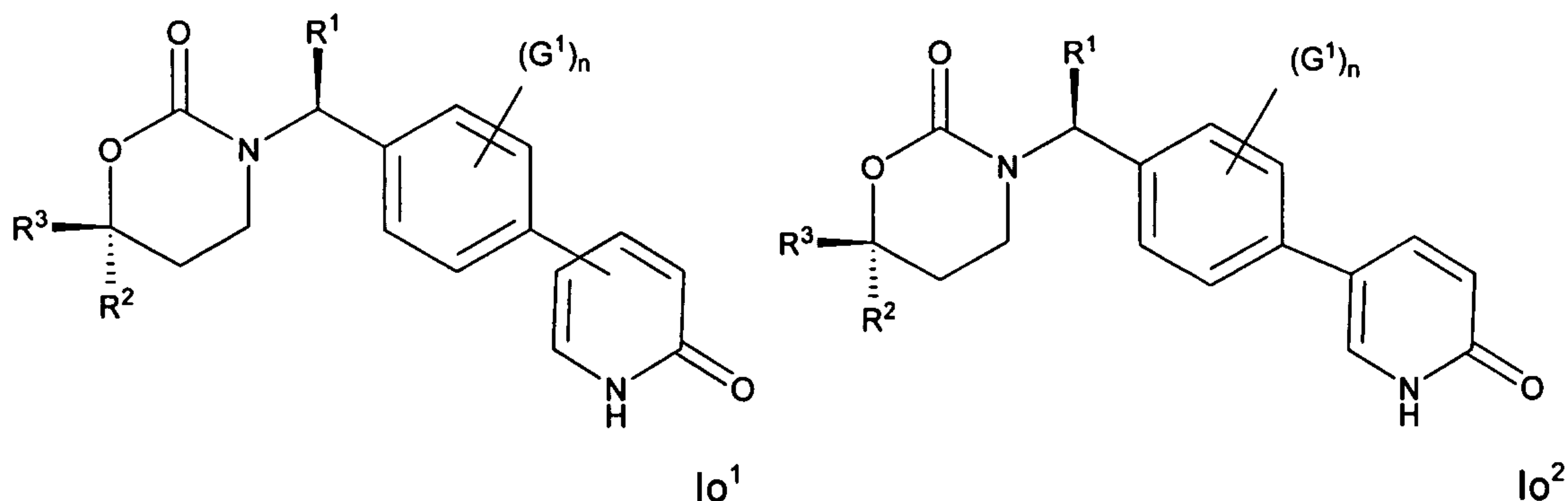
For each of the embodiments described in the paragraph immediately following Formulas In¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas In¹⁻¹², R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

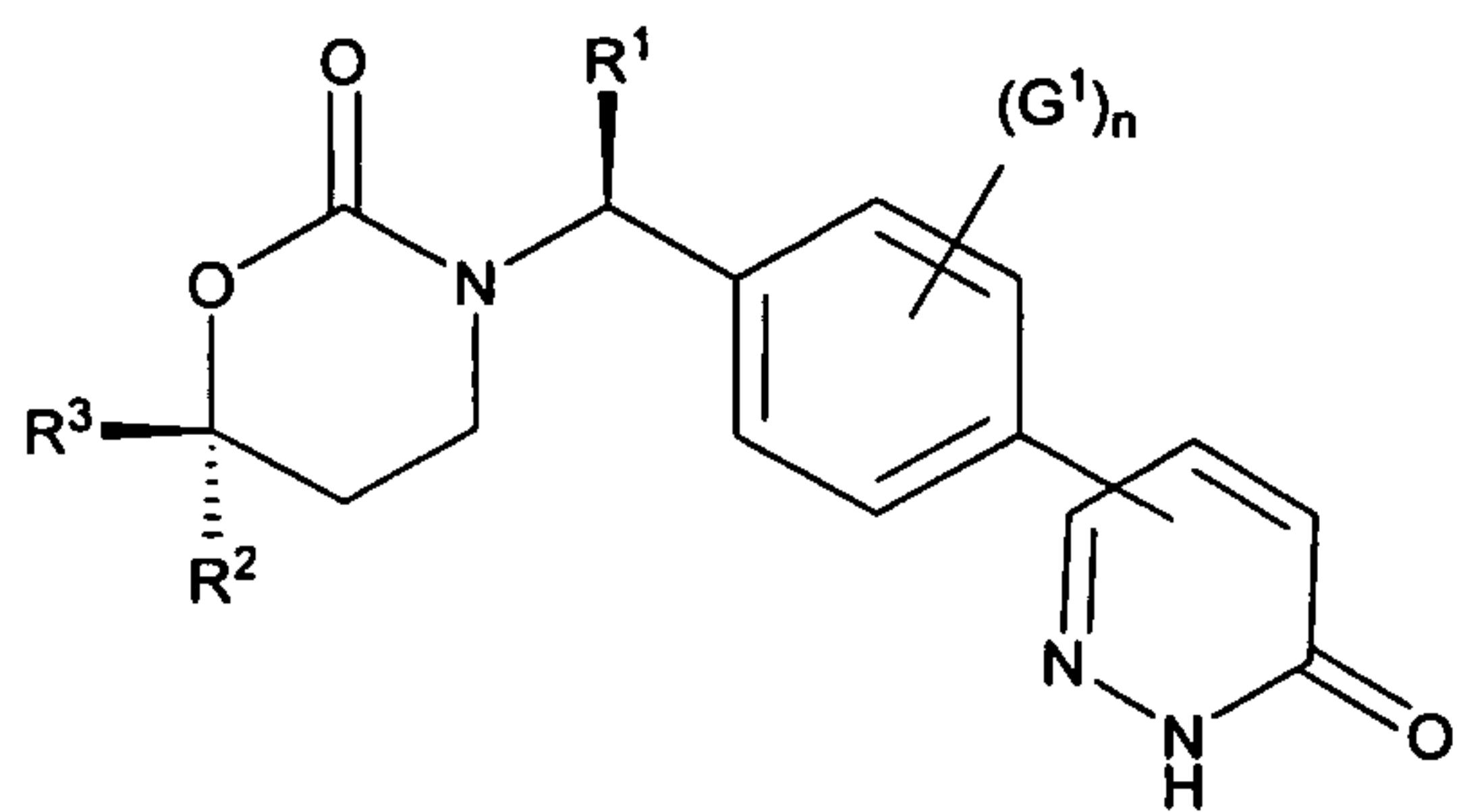
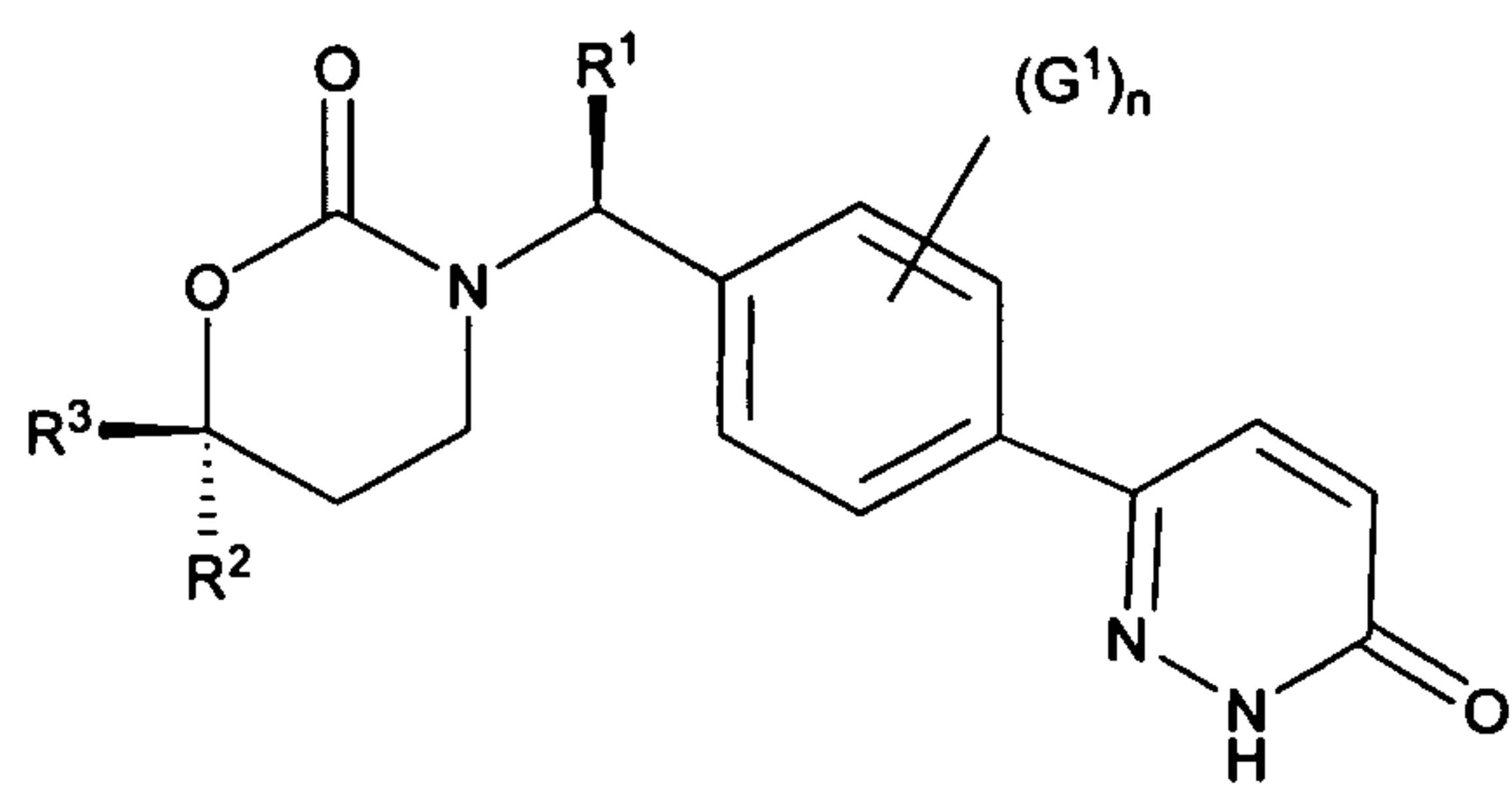
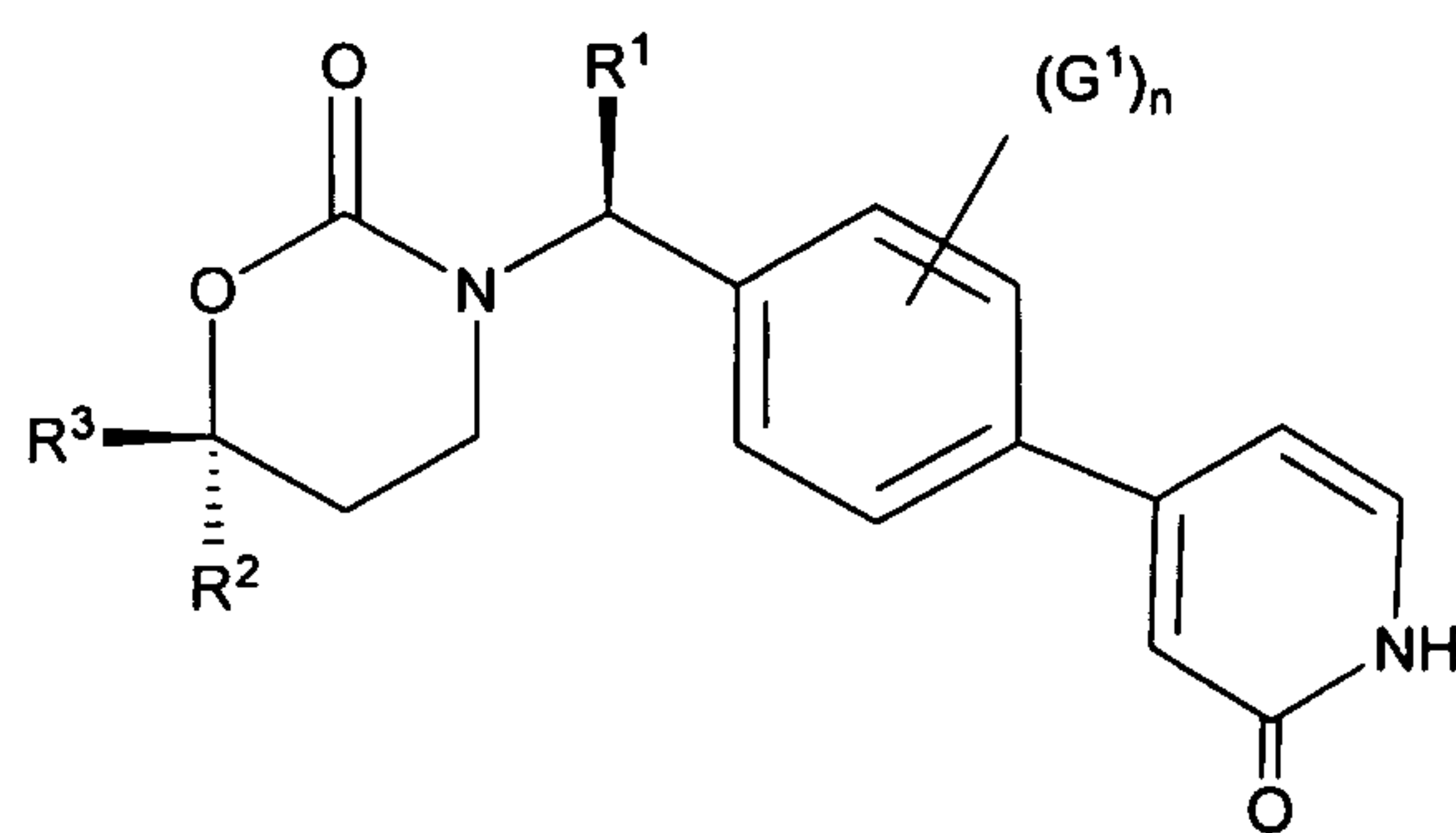
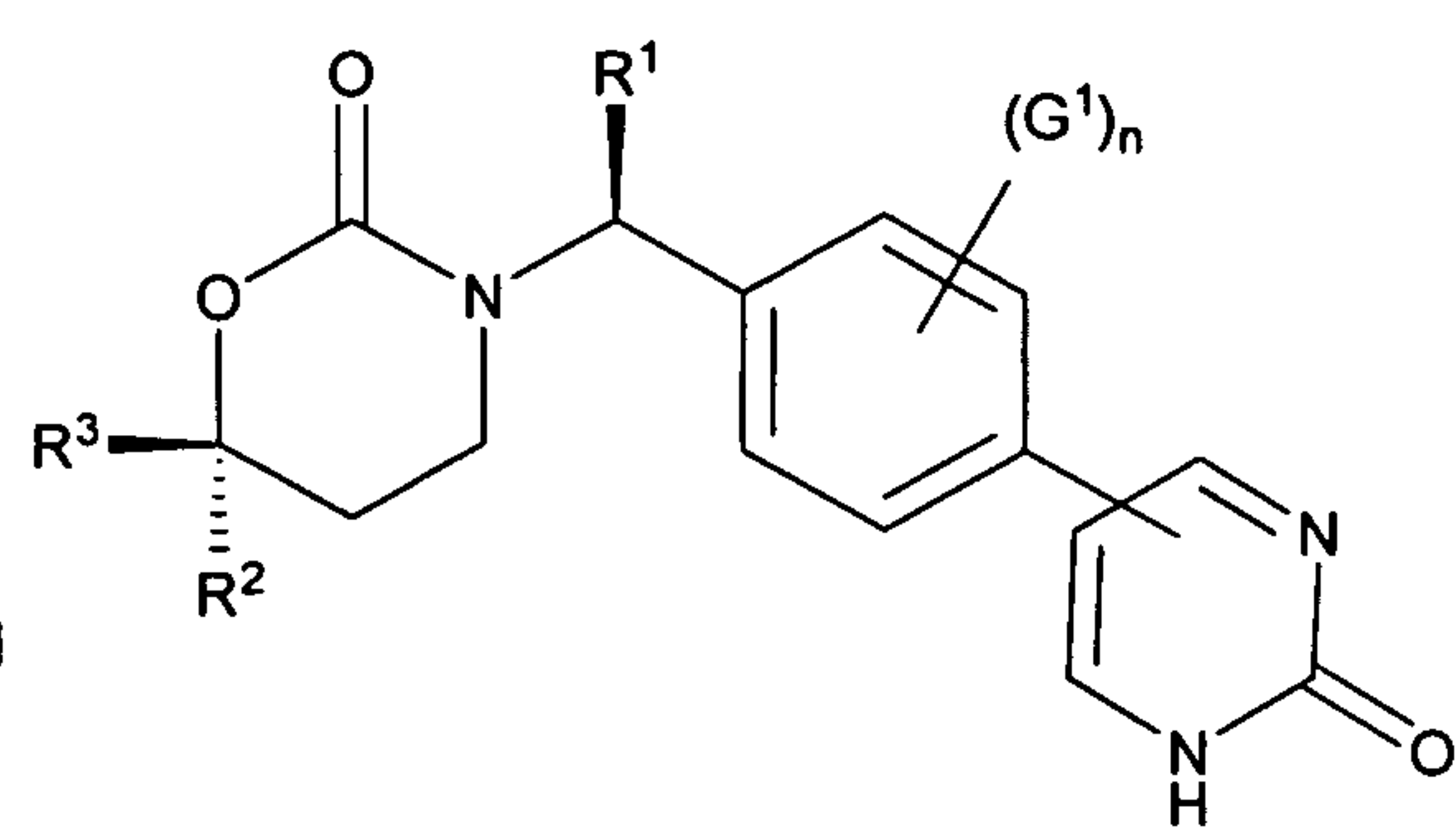
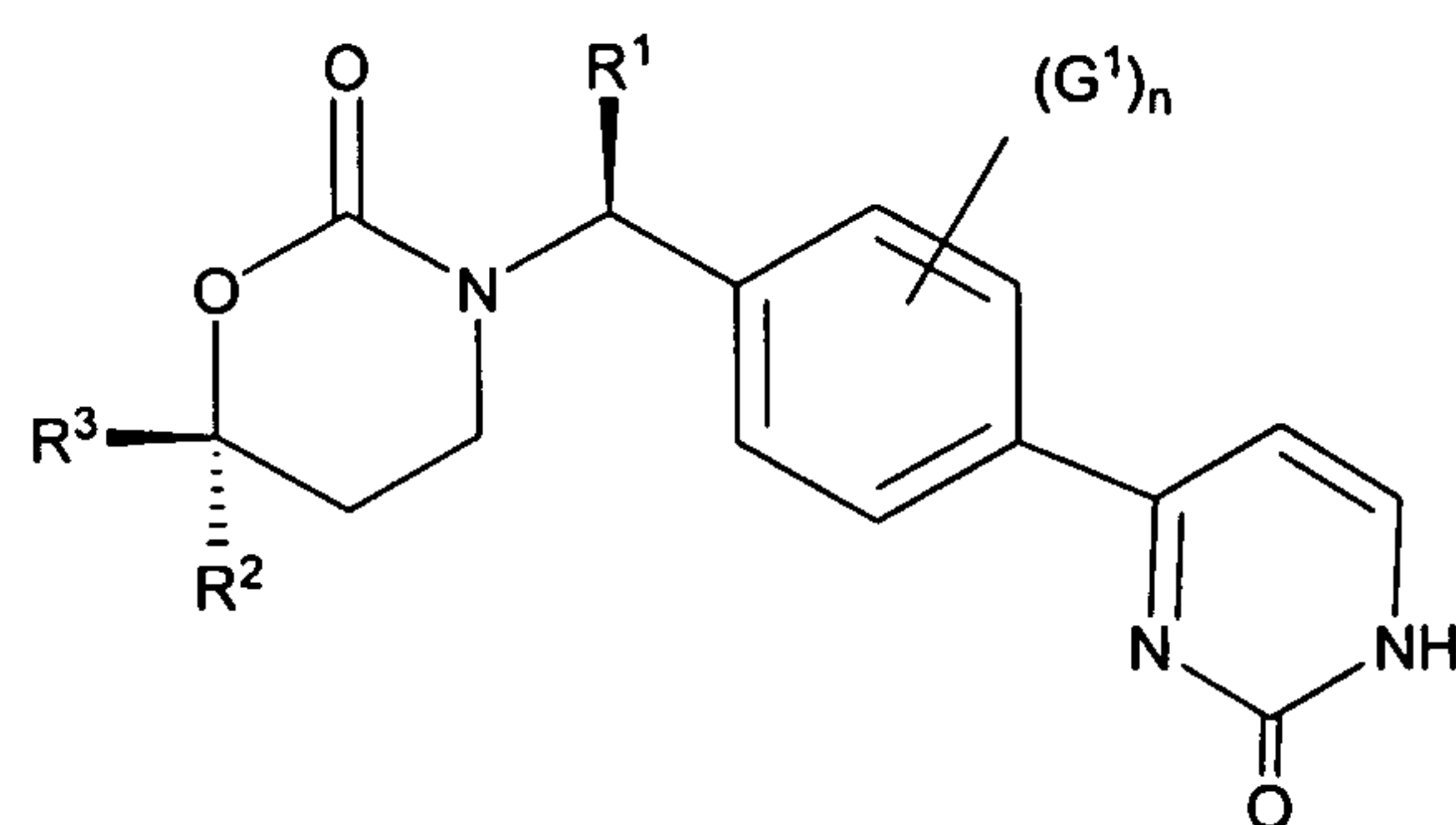
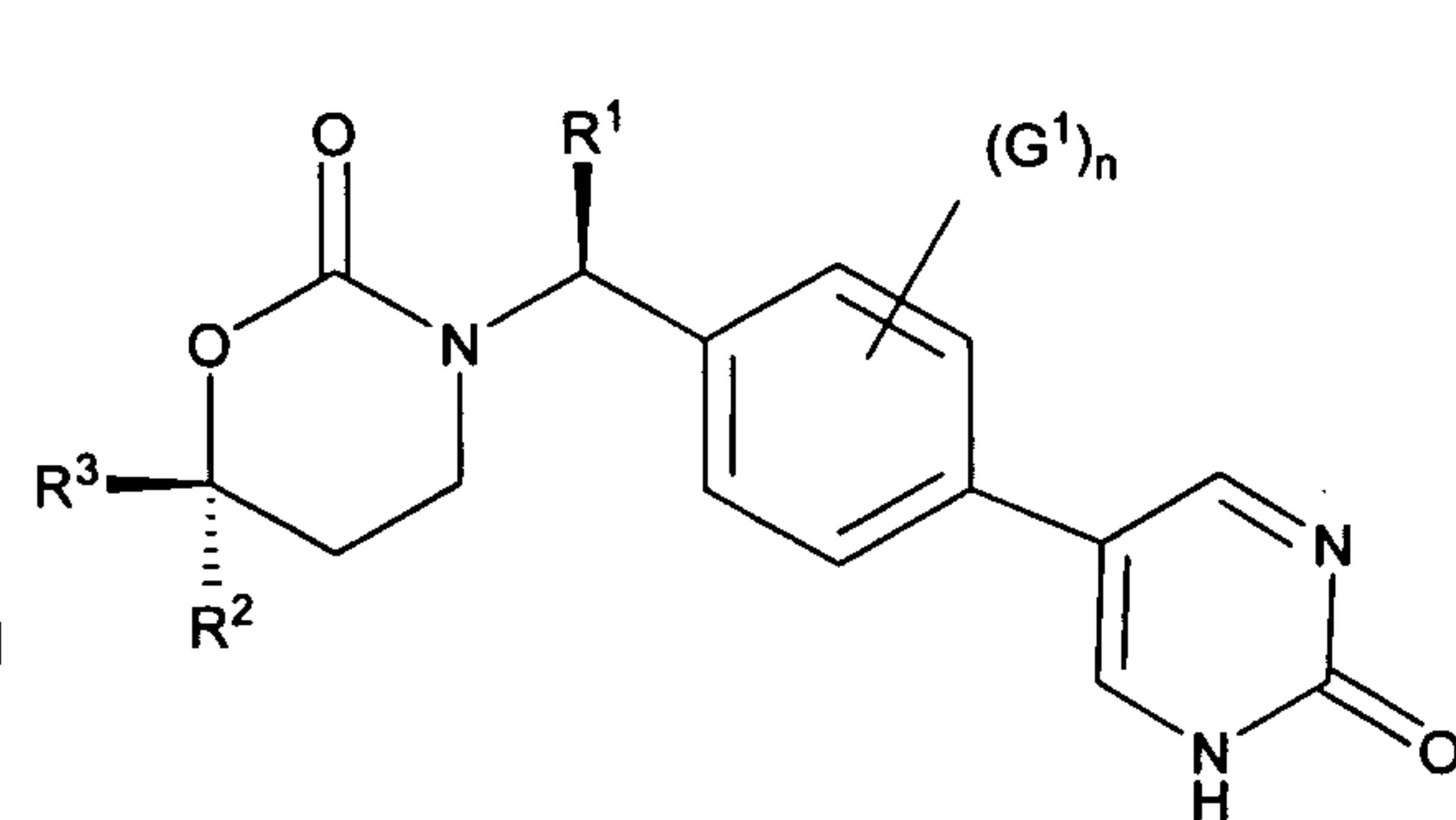
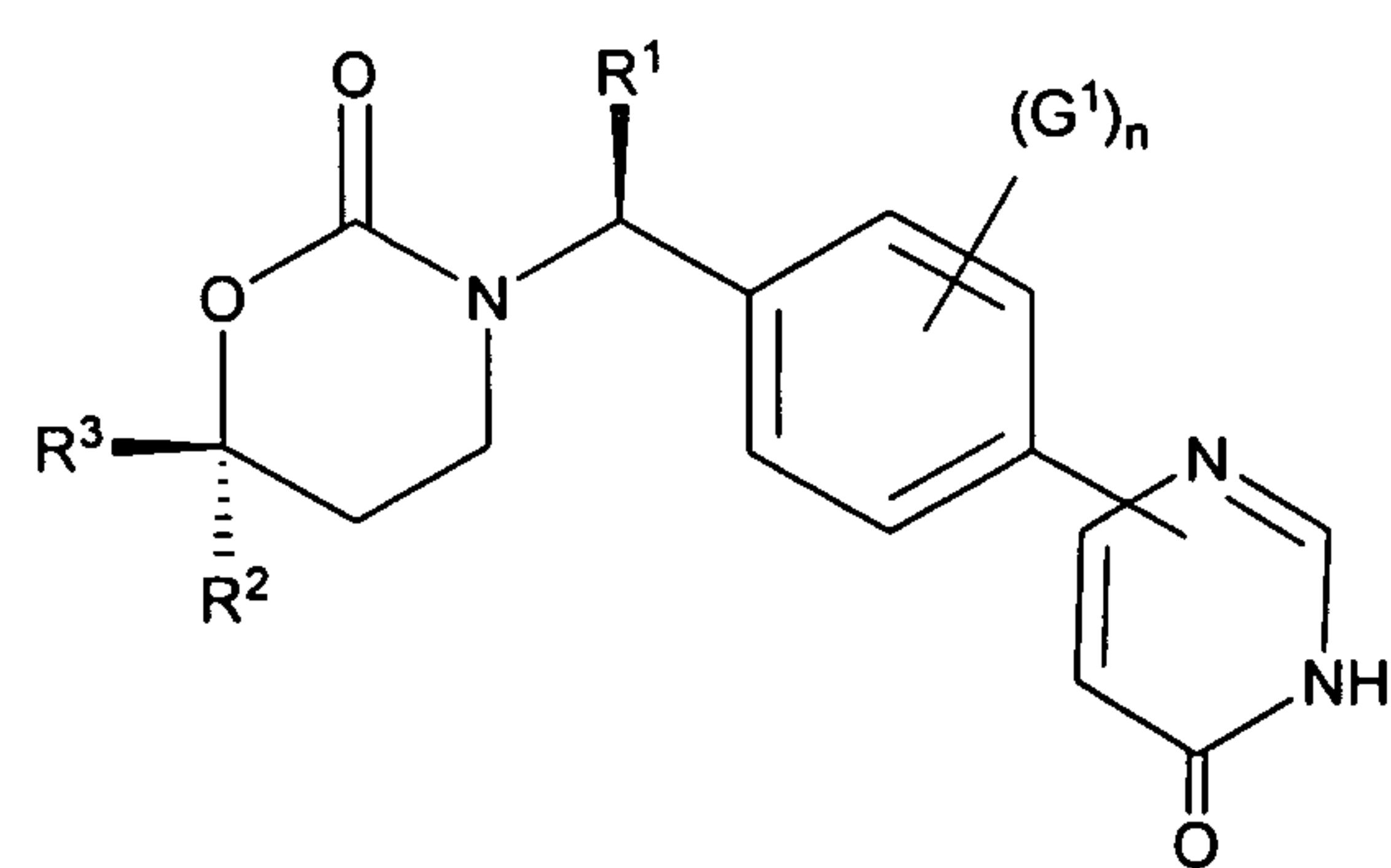
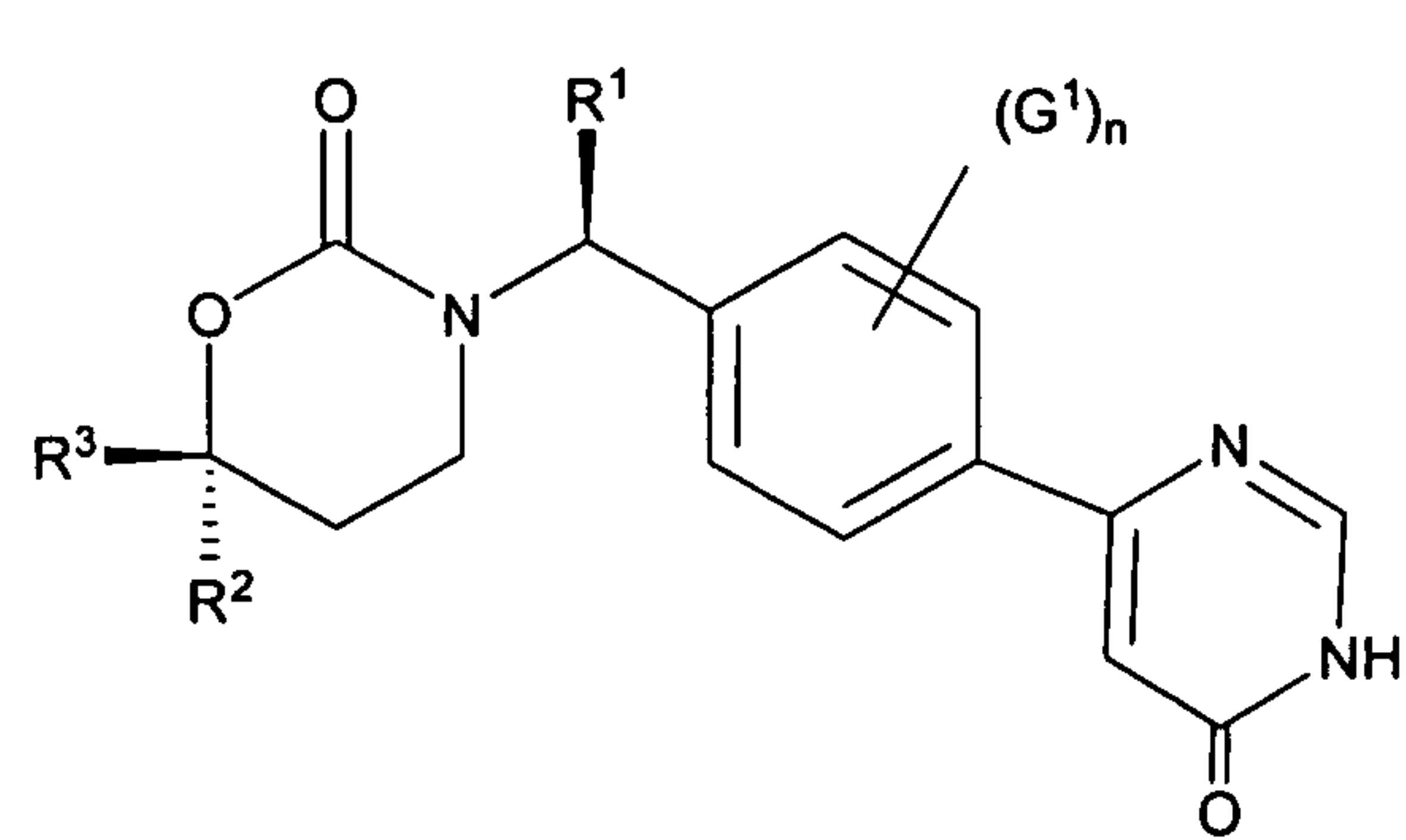
For each of the embodiments described in the paragraph immediately following Formulas In¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas In¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent on the substitutable ring nitrogen atom in the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas In¹⁻¹² is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, or (C₁-C₂)haloalkyl; and one or two ring carbon atoms in the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas In¹⁻¹² are optionally substituted with methyl or ethyl.

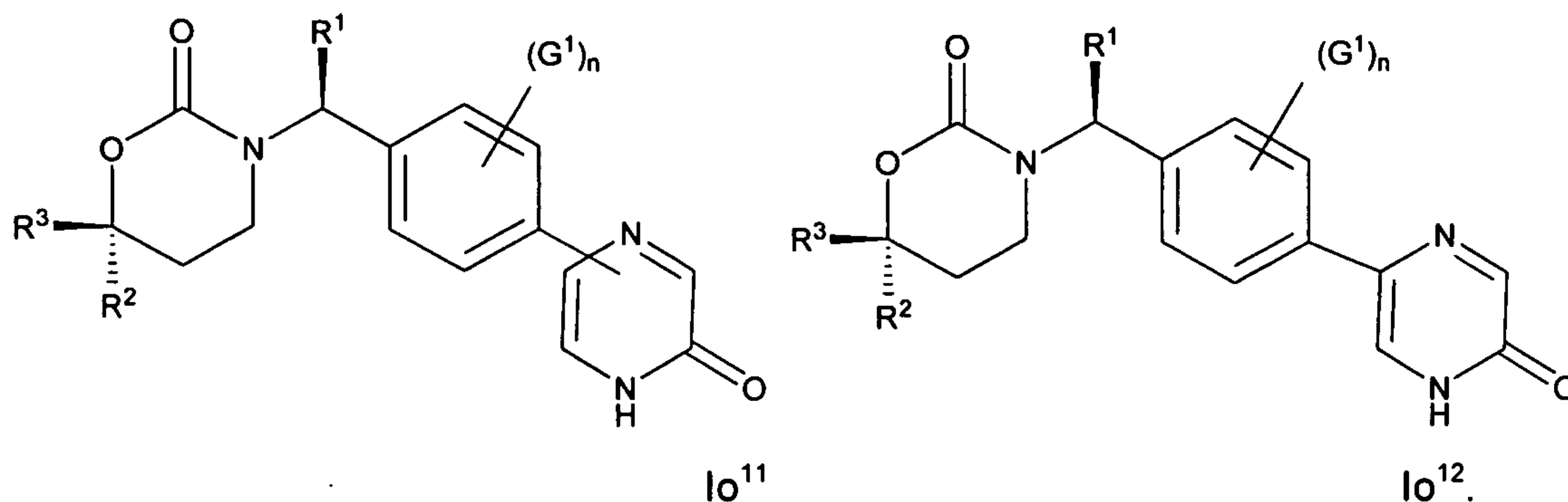
Another embodiment of the invention is a compound of any one for Formulas Io¹⁻¹², or a pharmaceutically acceptable salt thereof:



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 10^3  10^4  10^5  10^6  10^7  10^8  10^9  10^{10}

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In Formulas Io¹⁻¹², the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas Io¹⁻¹² are optionally substituted (substitution at ring carbons bonded to hydrogen and at nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a “substitutable ring nitrogen atom”) with up to four substituents as described above for Cy²; suitable values for G¹ are as described for G¹ in Formula If; n is 0, 1, 2 or 3; and suitable substituents for Cy² and suitable values for R¹, R² and R³ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, n is 0, 1, 2 or 3; suitable values for G¹ and substituents for the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas Io¹⁻¹² are as described for G¹ and G², respectively, in Formula If, and values for R¹, R² and R³ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, n is 0, 1, 2 or 3; suitable values for G¹ include (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom in the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas Io¹⁻¹² include C₁-C₄ alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl and C₁-C₄ haloalkyl; suitable substituents for a ring carbon atom in the oxopyridyl, oxopyridazinyl, oxopyrimidinyl and oxopyrazinyl rings in Formulas Io¹⁻¹² include fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl and (C₁-C₄)alkylcarbonylamino; and suitable values for R¹, R² and R³ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. In another alternative, the embodiments described in this paragraph exclude the compound exemplified in Example 221 and Example 313 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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For each of the embodiments described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹⁻¹², R¹ is preferably methyl or ethyl; and R³ is

5 MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹⁻¹², R¹ is preferably methyl or ethyl; and R³ is

10 H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-

15 C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl optionally

20 substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹⁻¹², R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-

25 methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately

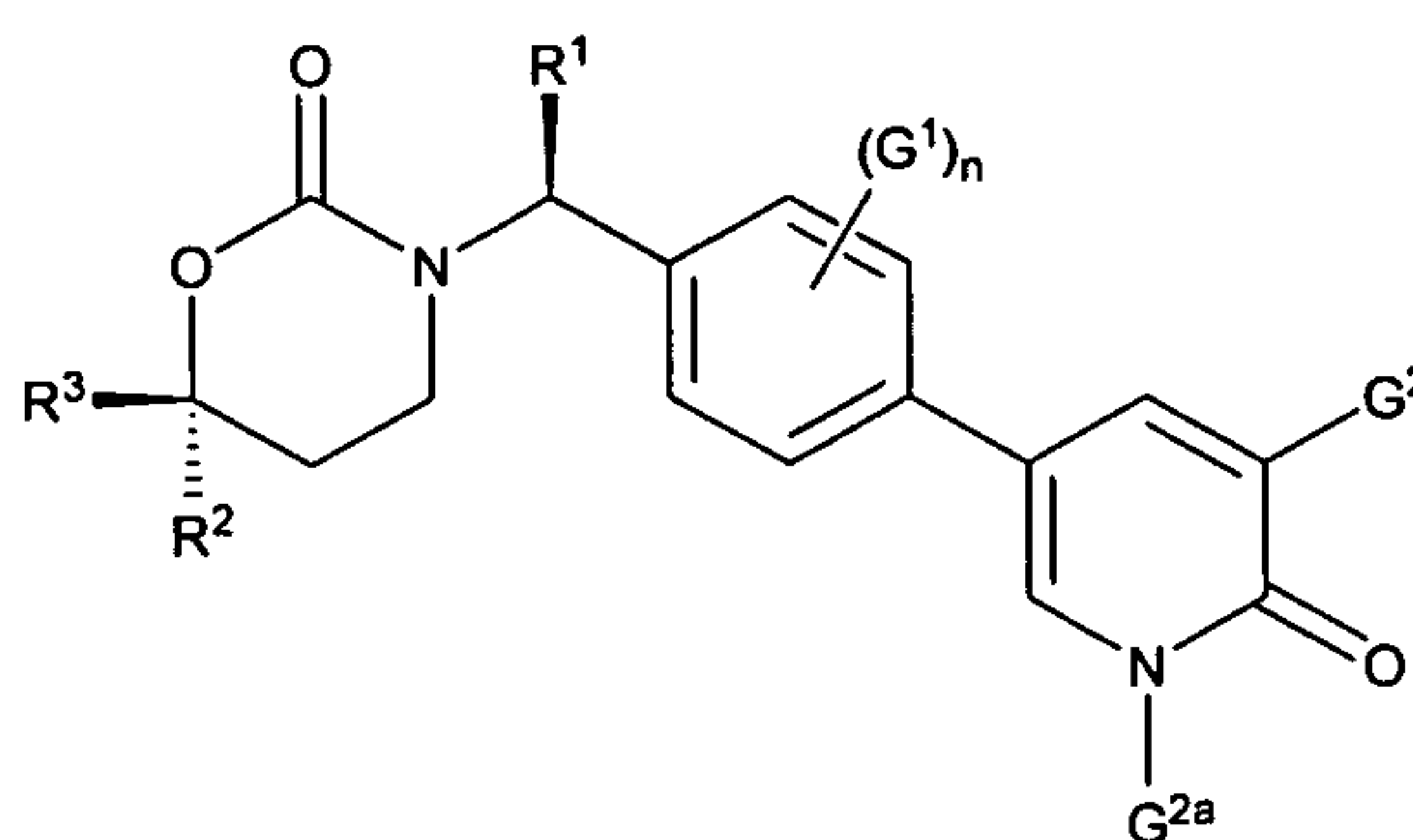
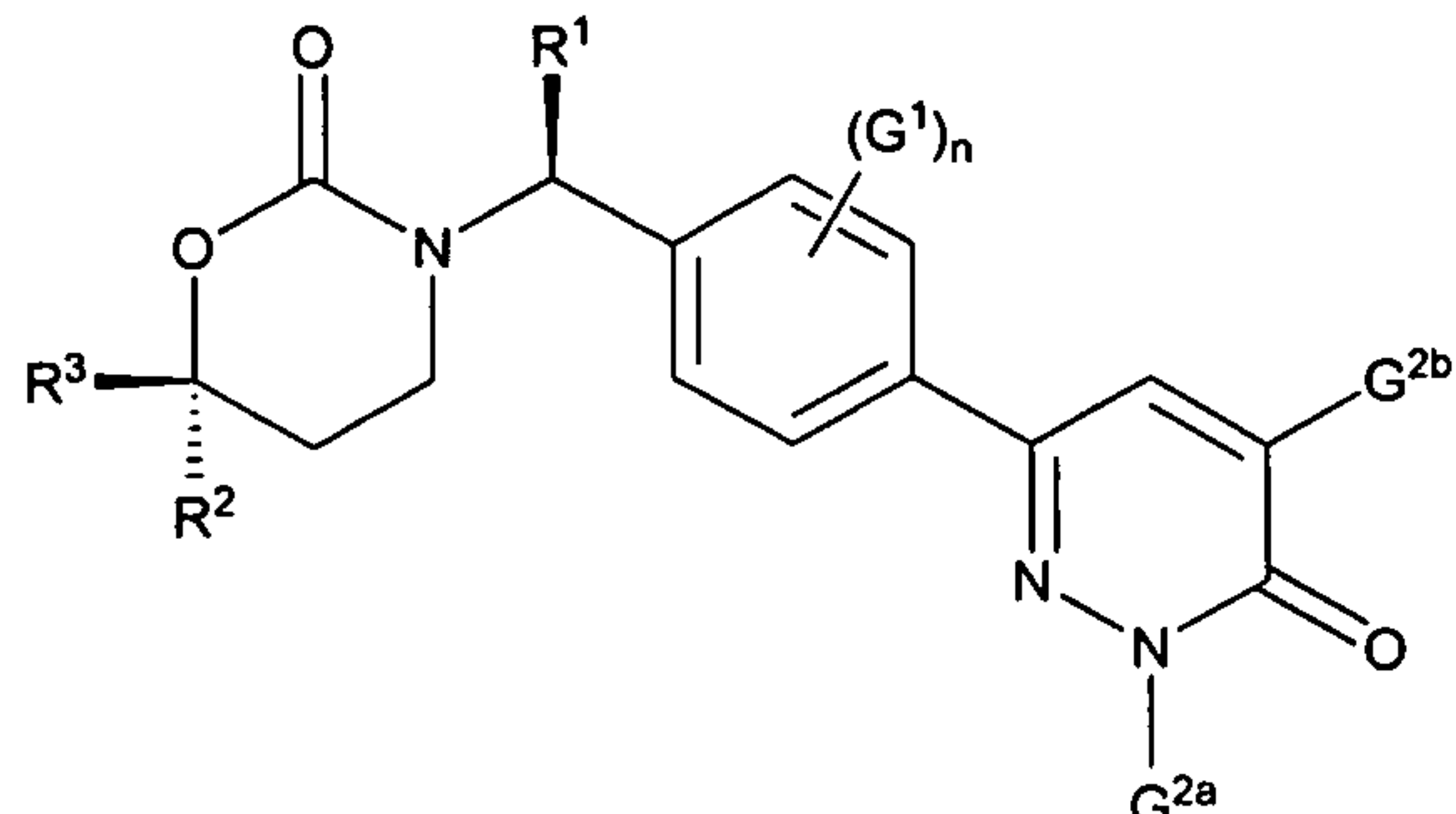
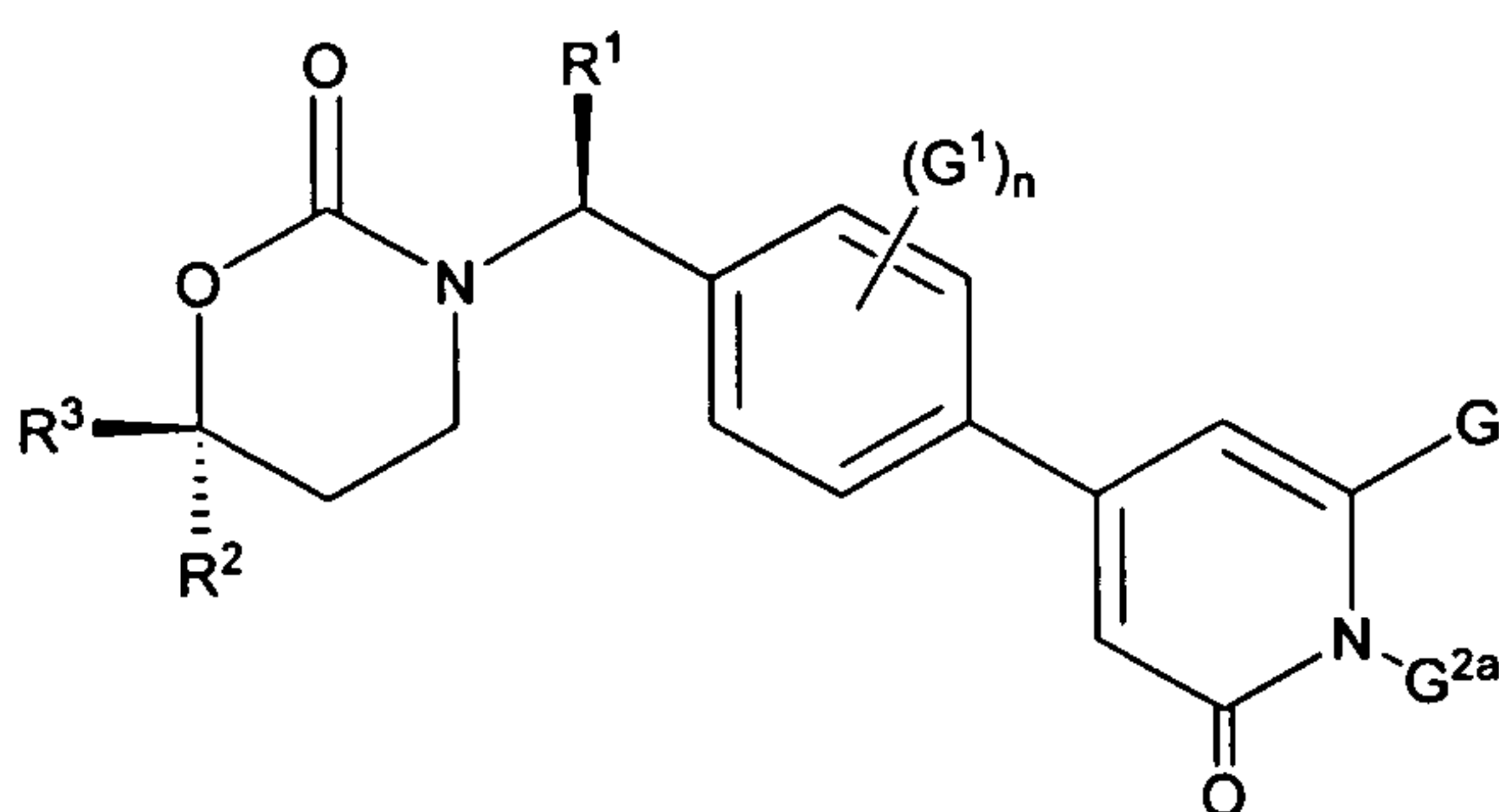
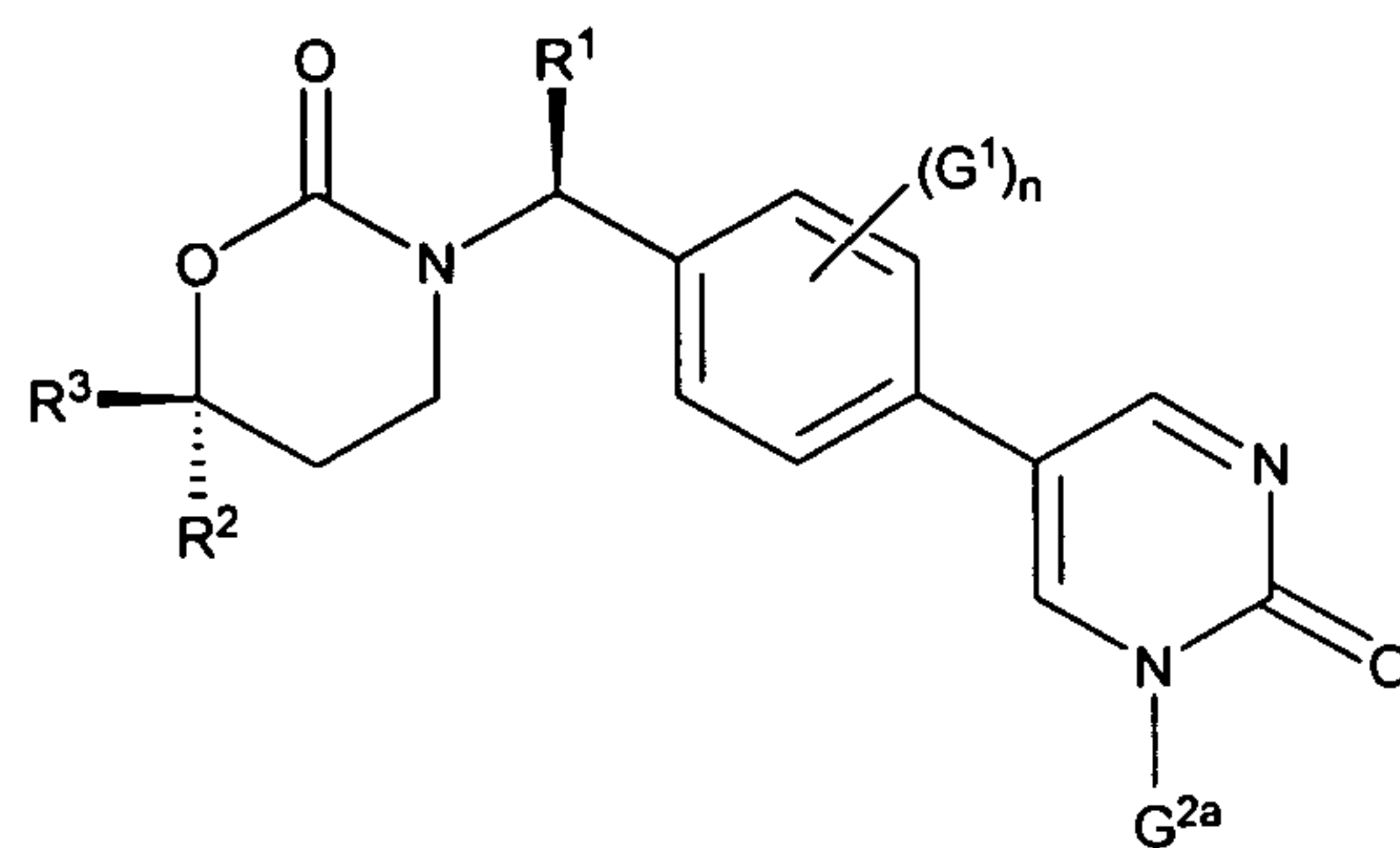
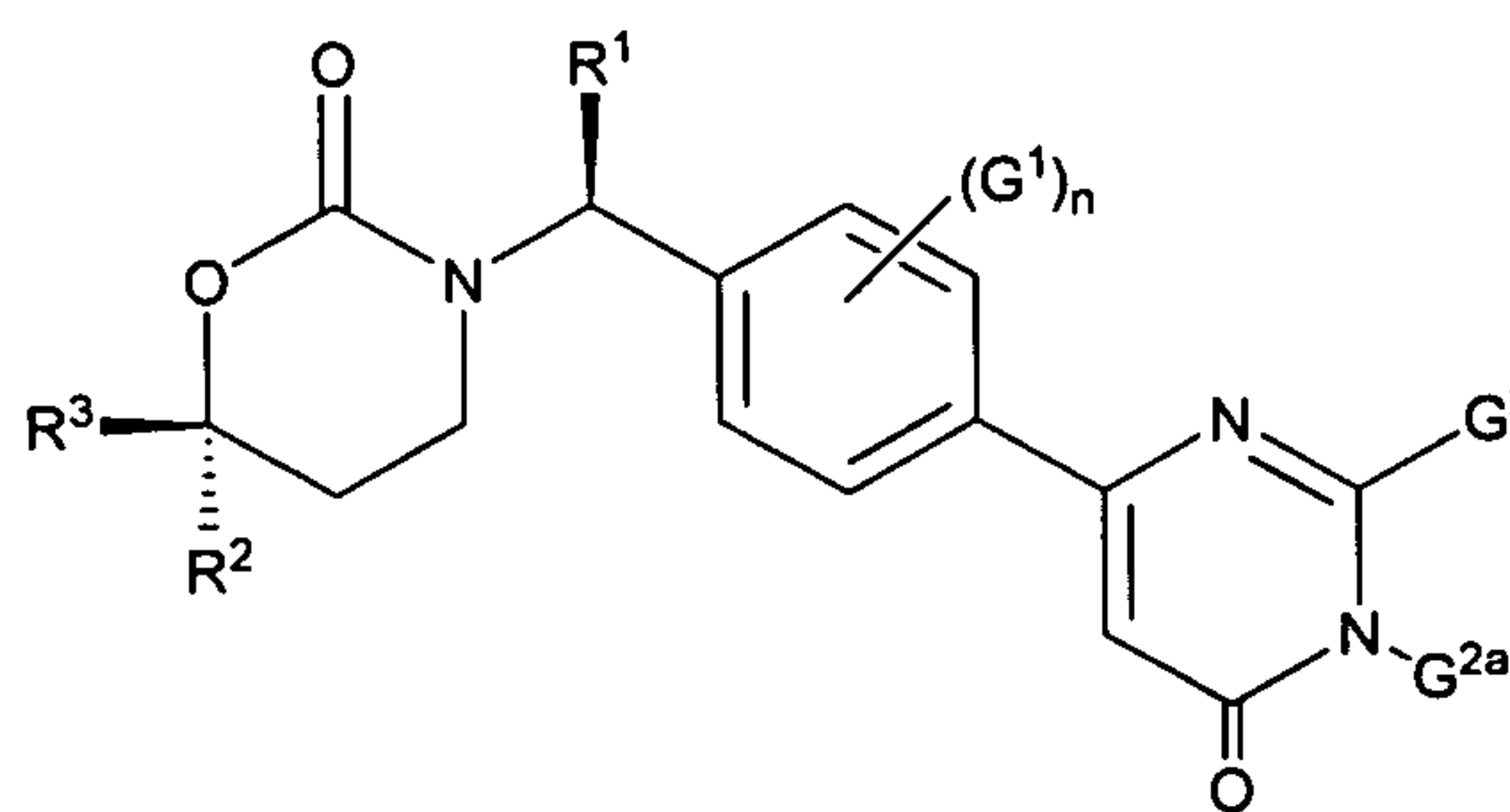
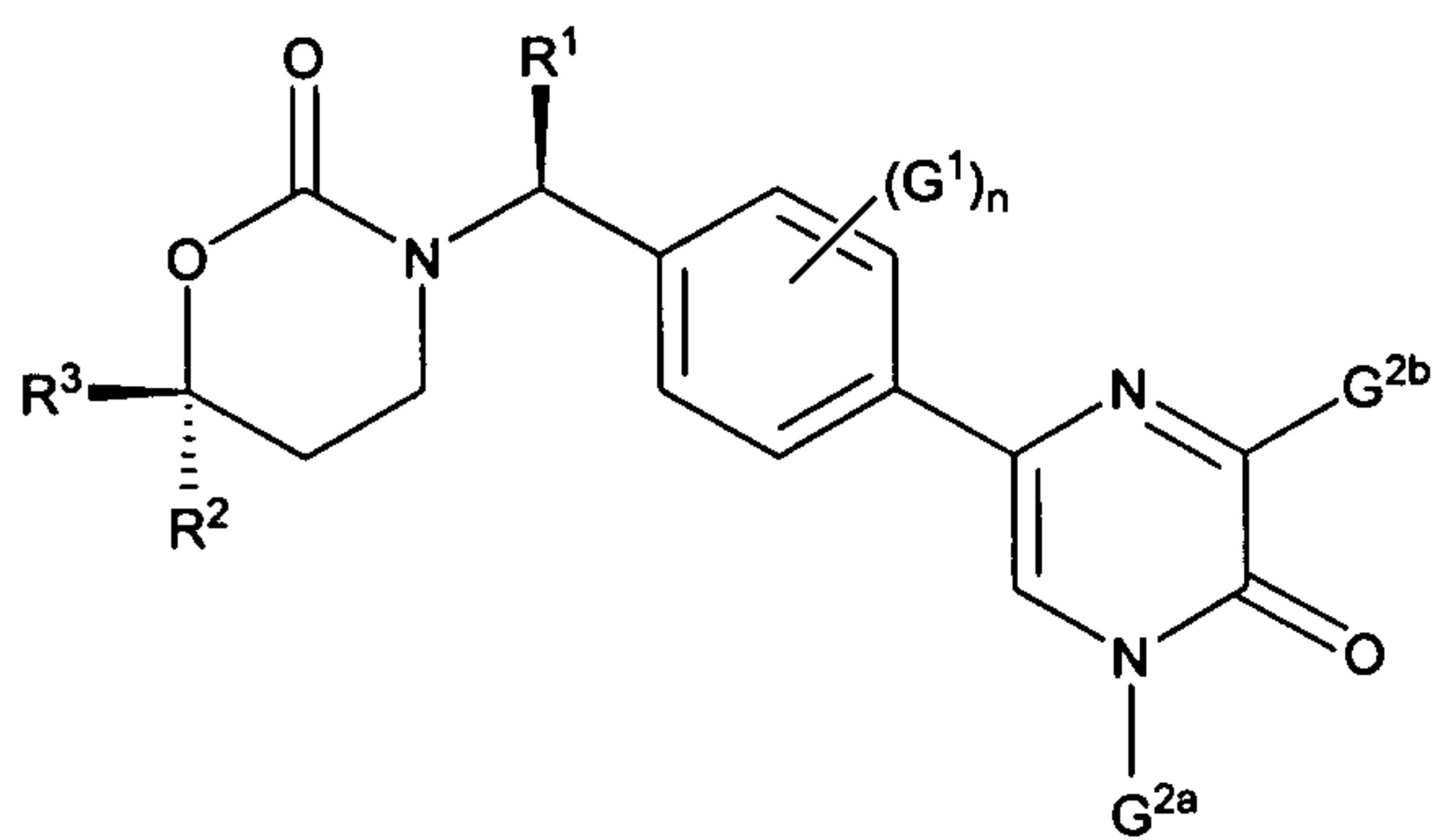
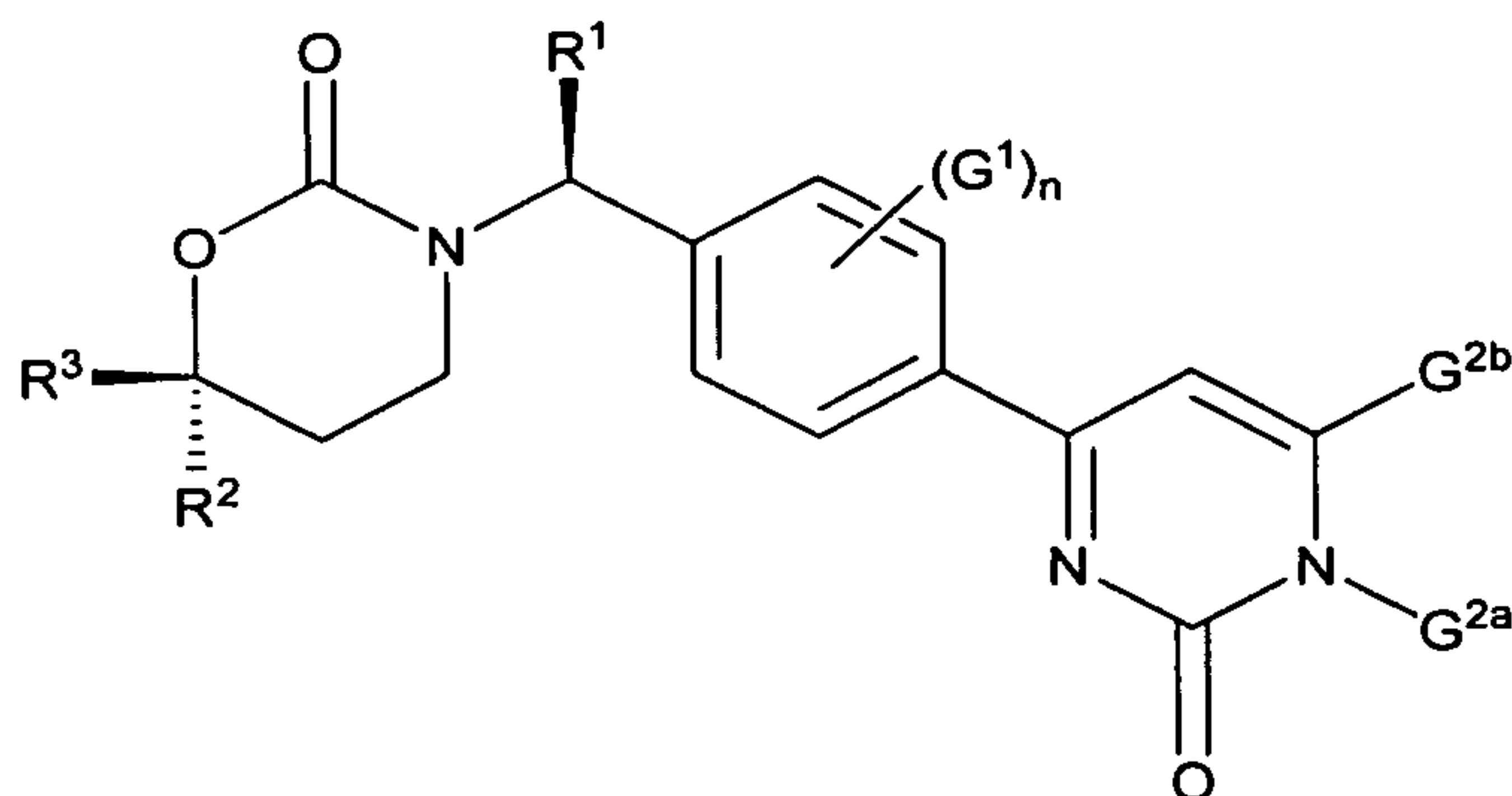
30 following Formulas Io¹⁻¹², R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent on the substitutable ring nitrogen atom in the oxodihydropyridyl, oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas Io¹⁻¹² is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, or

35 (C₁-C₂)haloalkyl; and one or two ring carbon atoms in the oxodihydropyridyl,

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oxodihydropyridazinyl, oxodihydropyrimidinyl and oxodihydropyrazinyl rings in Formulas I^{o1-12} are optionally substituted with methyl or ethyl.

Another embodiment of the invention is a compound represented by any one of Formulas I^{p1-7}, or a pharmaceutically acceptable salt thereof:

Ip¹Ip²Ip³Ip⁴Ip⁵Ip⁶Ip⁷.

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In Formulas Ip¹⁻⁷, G¹ is (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano or nitro; n is 0, 1 or 2; G^{2a} is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl or (C₁-C₄)haloalkyl; G^{2b} is hydrogen, fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl or (C₁-C₄)alkylcarbonylamino; and suitable values for R¹, R² and R³ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. In another alternative, the embodiments in this paragraph exclude the compound exemplified in Example 221 and Example 313 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

For each of the embodiments described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiments described in the paragraph immediately following Formulas Ip¹⁻⁷, R¹ is preferably methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Ip¹⁻⁷, R¹ is preferably methyl or ethyl; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Ip¹⁻⁷, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Ip¹⁻⁷, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

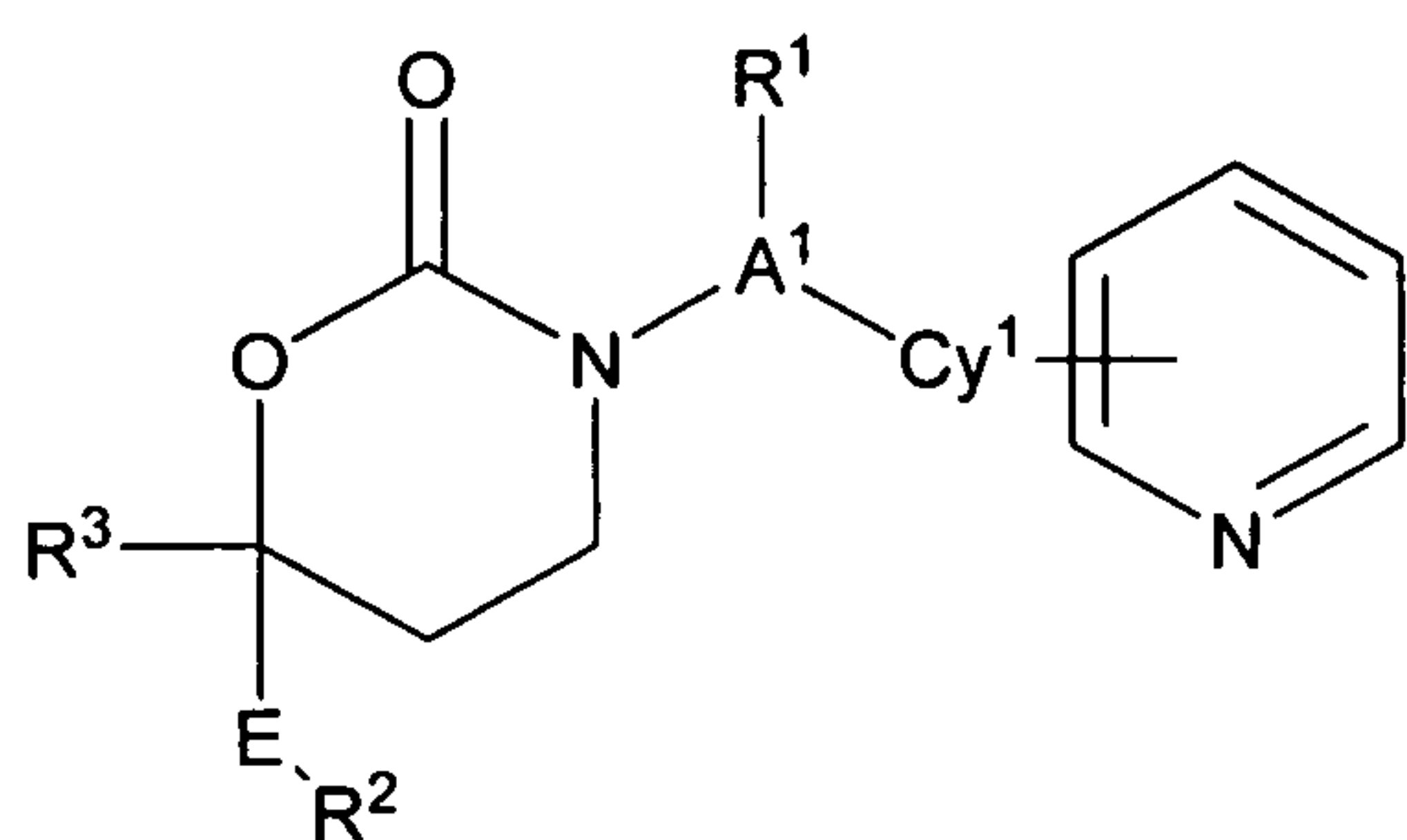
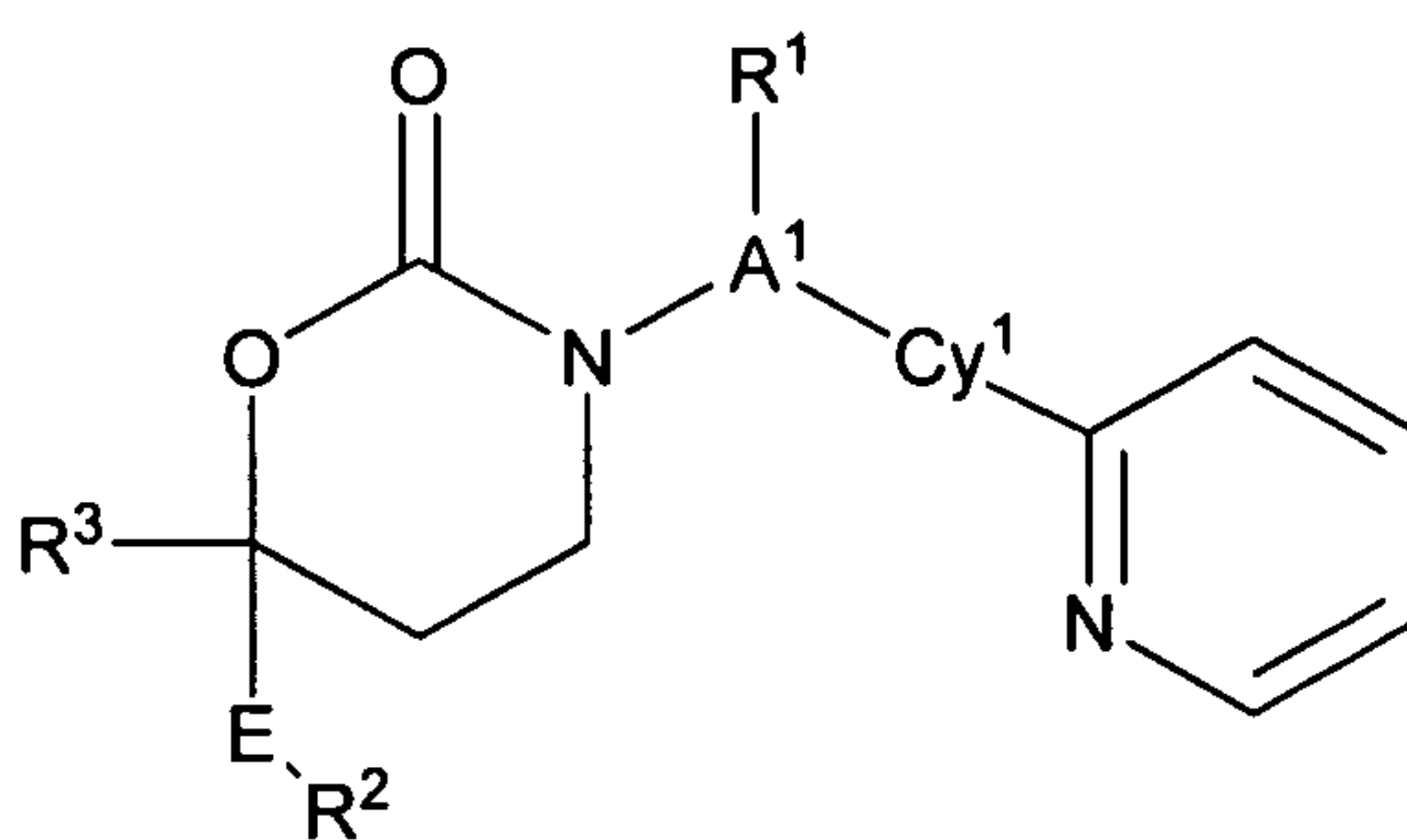
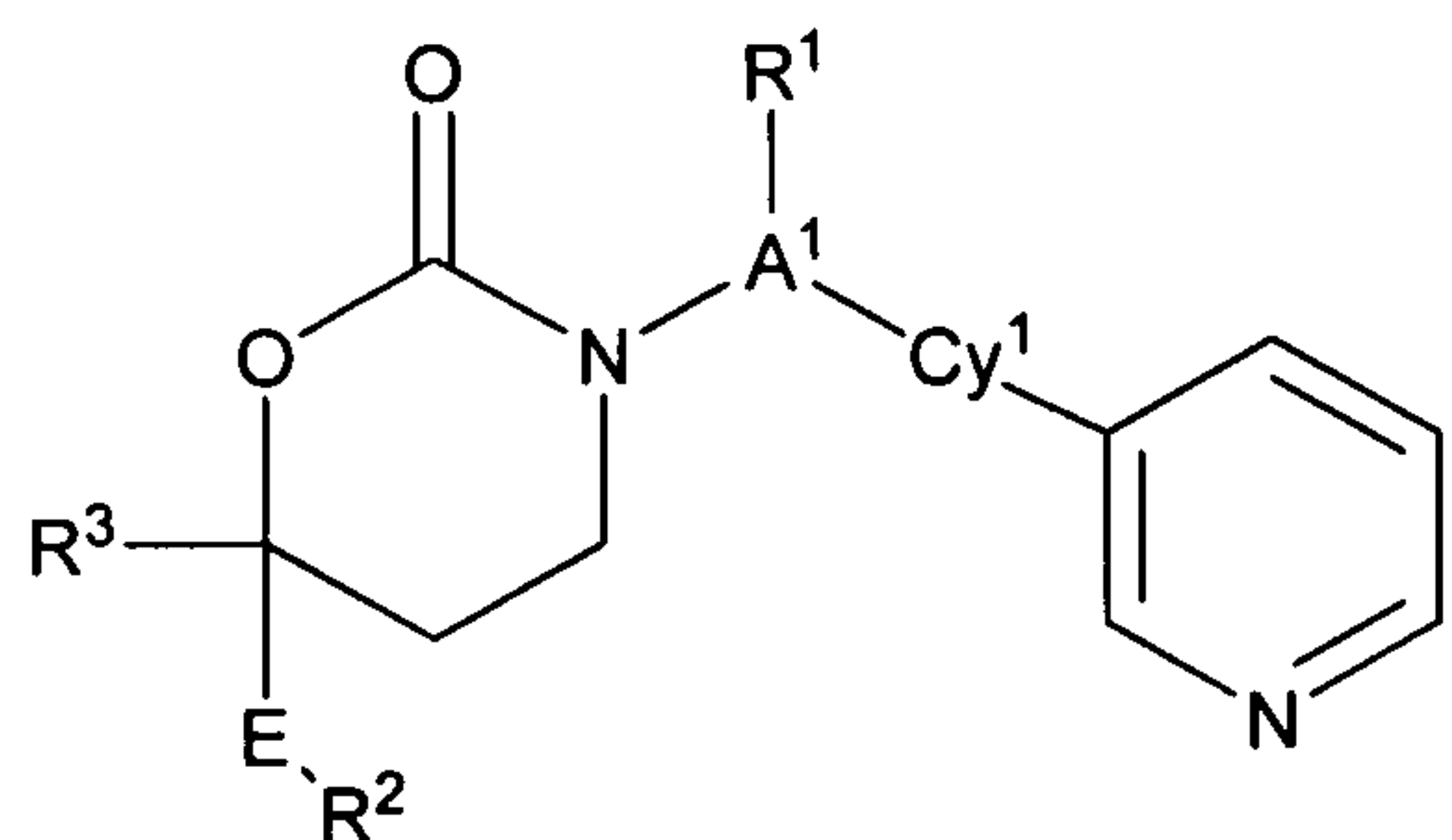
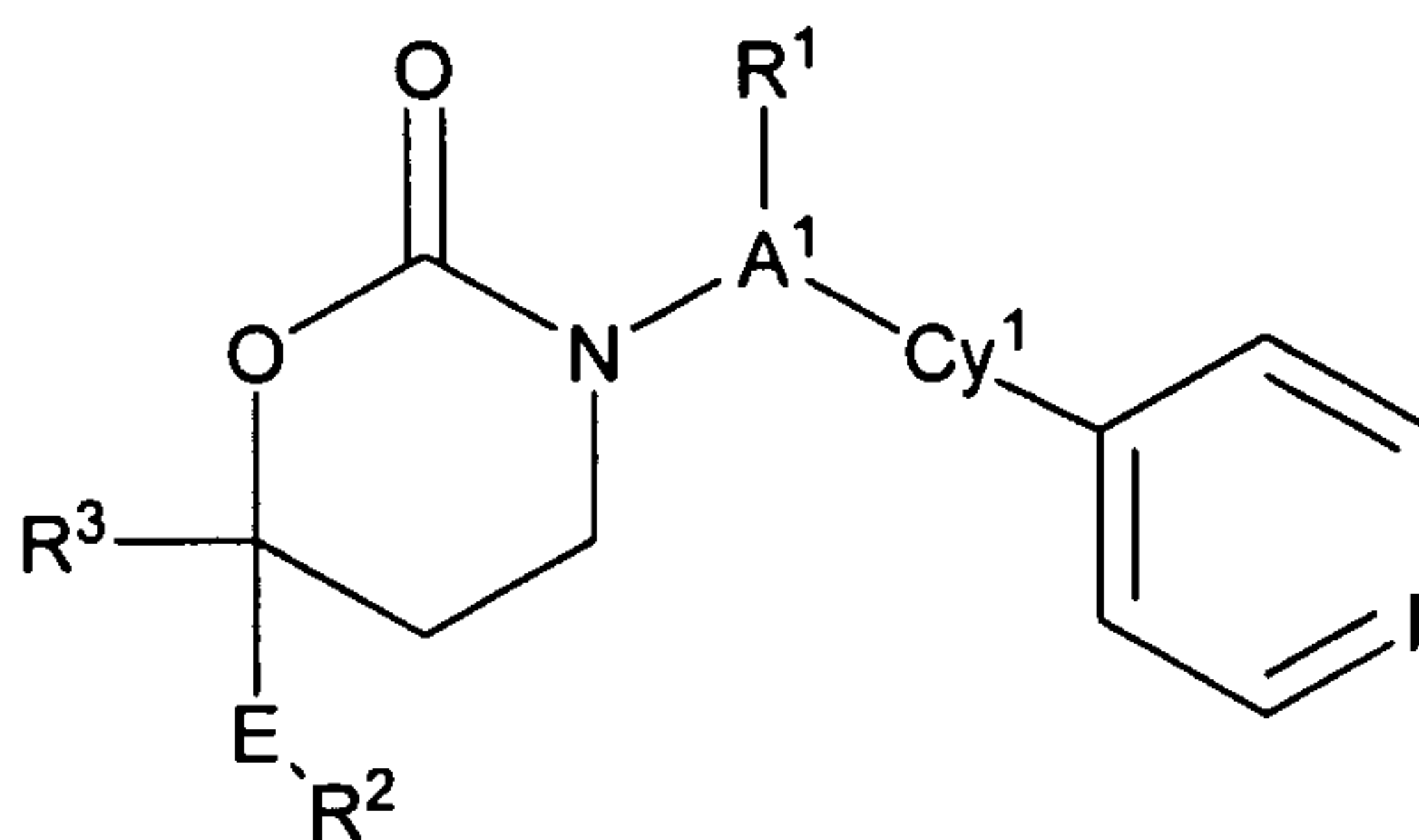
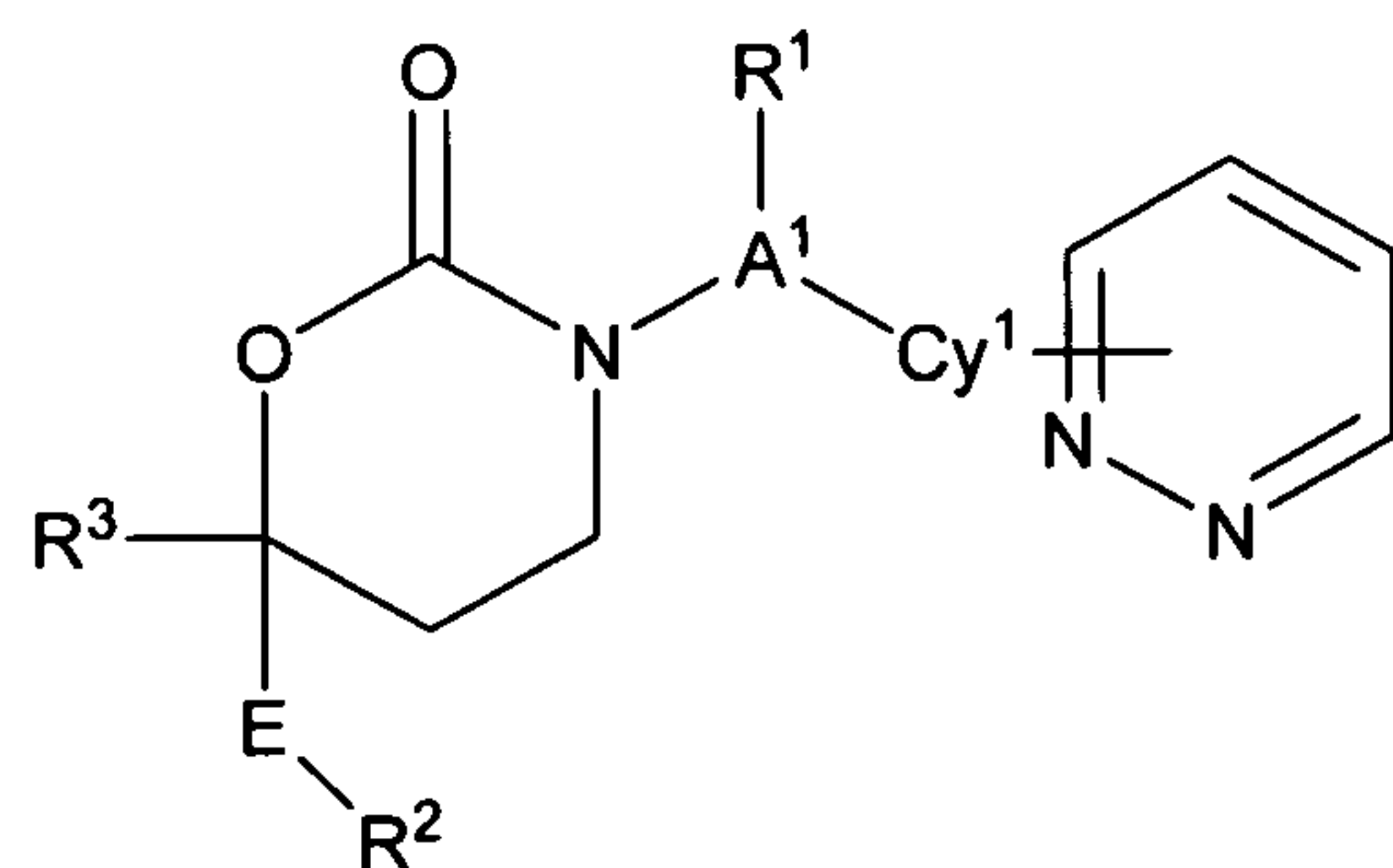
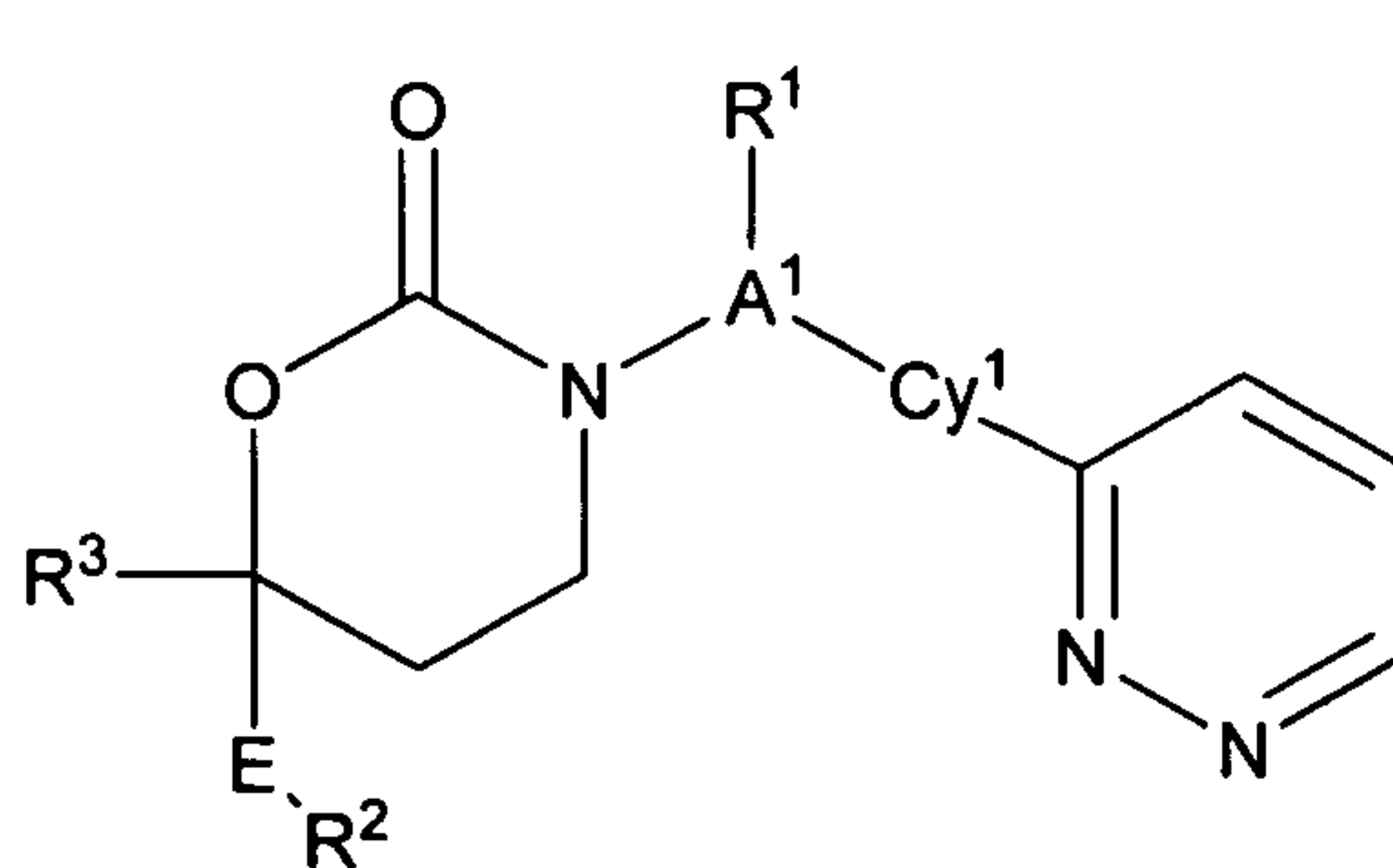
For each of the embodiments described in the paragraph immediately following Formulas Ip¹⁻⁷, R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

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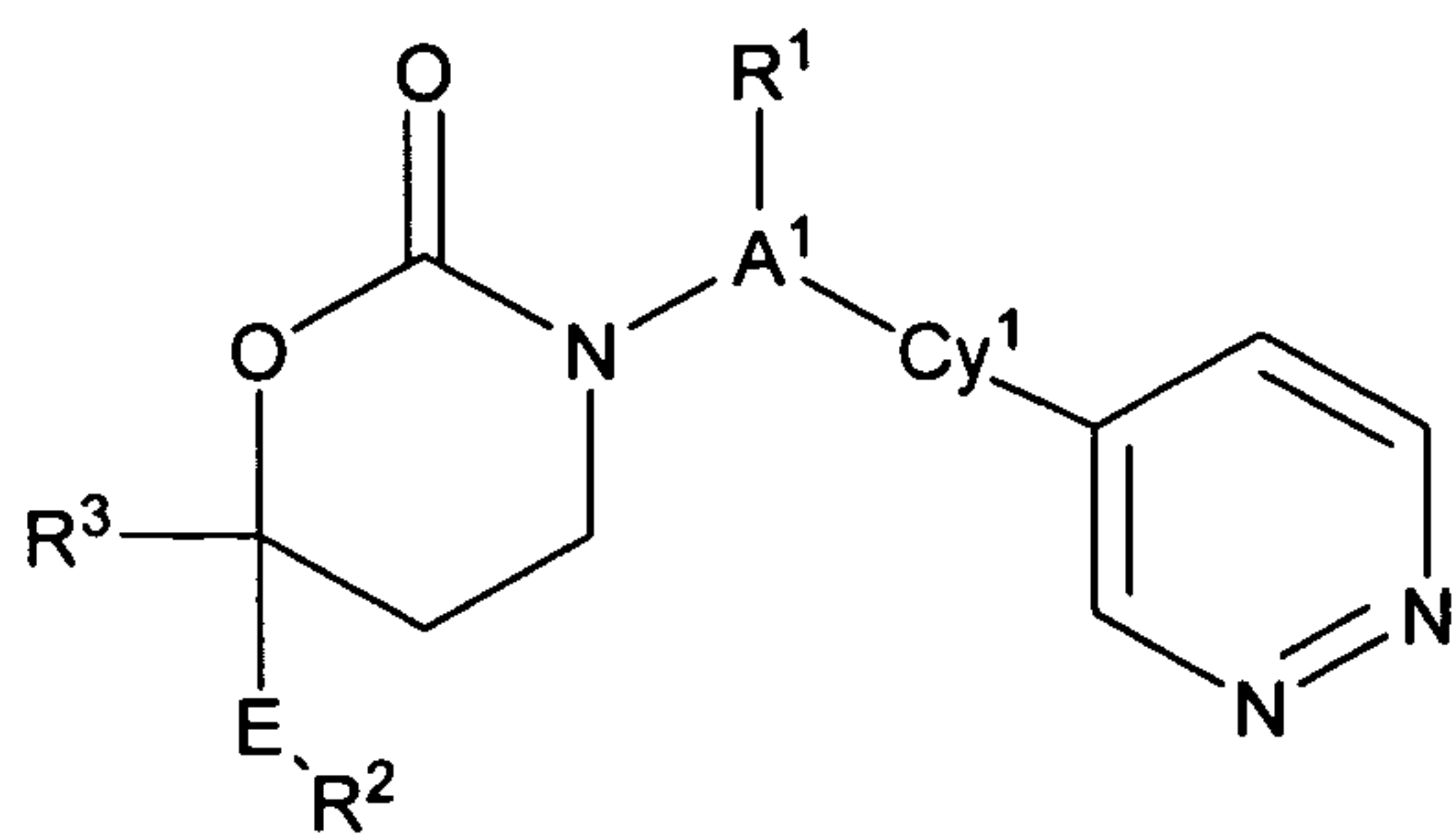
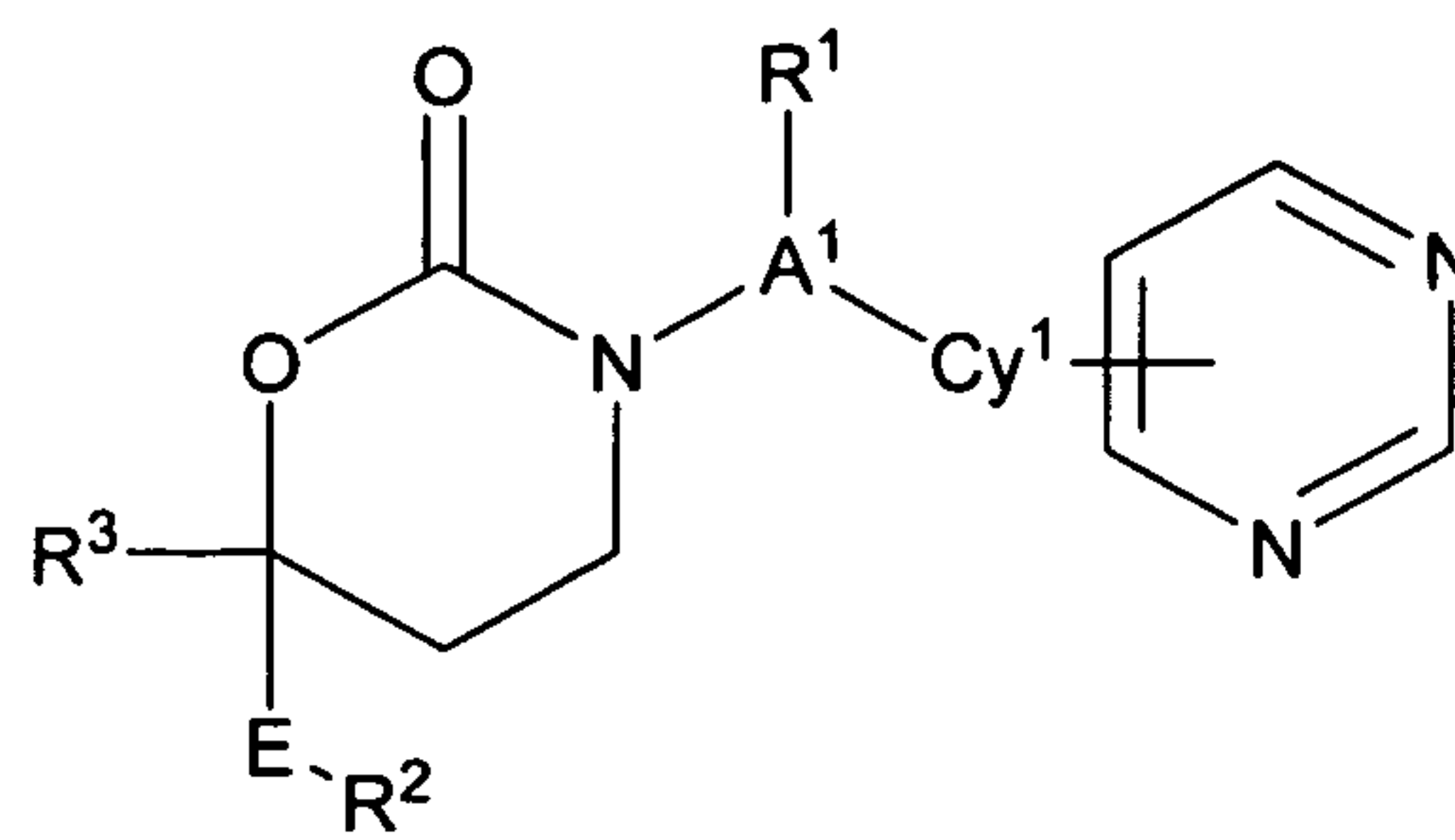
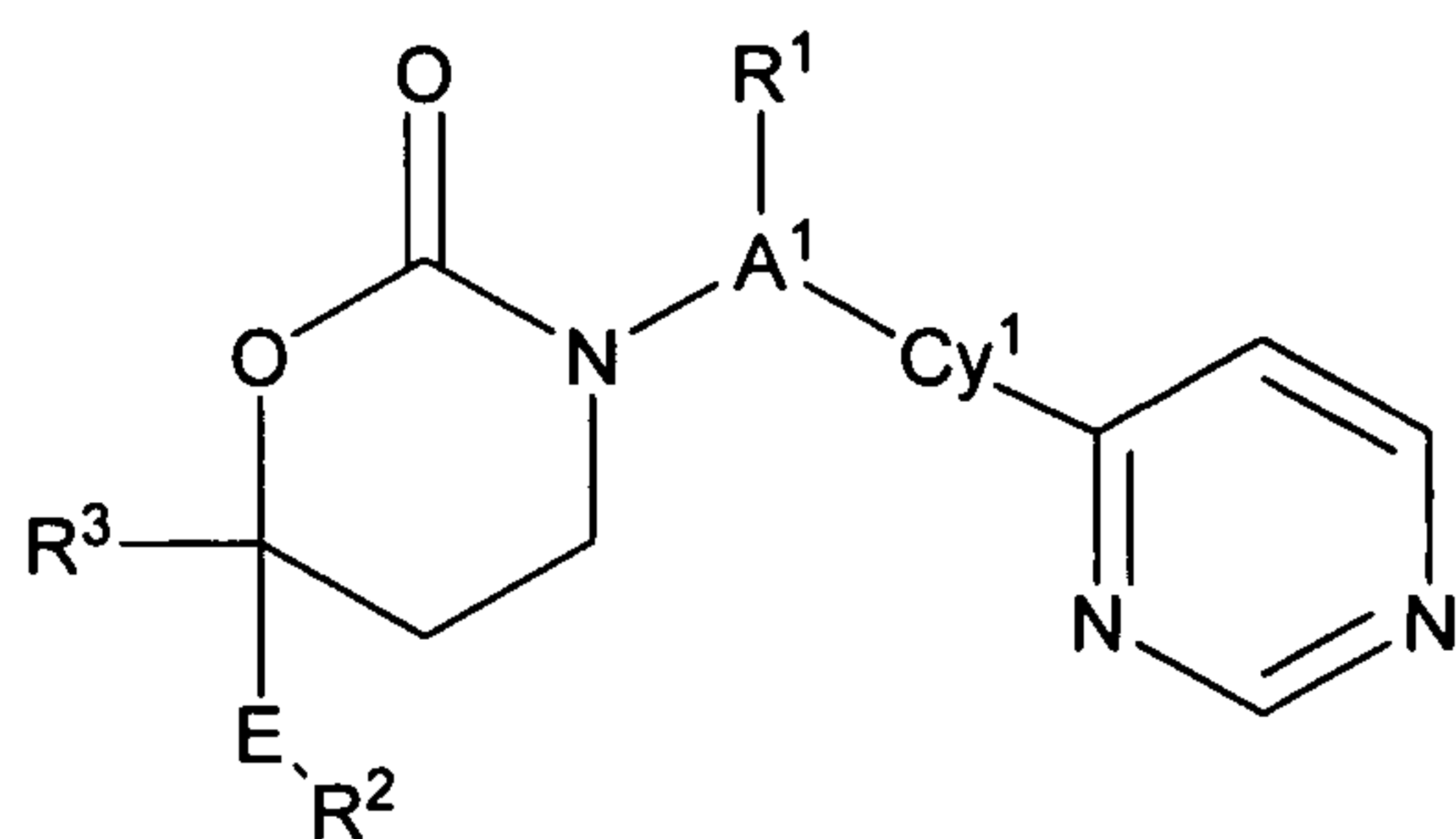
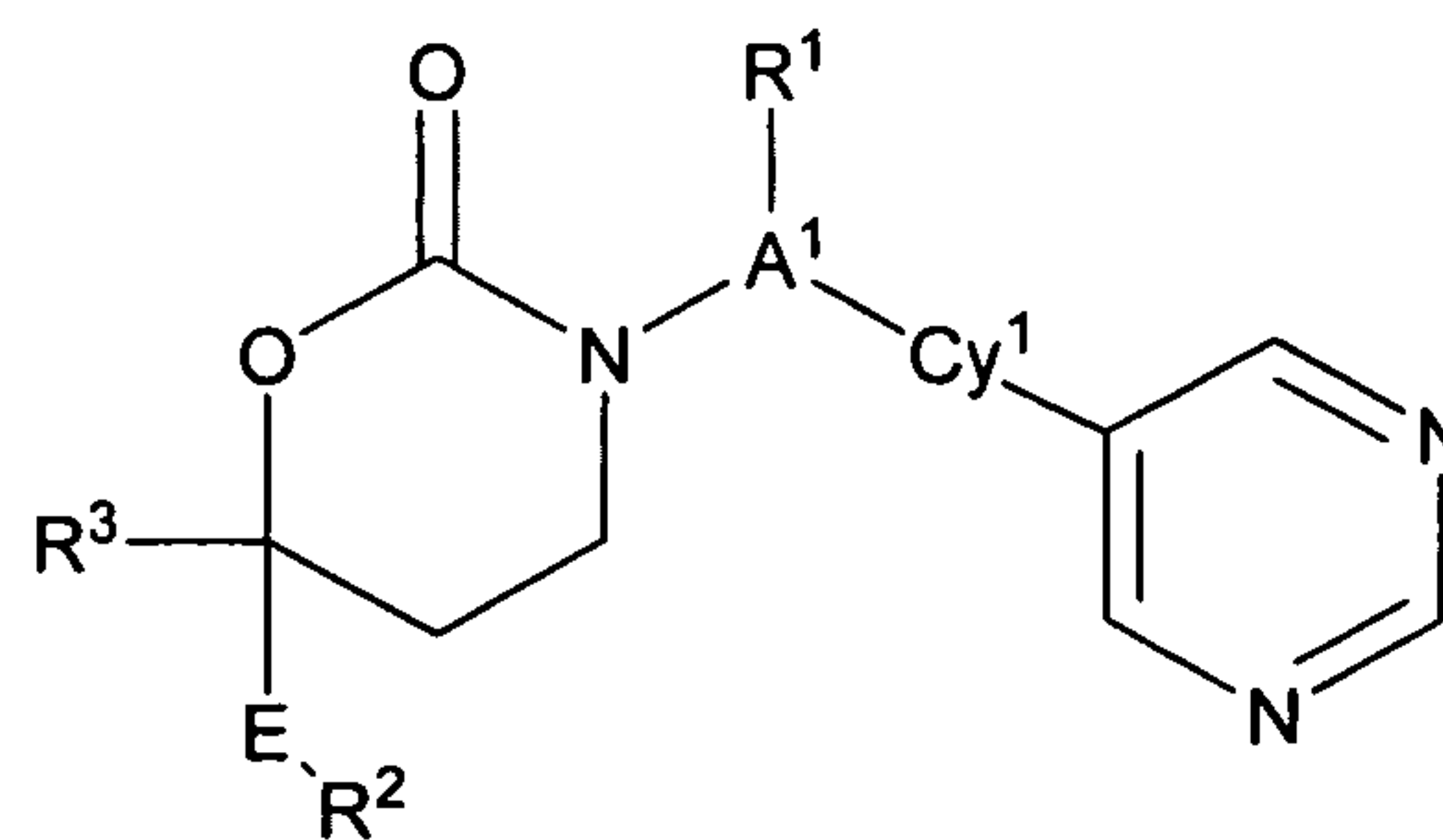
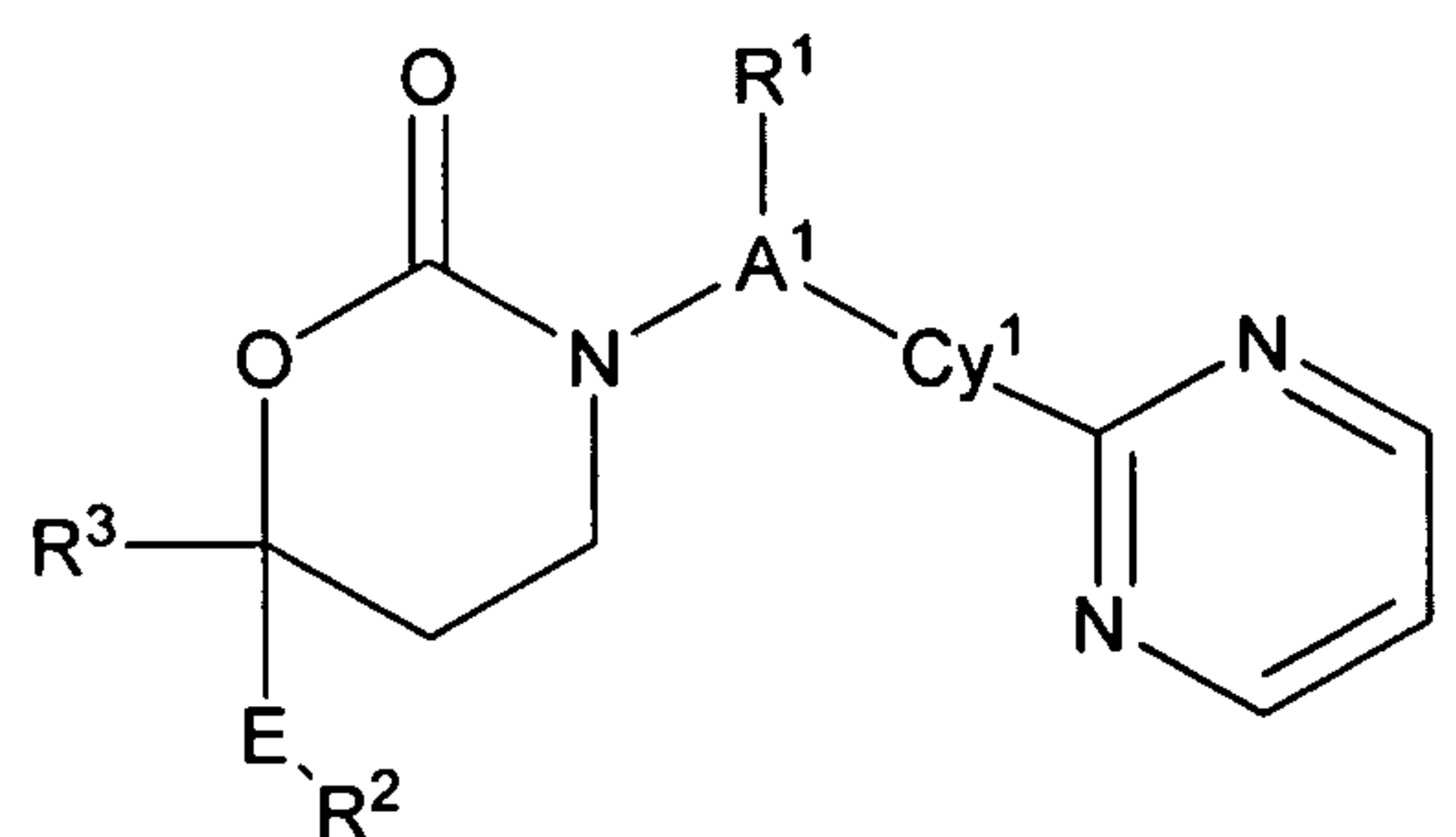
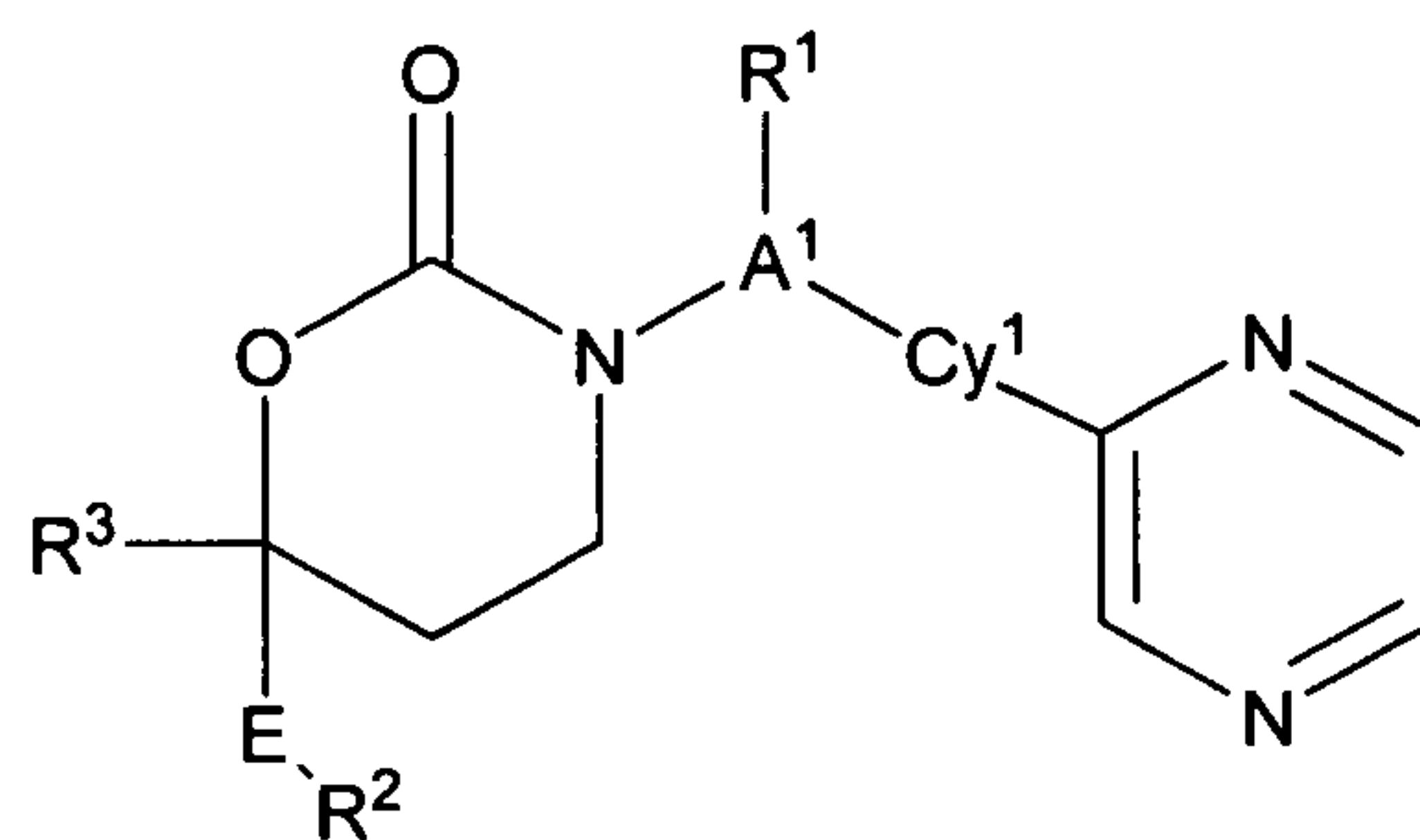
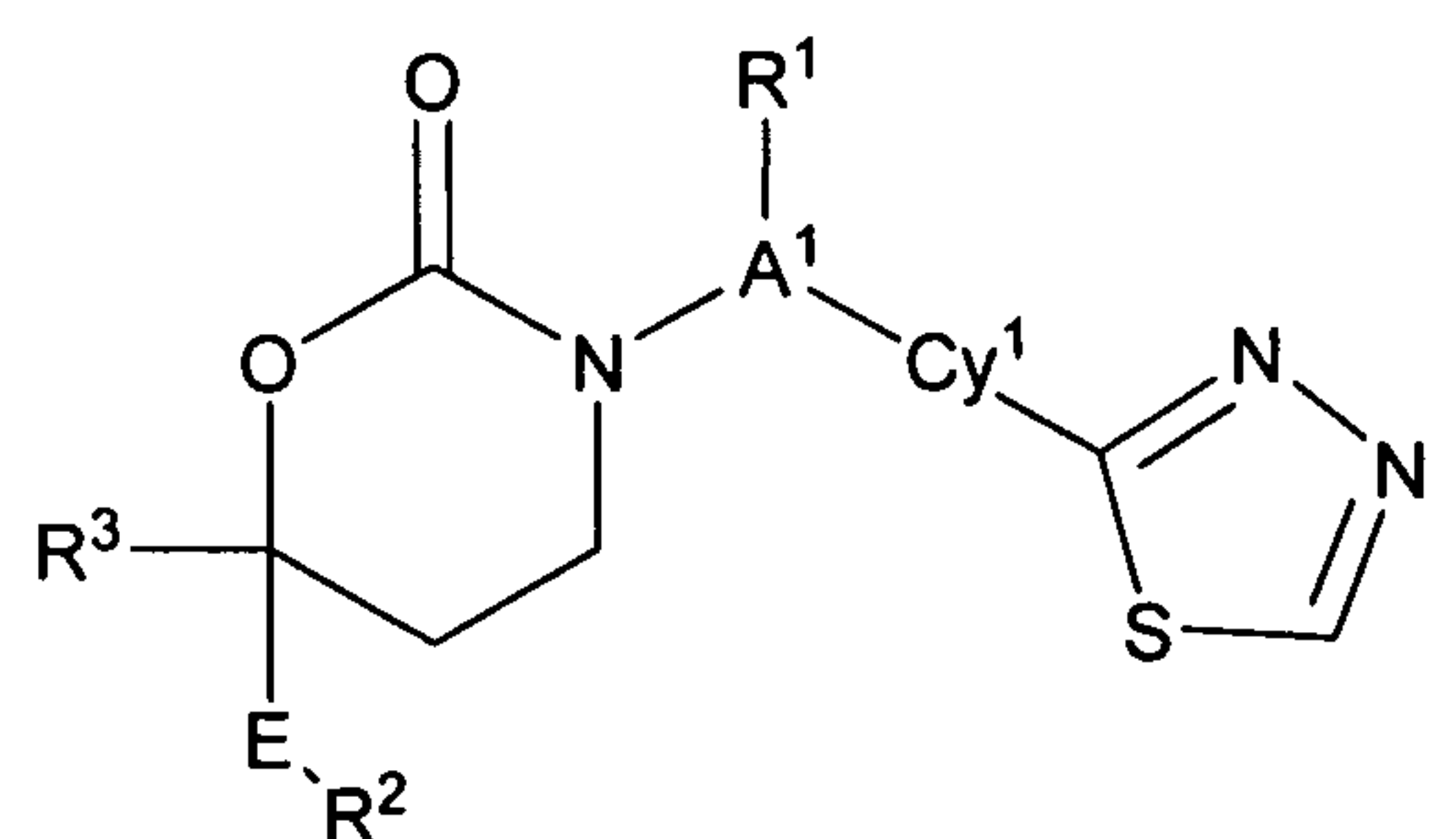
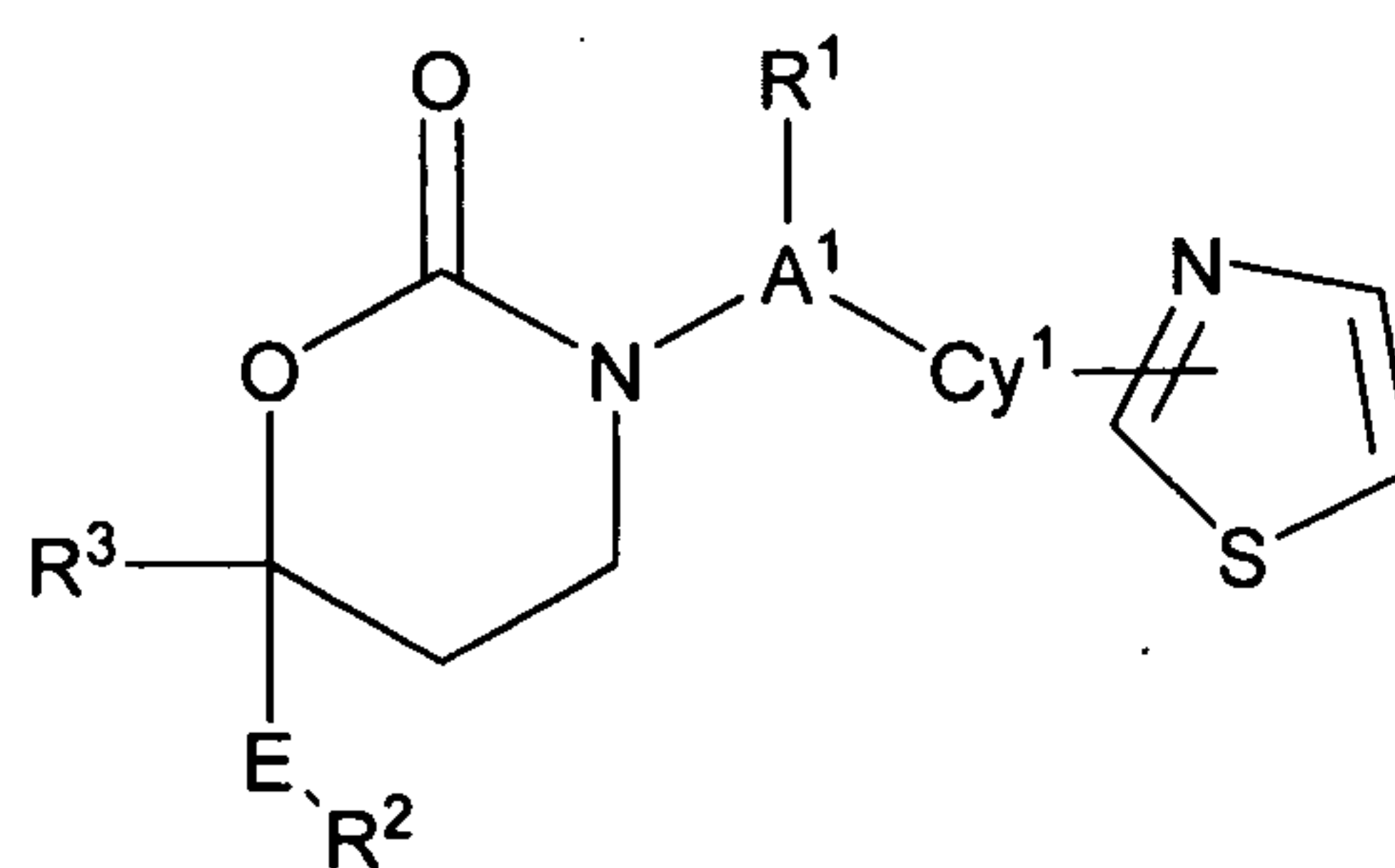
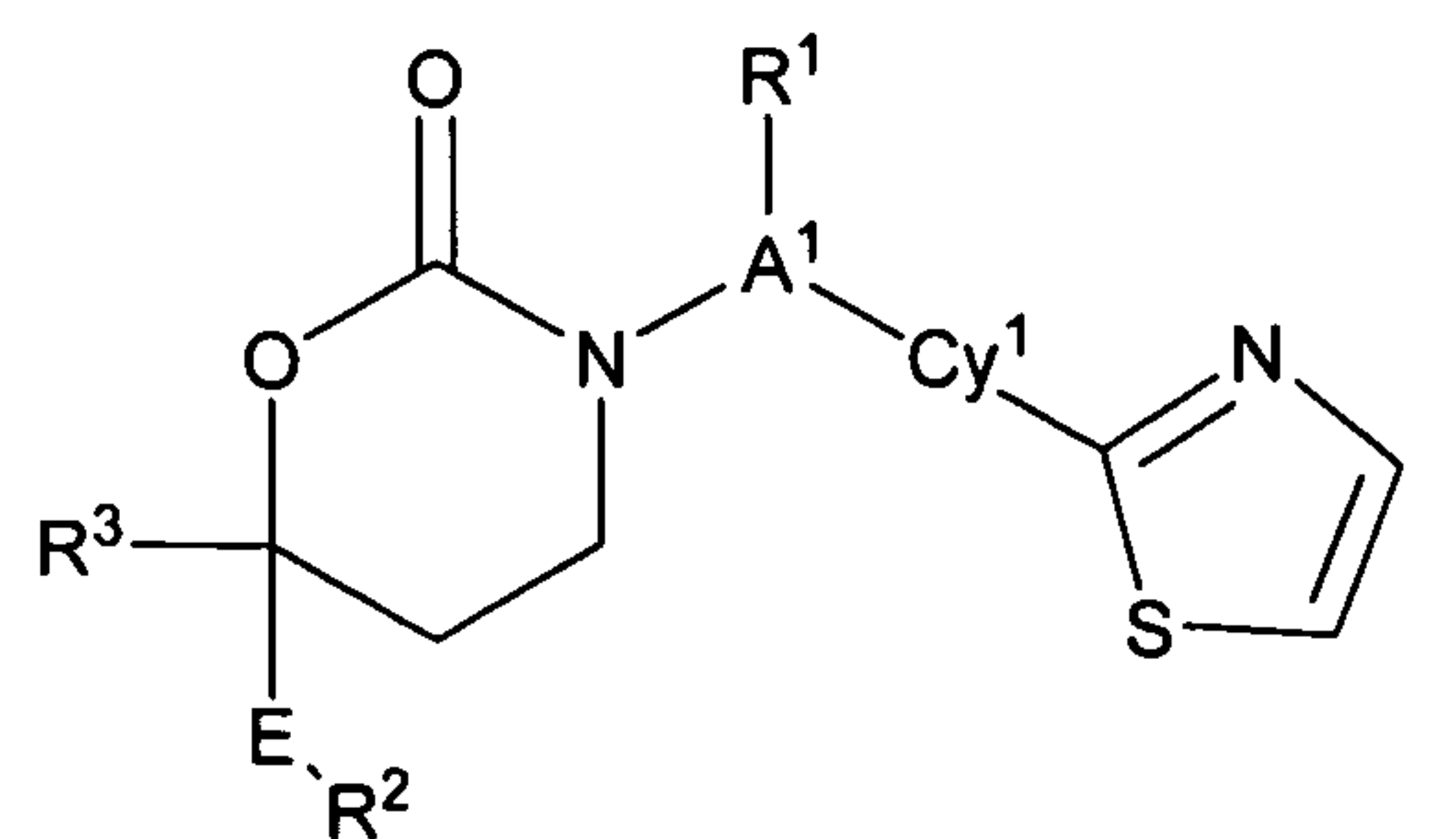
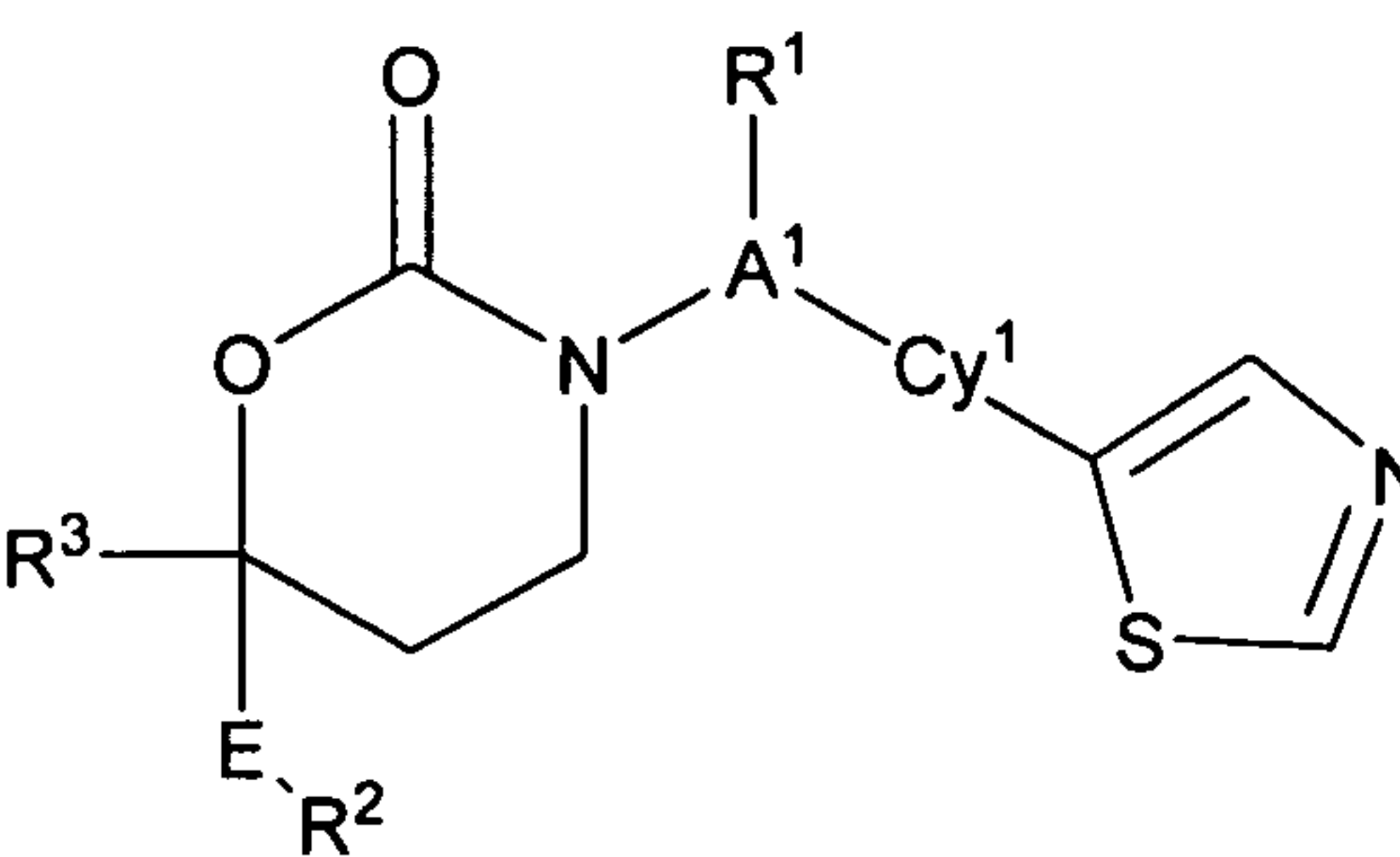
For each of the embodiments described in the paragraph immediately following Formulas Ip¹⁻⁷, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas Ip¹⁻⁷, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent G^{2a} is selected from (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₂)haloalkyl; and G^{2b} is optionally selected from hydrogen, methyl or ethyl.

Another embodiment of the invention is a compound of any one of Formulas Iq¹⁻²⁰ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof:

Iq¹Iq²Iq³Iq⁴Iq⁵Iq⁶

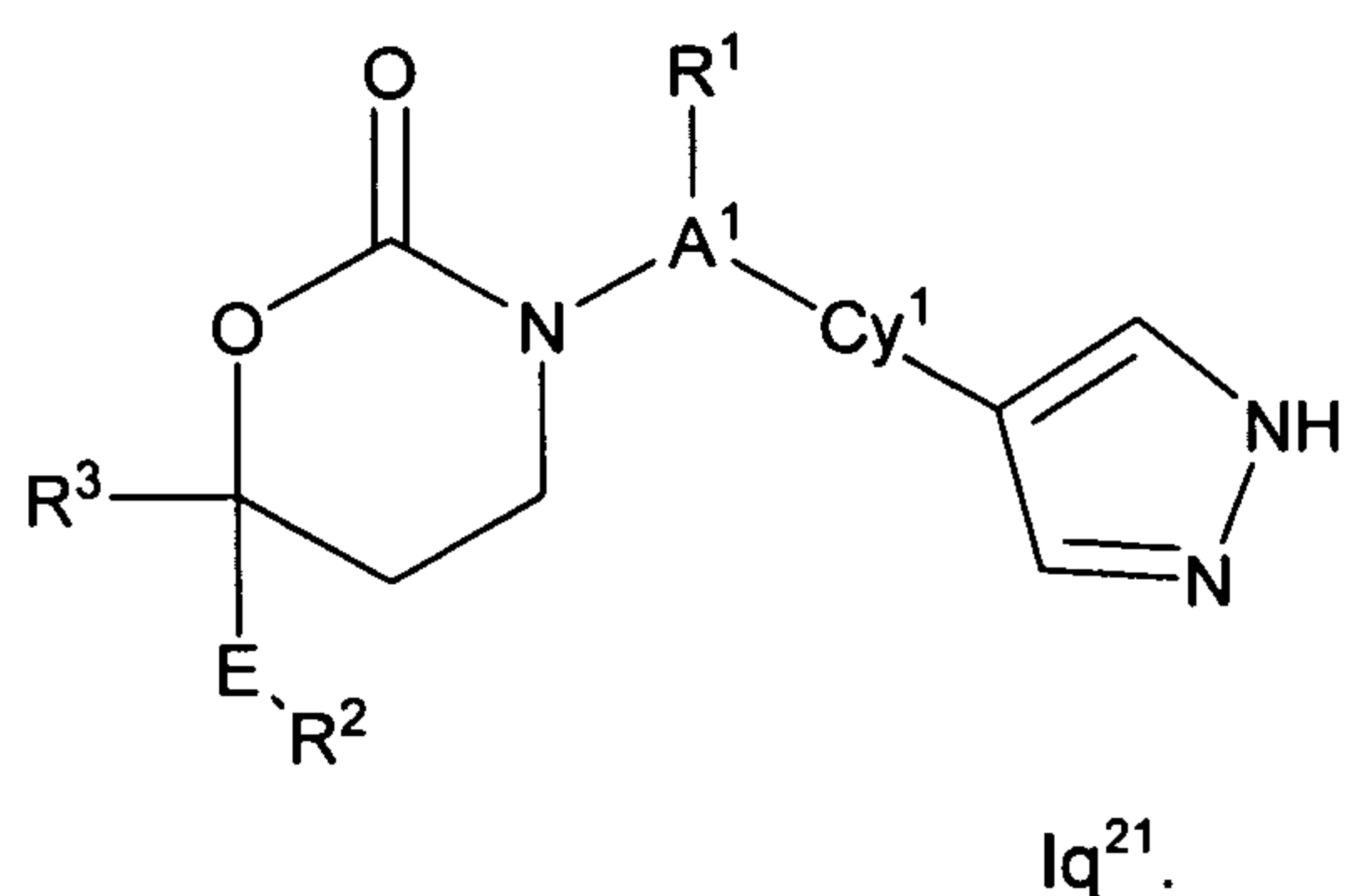
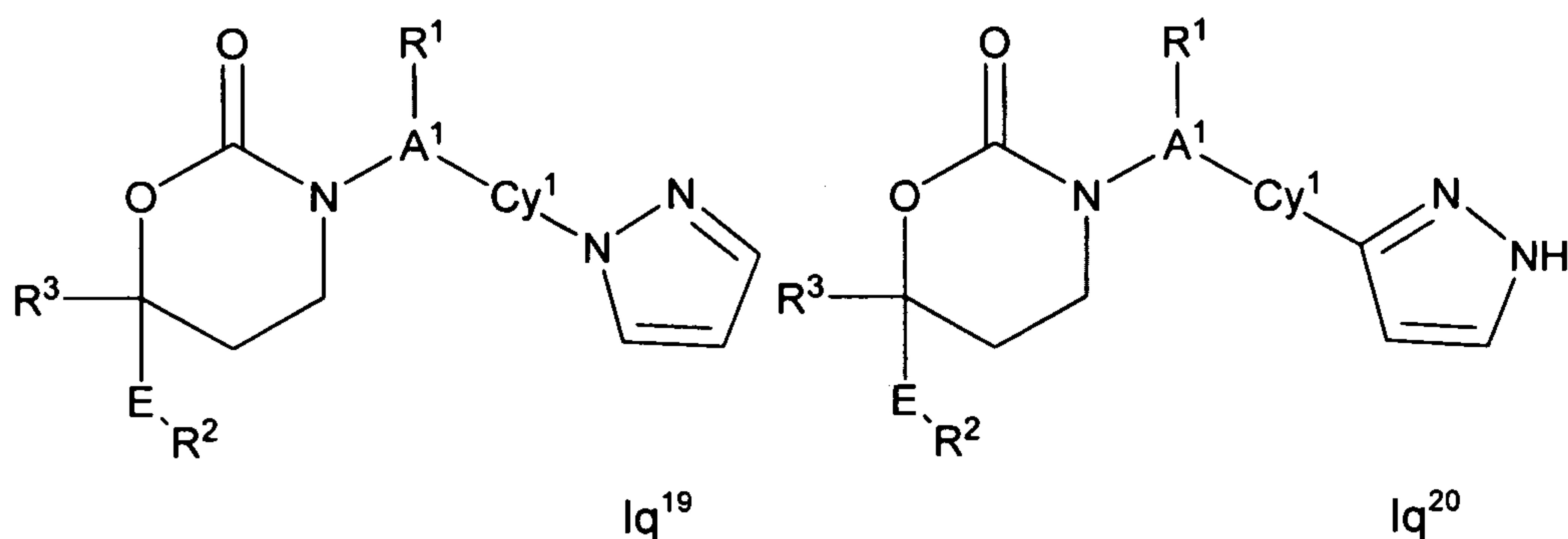
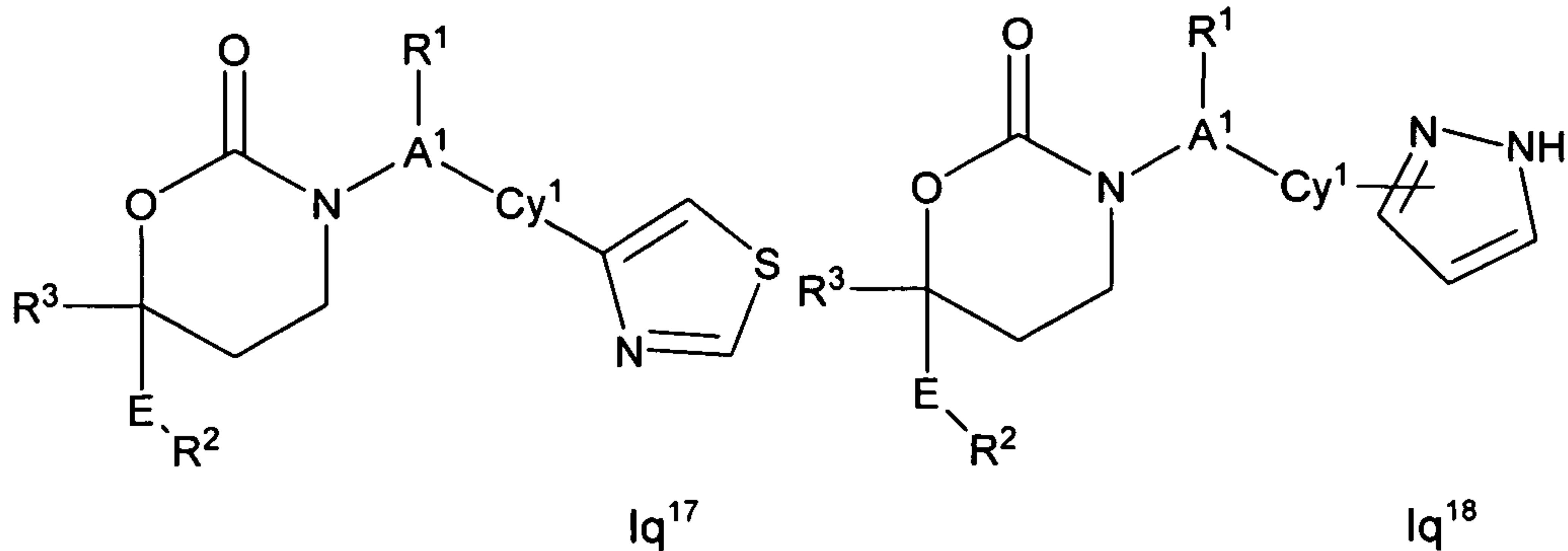
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Iq⁷Iq⁸Iq⁹Iq¹⁰Iq¹¹Iq¹²Iq¹³Iq¹⁴Iq¹⁵Iq¹⁶

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In Formulas Iq¹⁻²¹, the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iq¹⁻²¹ are optionally substituted (substitution at ring carbons bonded to hydrogen and ring nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a “substitutable ring nitrogen atom”) with up to four substituents as described above for Cy². Suitable substituents for Cy² and suitable values for R¹, R², R³, A¹, Cy¹ and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, suitable substituents for Cy¹ and the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iq¹⁻²¹ are as described for G¹ and G², respectively, in Formula If, and values for R¹, R², R³, A¹, Cy¹ and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, suitable substituents for Cy¹ include (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom in the pyrazole rings

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in Formulas Iq¹⁸, Iq²⁰ and Iq²¹ include (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₄)haloalkyl; suitable substituents for a ring carbon atom in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iq¹⁻²¹ include fluorine, chlorine, cyano, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl, (C₃-C₄)cycloalkylaminocarbonyl, {(C₁-C₄)alkyl}{(C₃-C₄)cycloalkyl}aminocarbonyl and (C₁-C₄)alkylcarbonylamino; the ring nitrogen in the pyridine rings in Formulas Iq¹⁻⁴ is optionally substituted by oxo; and suitable values for R¹, R², R³, A¹, Cy¹ and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. In another alternative, the embodiments in this paragraph exclude the compound exemplified in Example 205, Example 211, Example 214, Example 222, Example 226, Example 235, Example 236, Example 281, Example 292, Example 295, Example 298, Example 300, Example 302, Example 305, Example 304, Example 306, Example 307, Example 210, Example 296, Example 311, Example 230, Example 244, Example 258 and Example 291 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

For each of the embodiments described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiments described in the paragraph immediately following Formulas Iq¹⁻²¹, R¹ is preferably methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Iq¹⁻²¹, R¹ is preferably methyl or ethyl; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Iq¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

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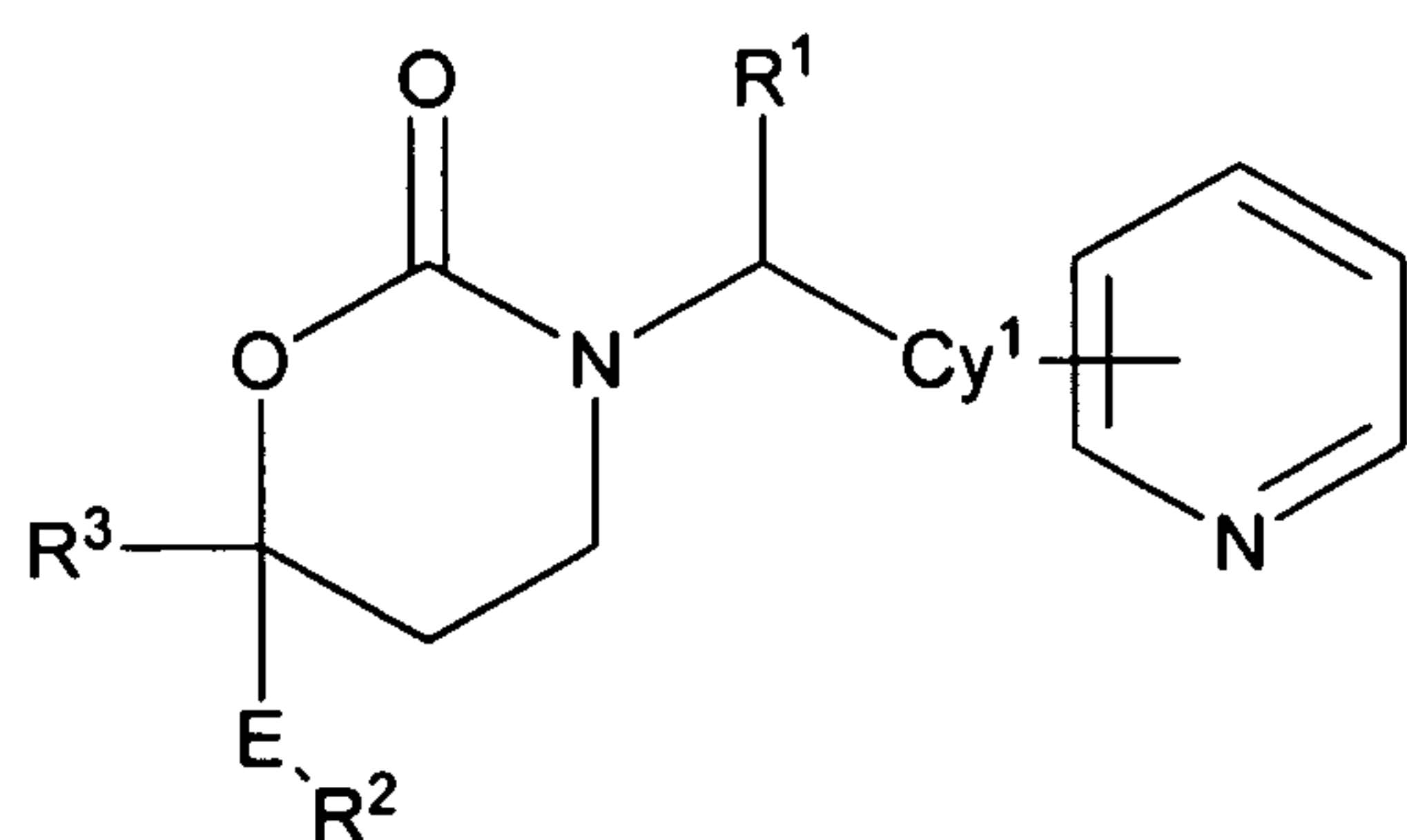
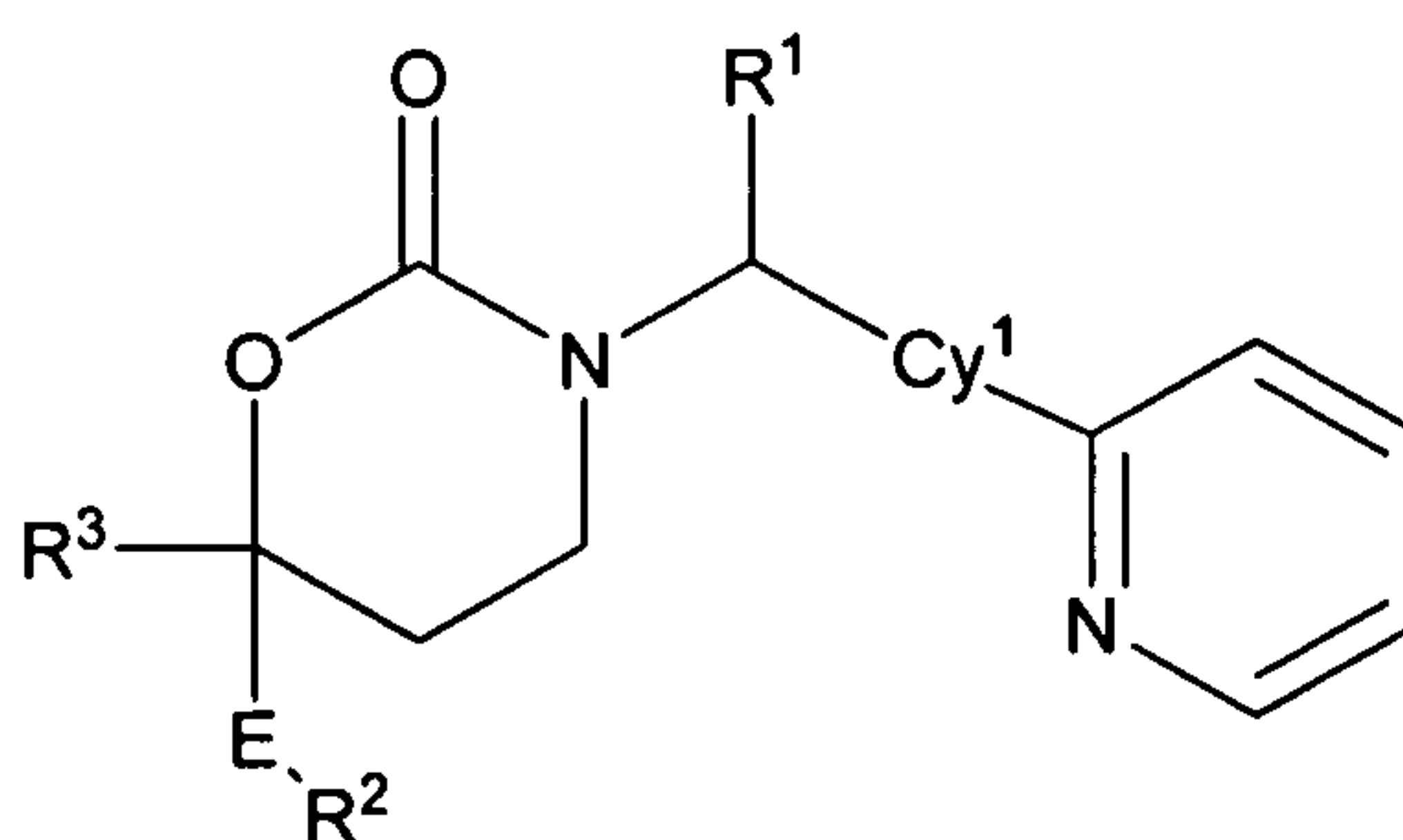
For each of the embodiments described in the paragraph immediately following Formulas Iq¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Iq¹⁻²¹, R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

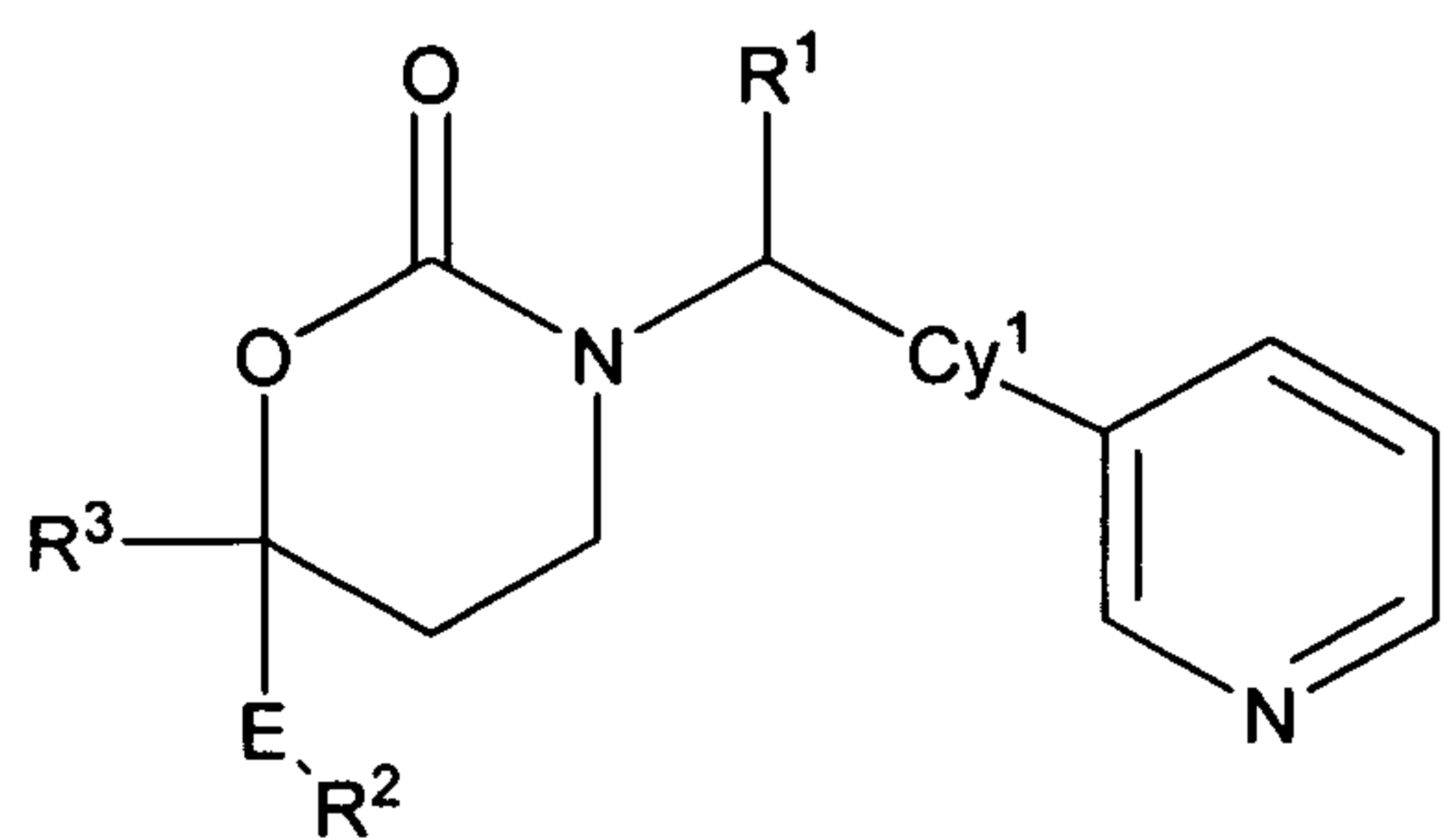
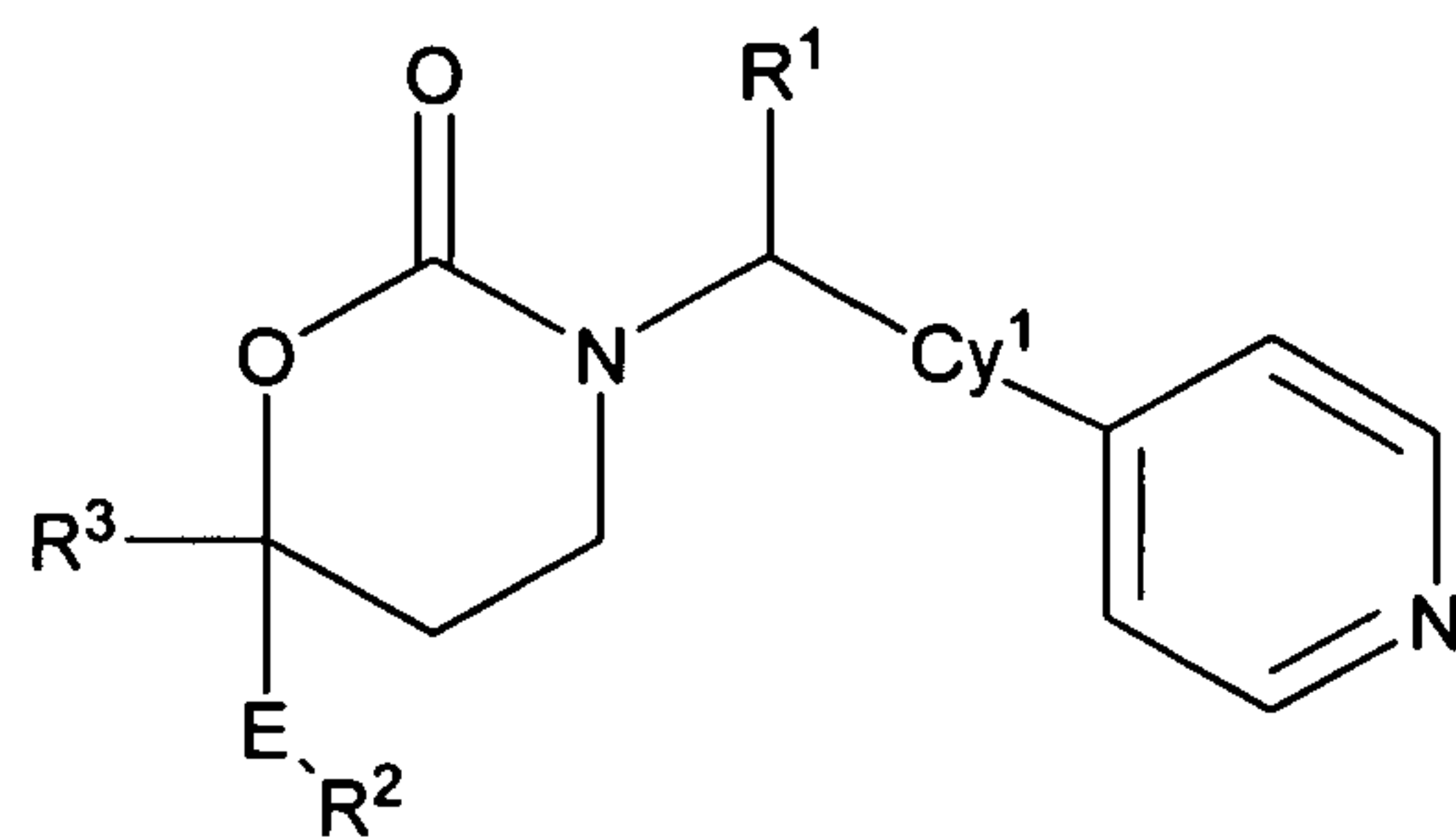
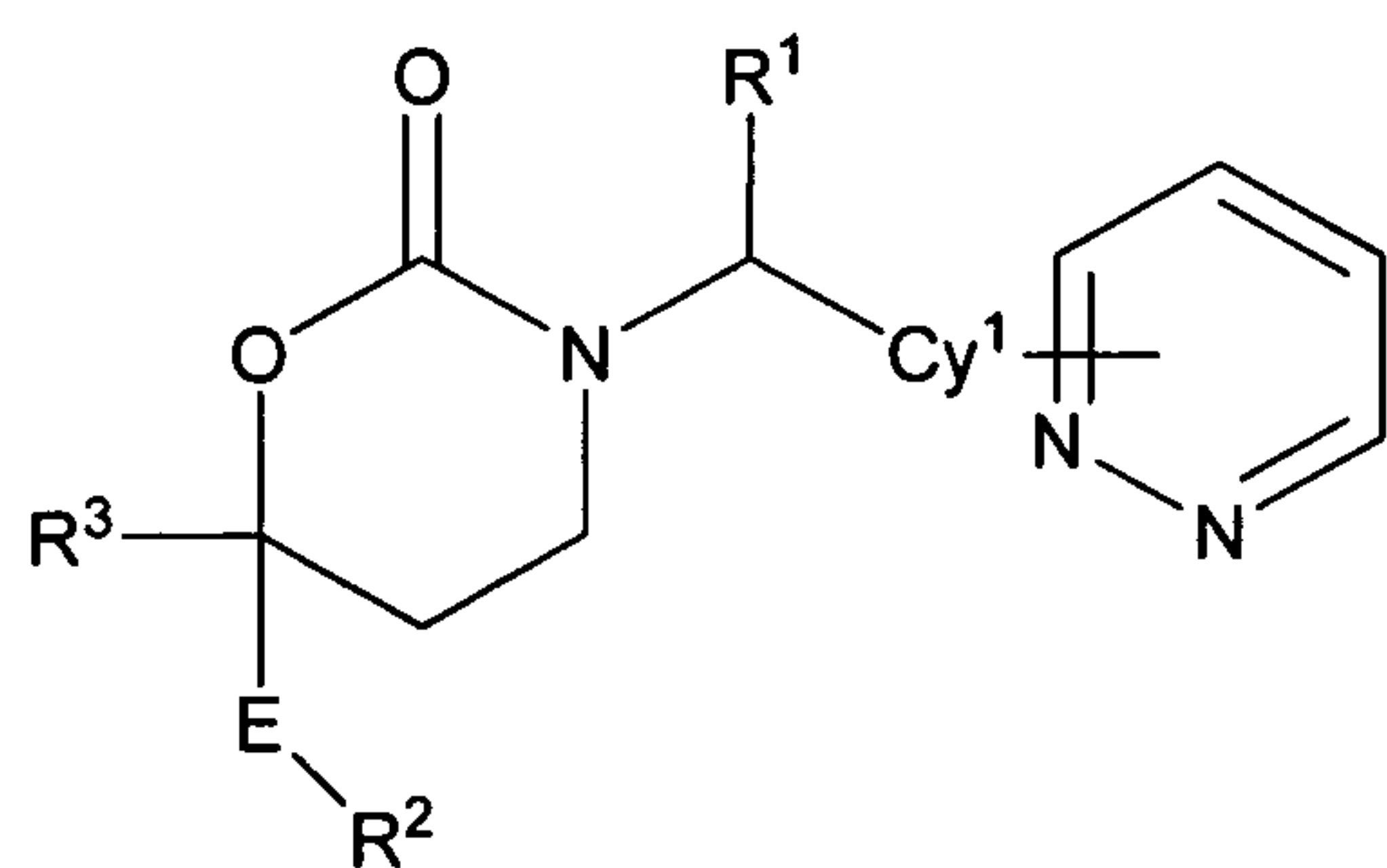
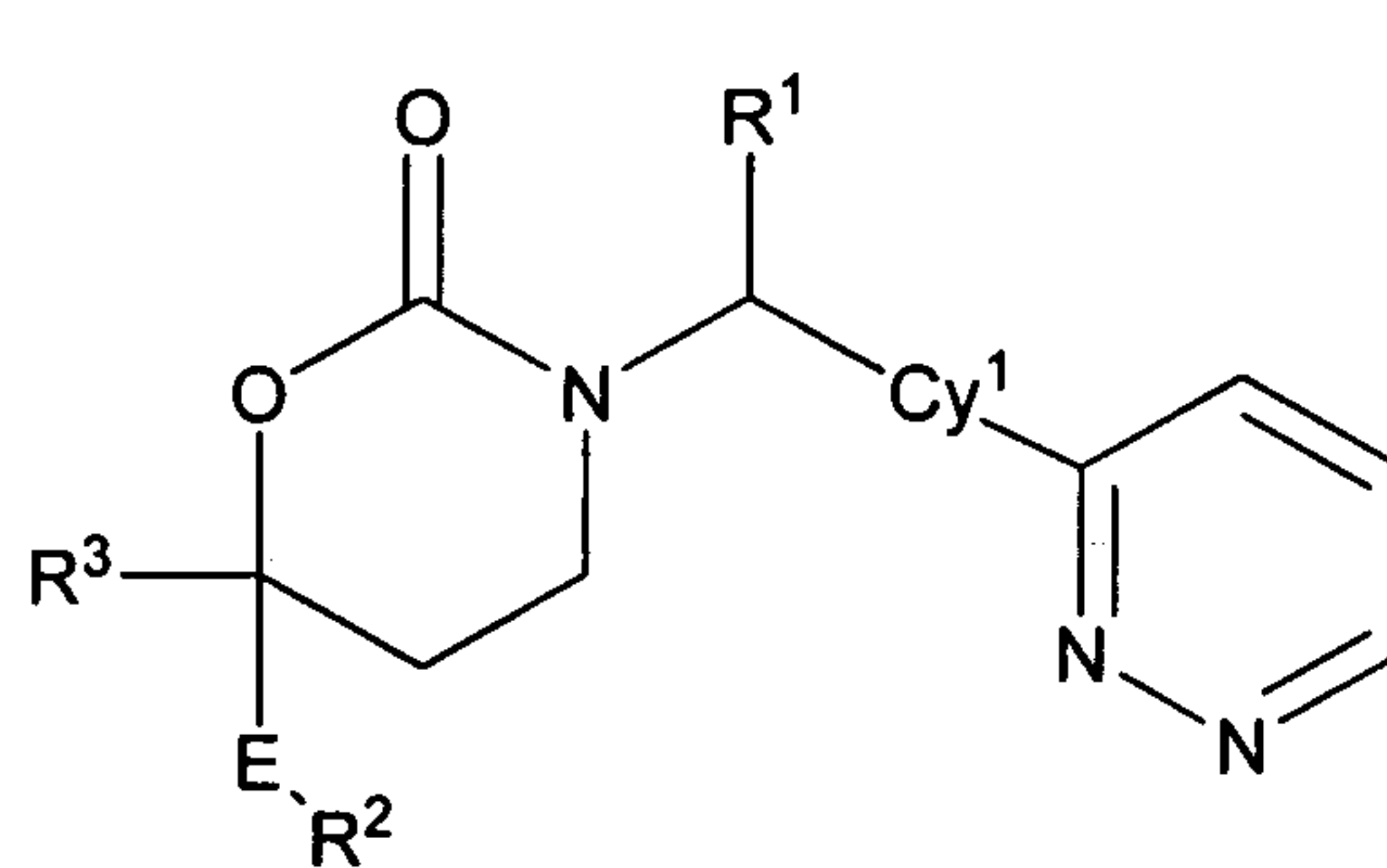
For each of the embodiments described in the paragraph immediately following Formulas Iq¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Iq¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; one or two ring carbon atoms in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iq¹⁻²¹ are optionally substituted with fluoro, chloro, cyano, CONH₂, CONHMe, CONMe₂, CONHc-Pr, methoxy, ethoxy, methyl, ethyl or CF₃. the substitutable ring nitrogen atom in the pyrazole rings in Formulas Iq¹⁸, Iq²⁰ and Iq²¹ are optionally substituted with (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, or (C₁-C₂)haloalkyl, the ring nitrogen in the pyridine rings in Formulas Iq¹⁻⁴ is optionally substituted by oxo.

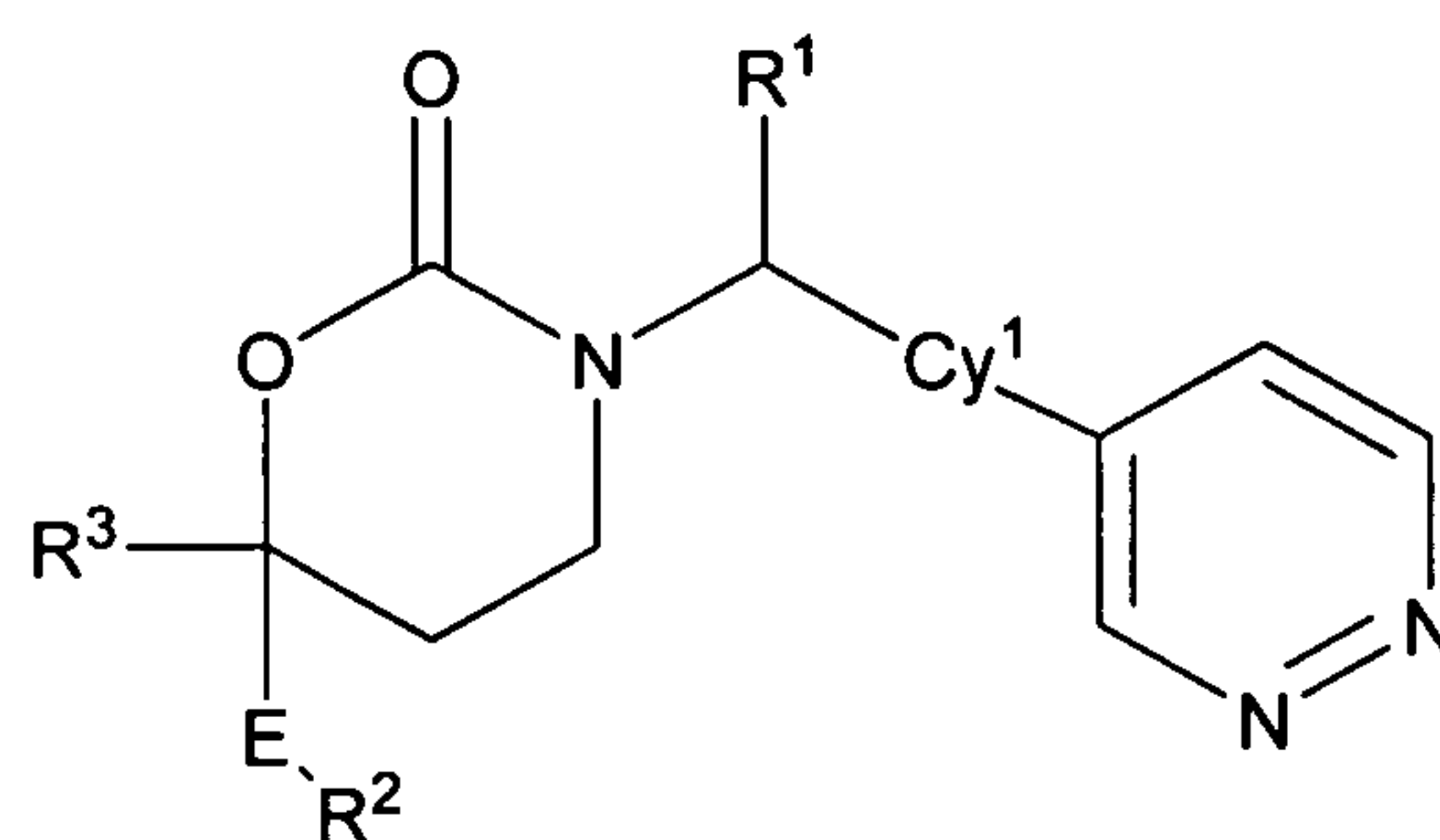
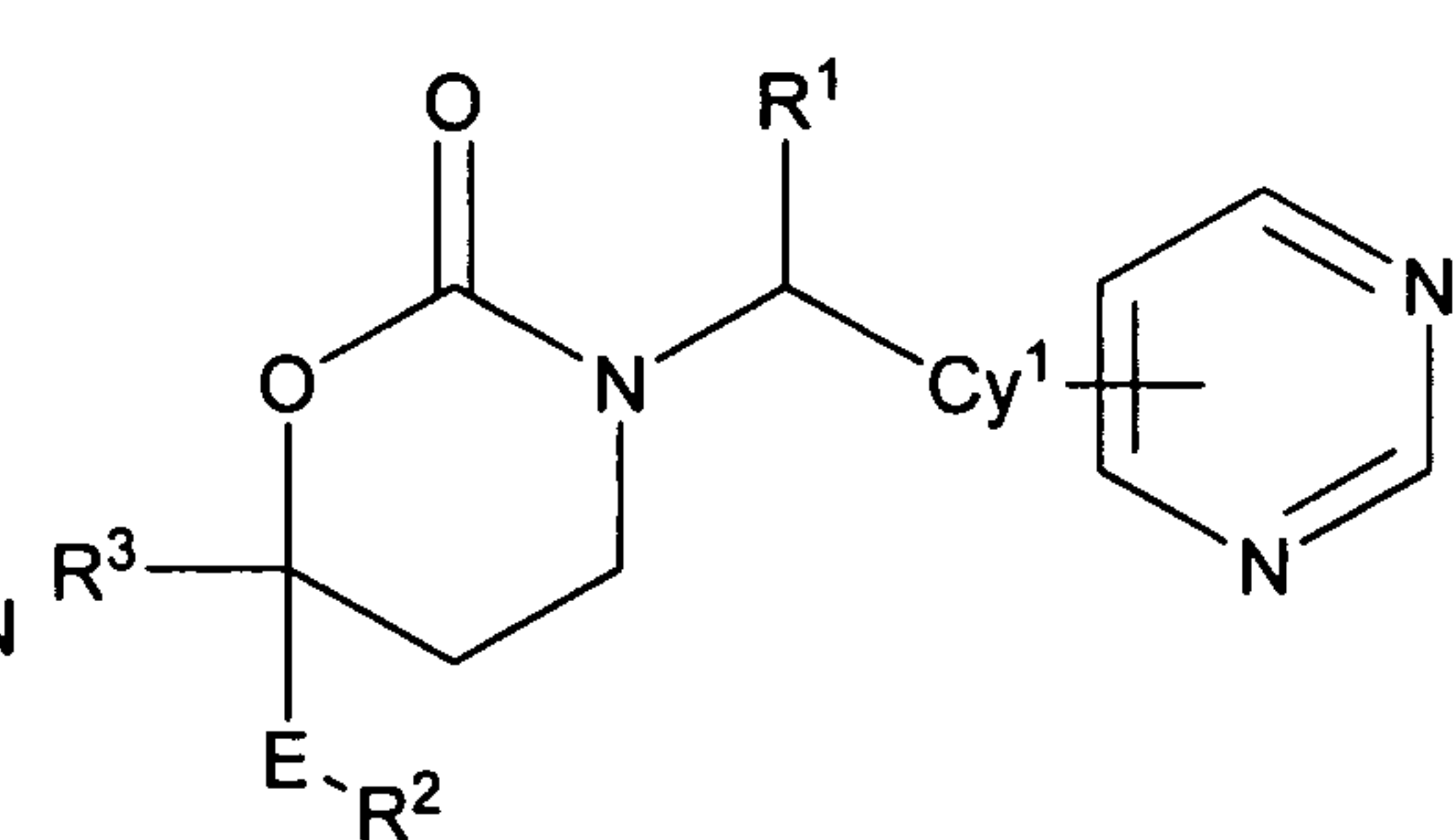
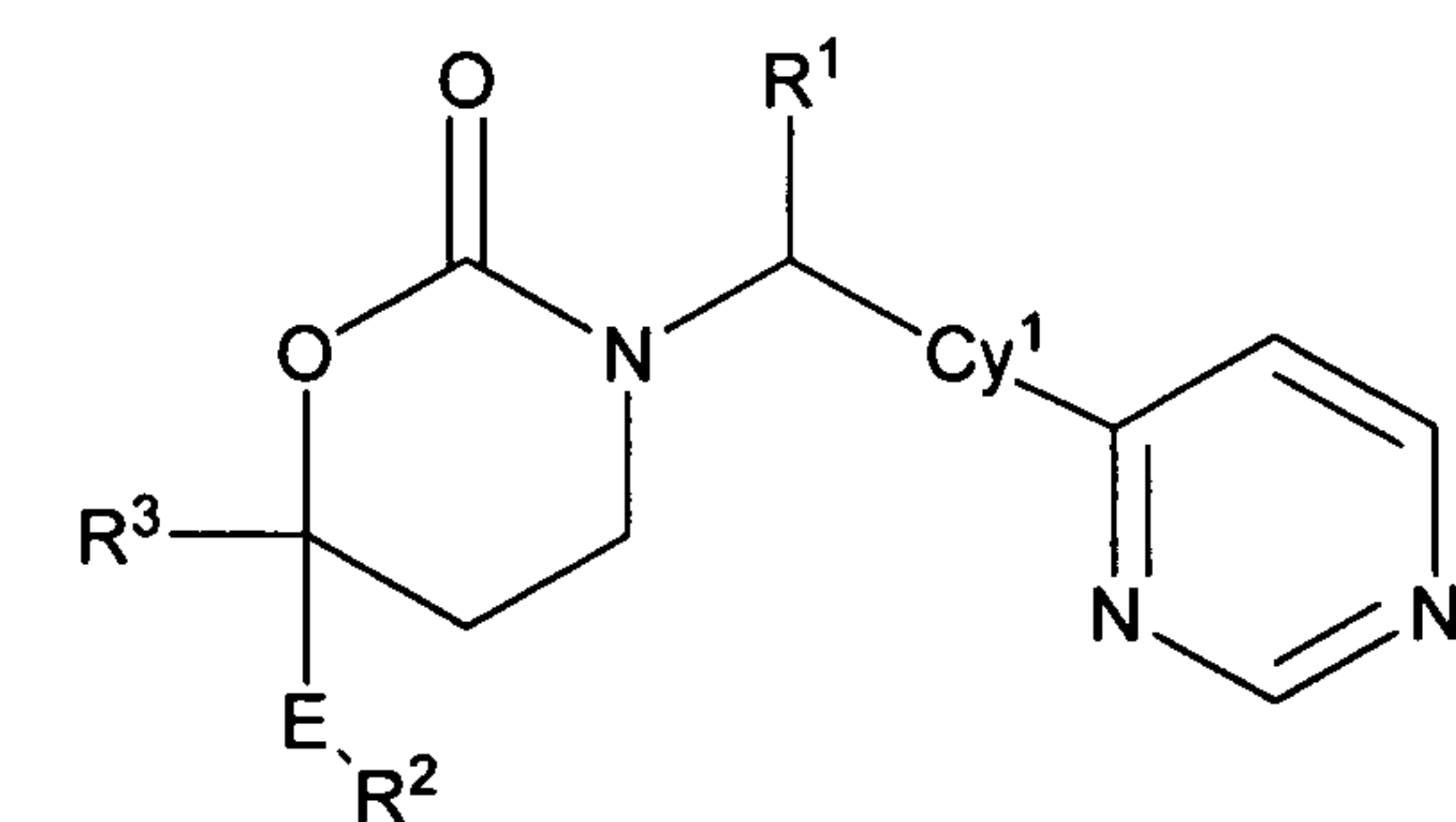
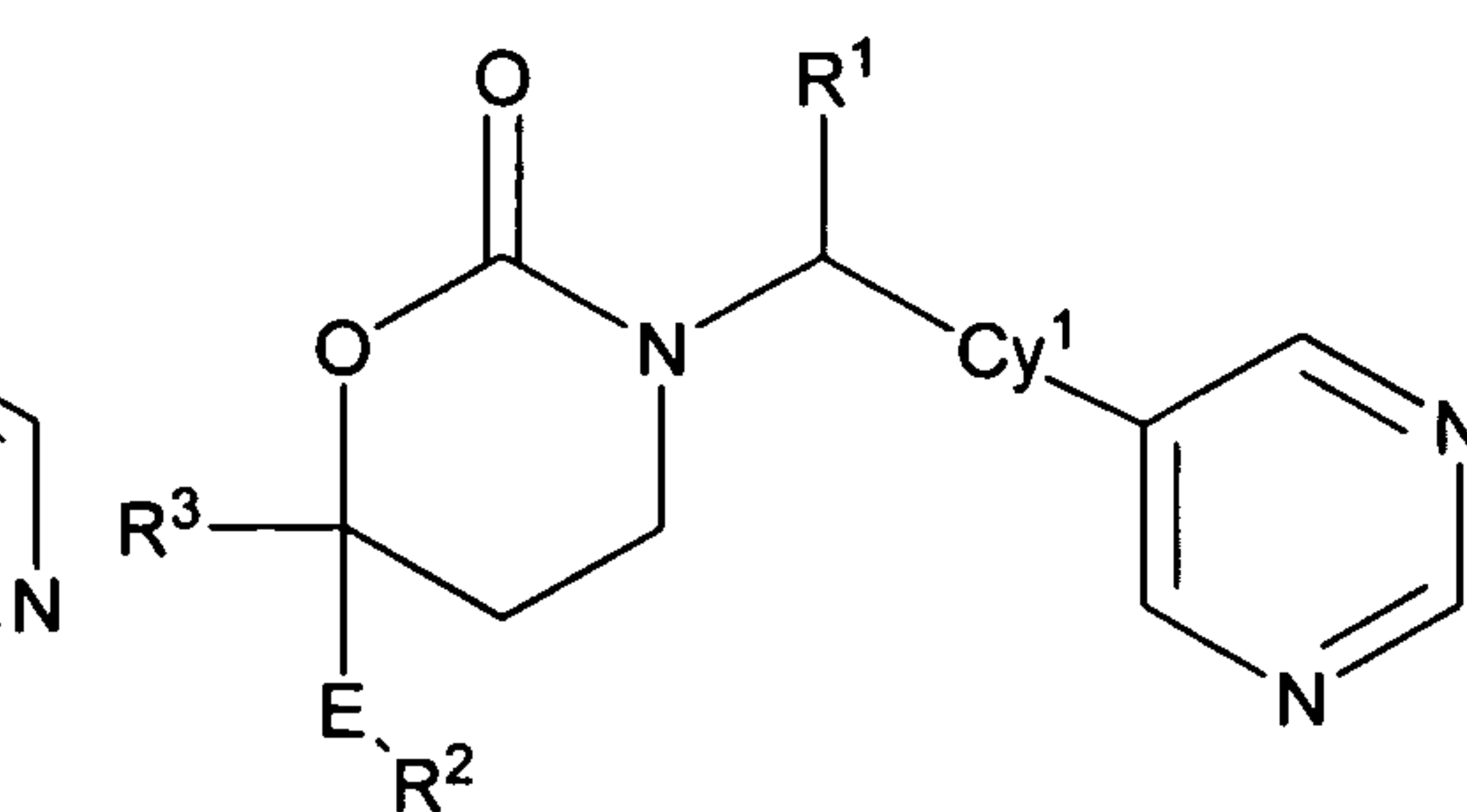
Another embodiment of the invention is a compound of any one of Formulas Ir¹⁻²¹, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof:

Ir¹Ir²

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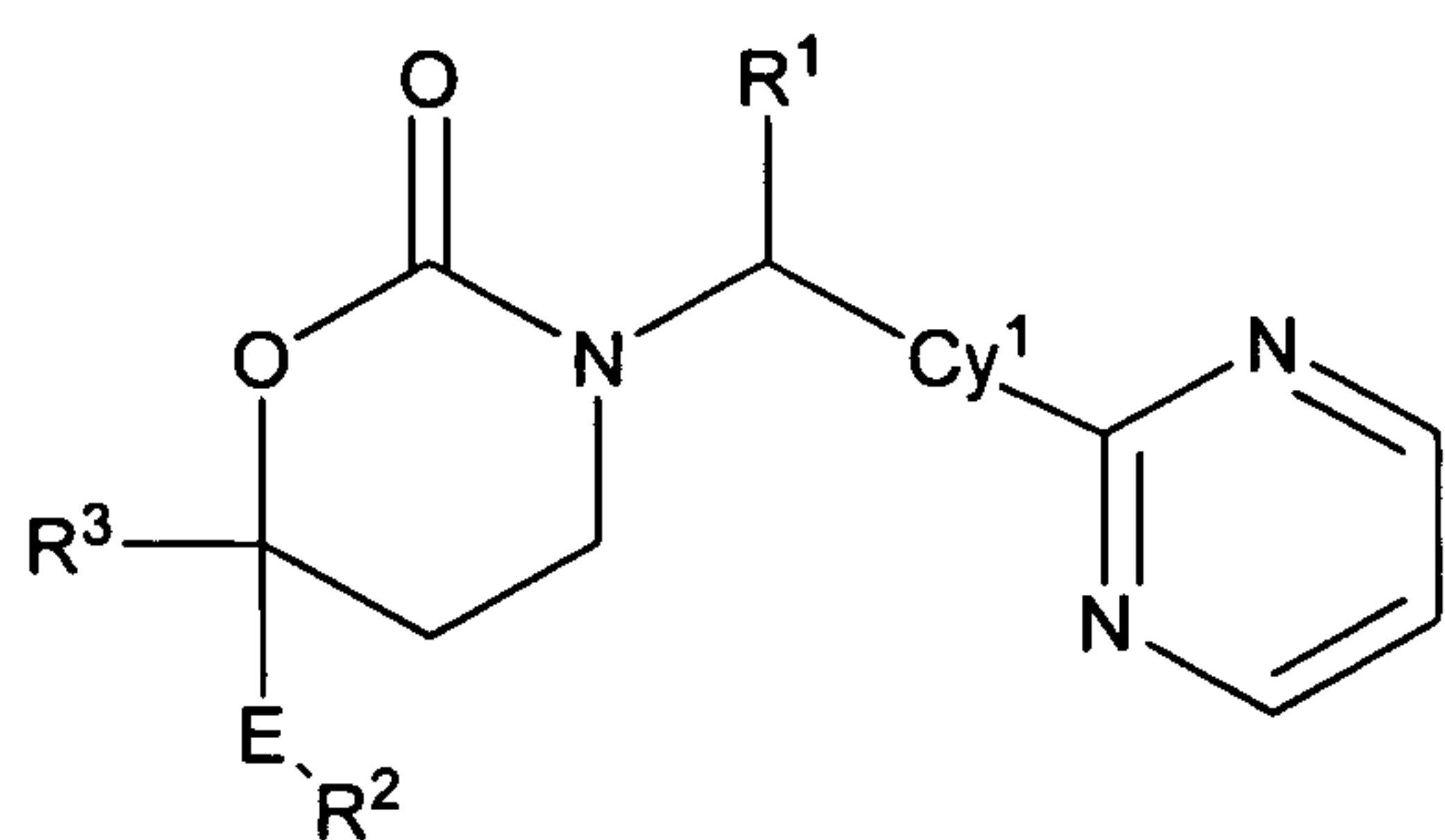
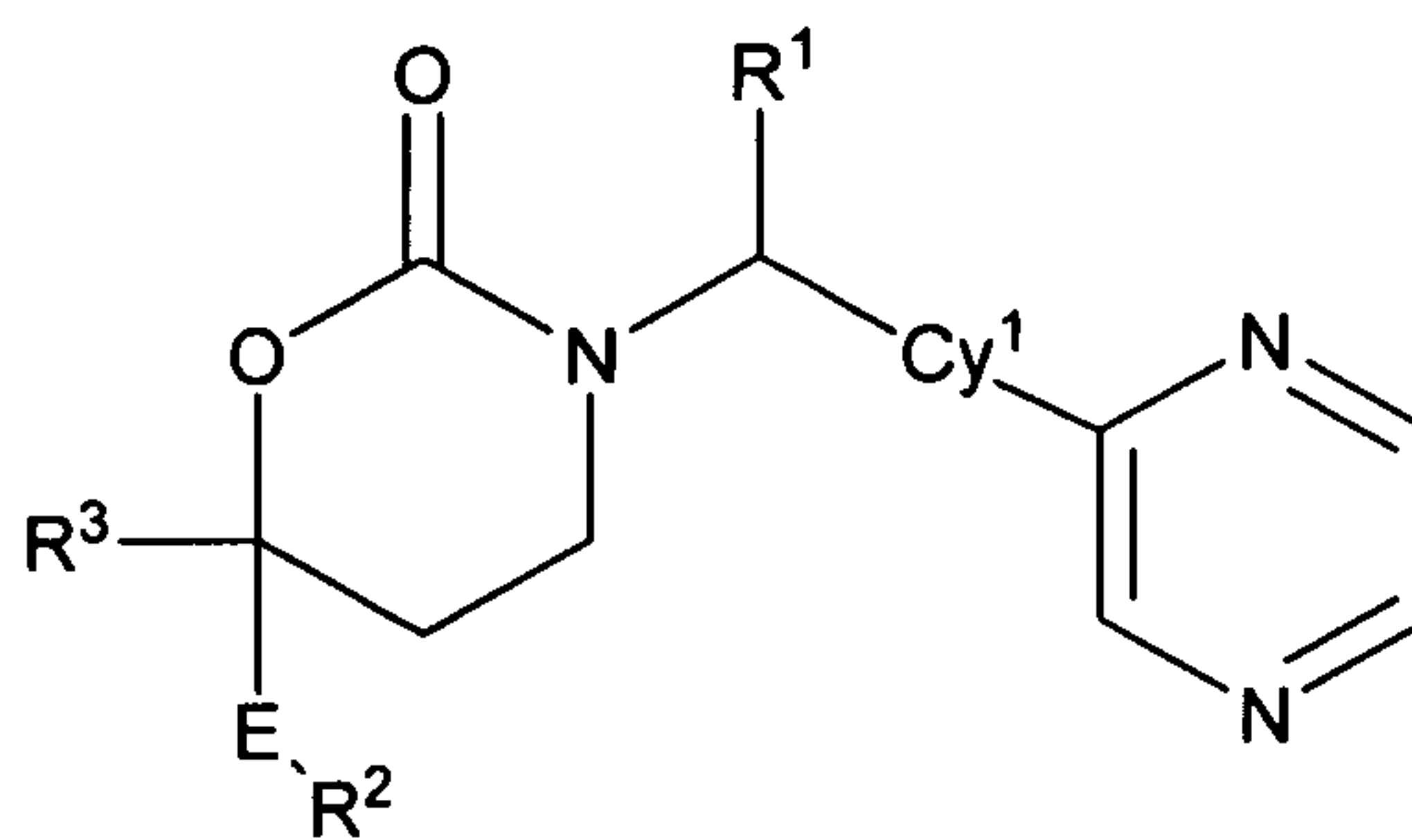
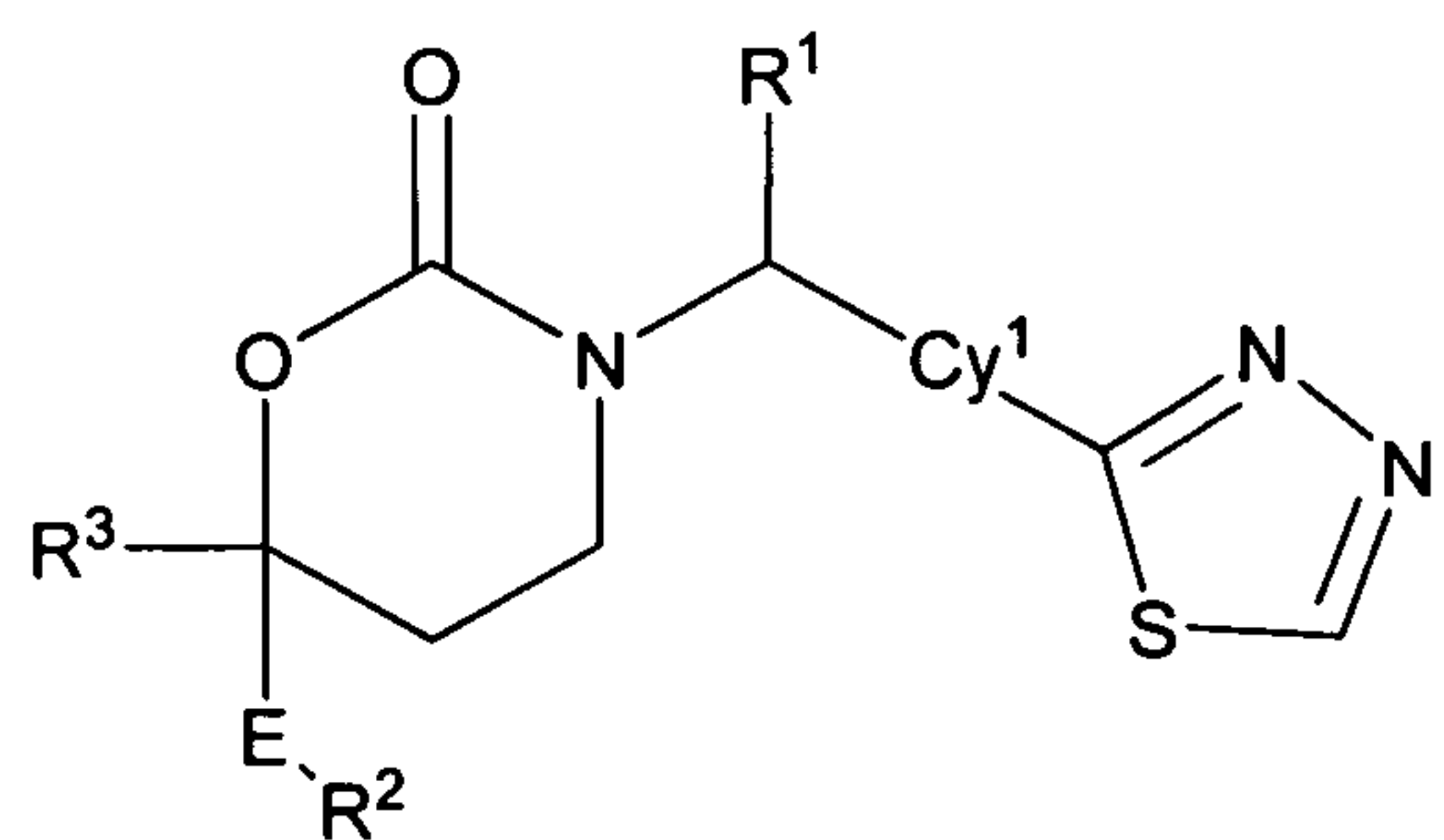
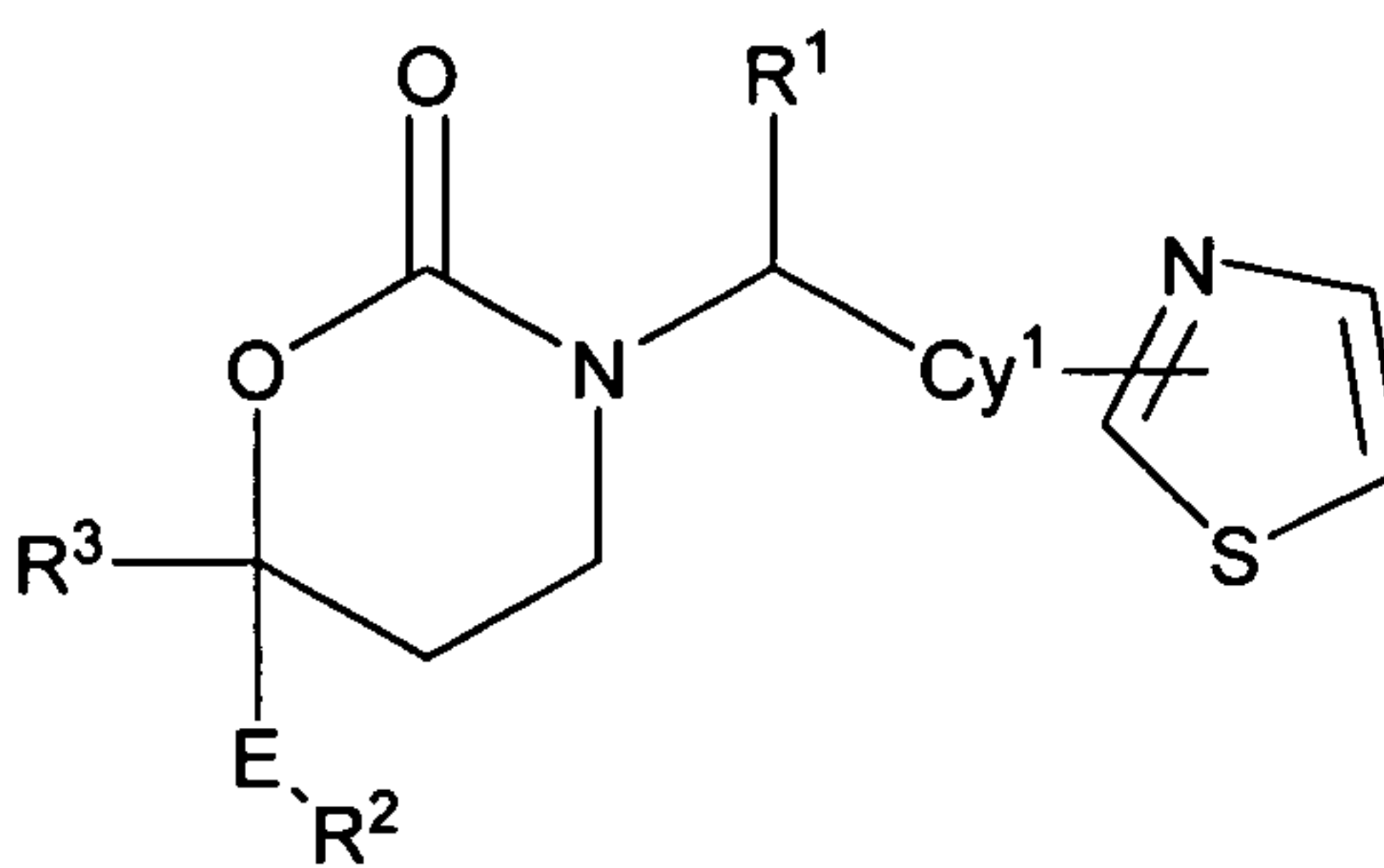
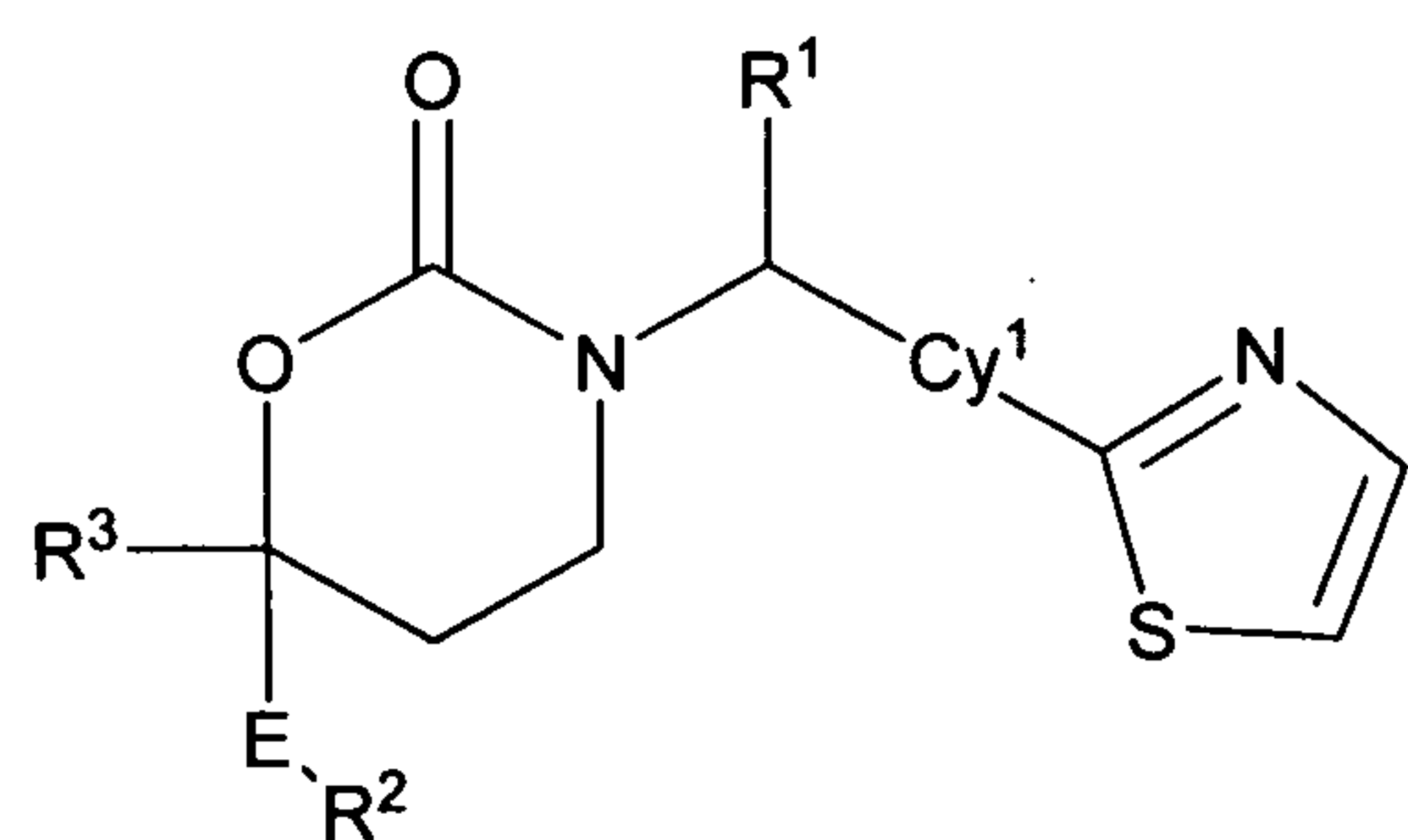
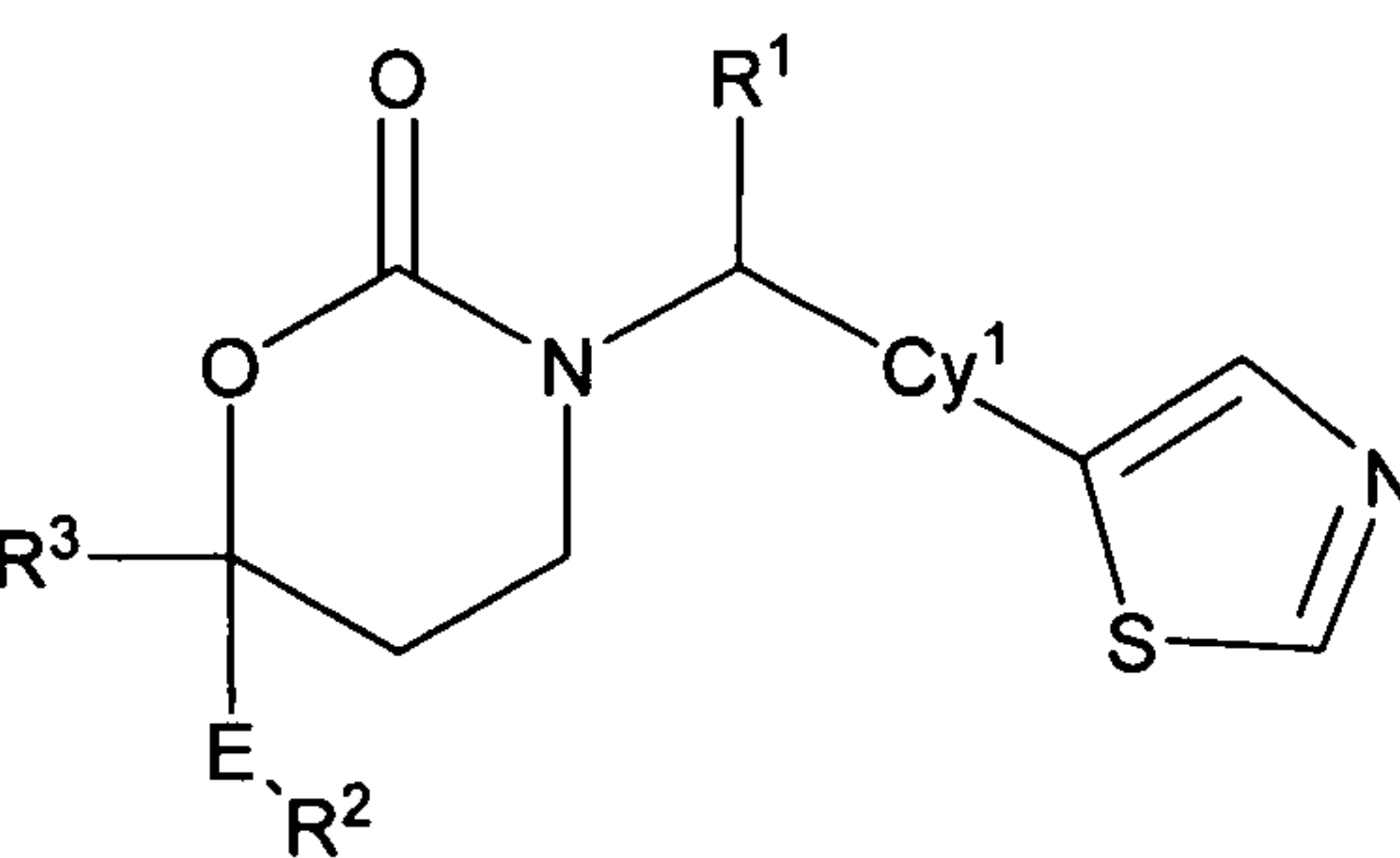
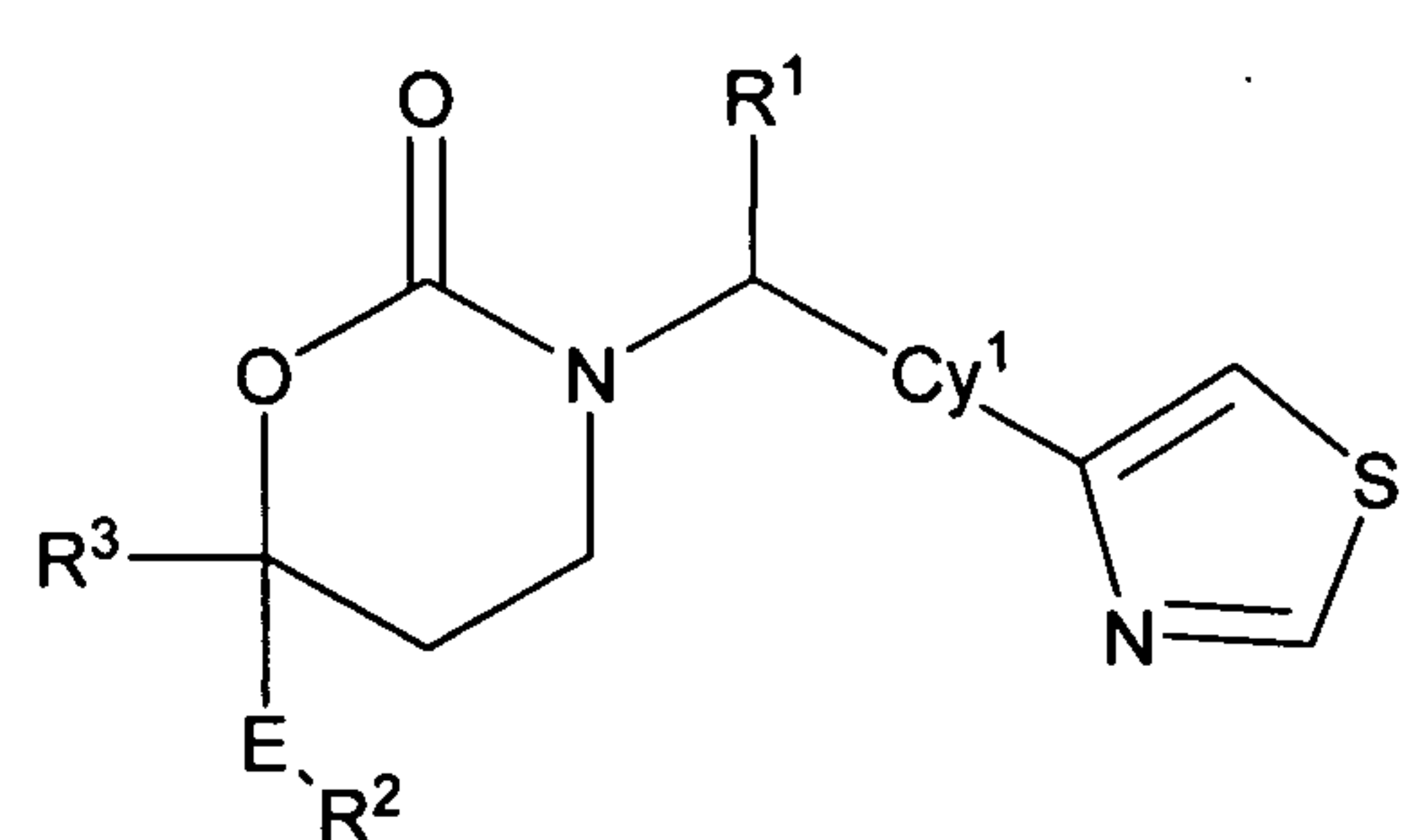
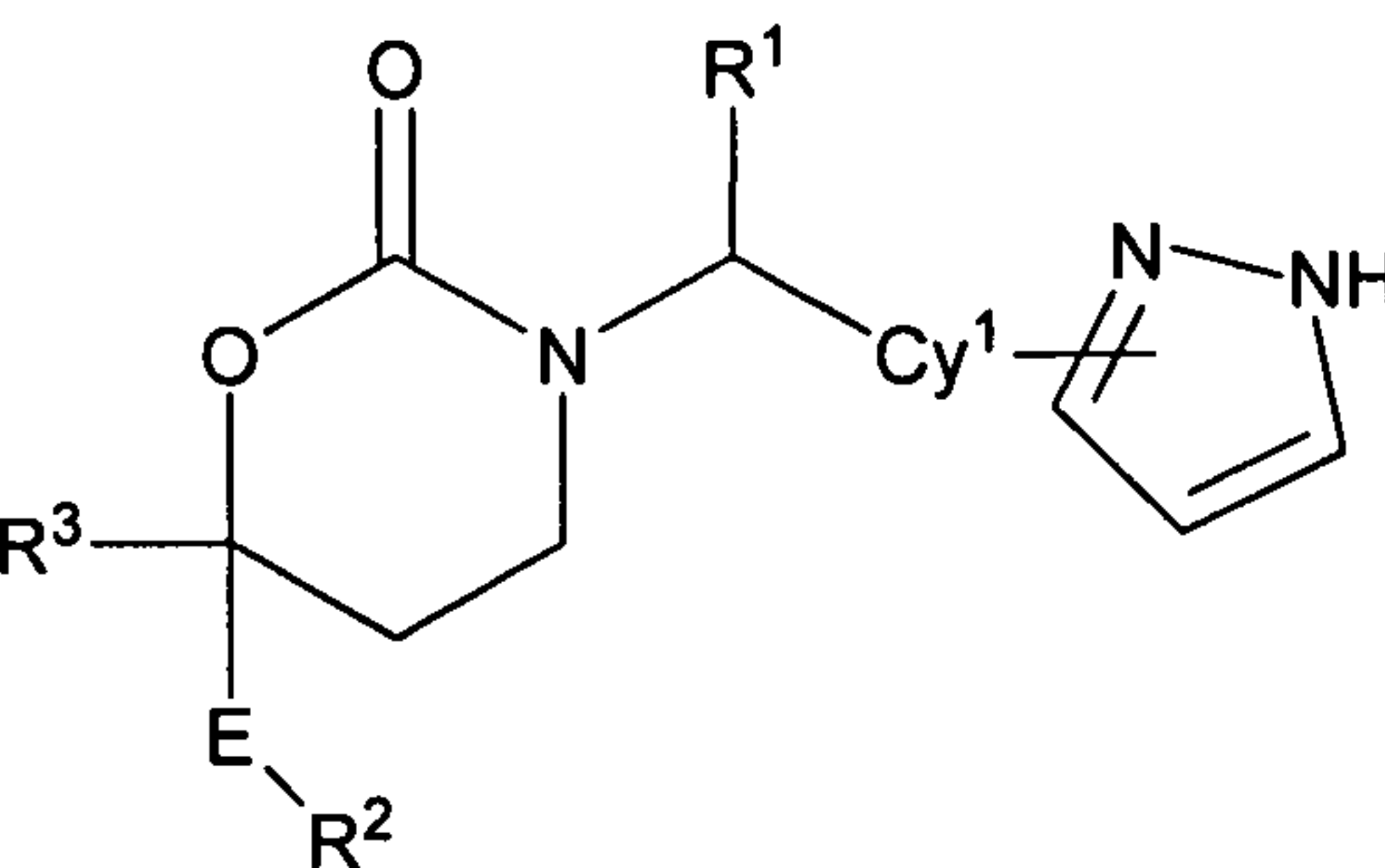
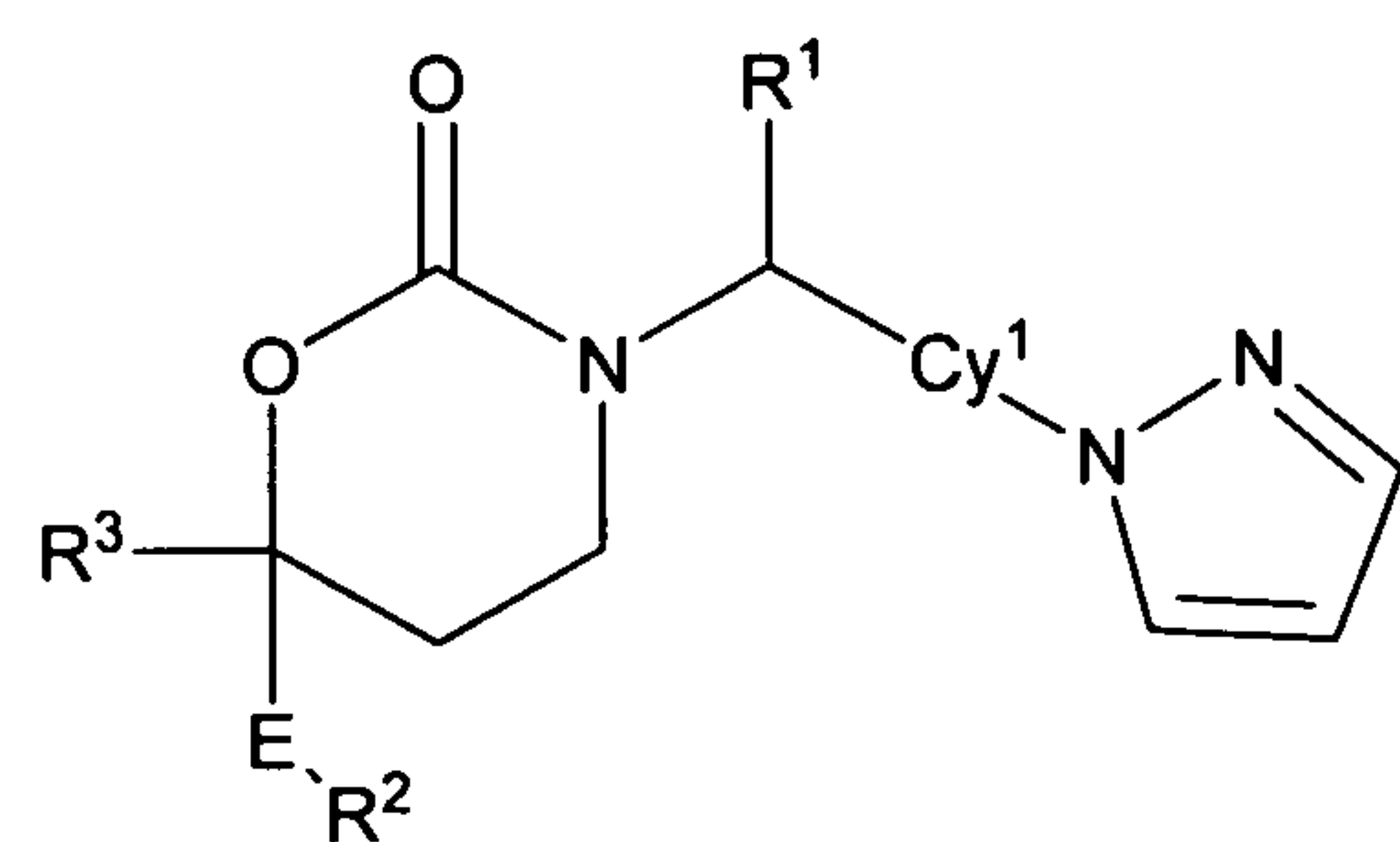
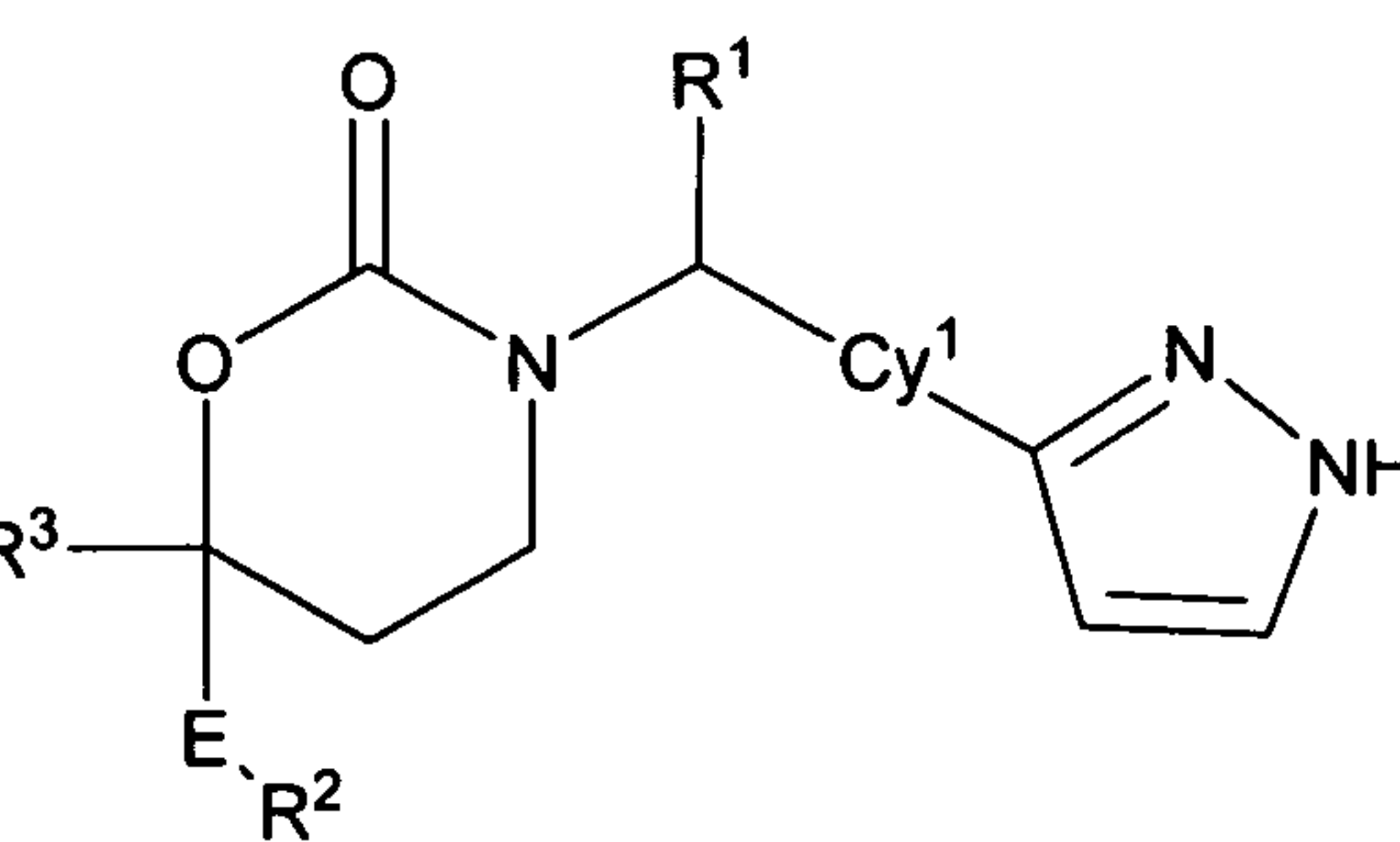
Ir³Ir⁴Ir⁵Ir⁶

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Ir⁷Ir⁸Ir⁹Ir¹⁰

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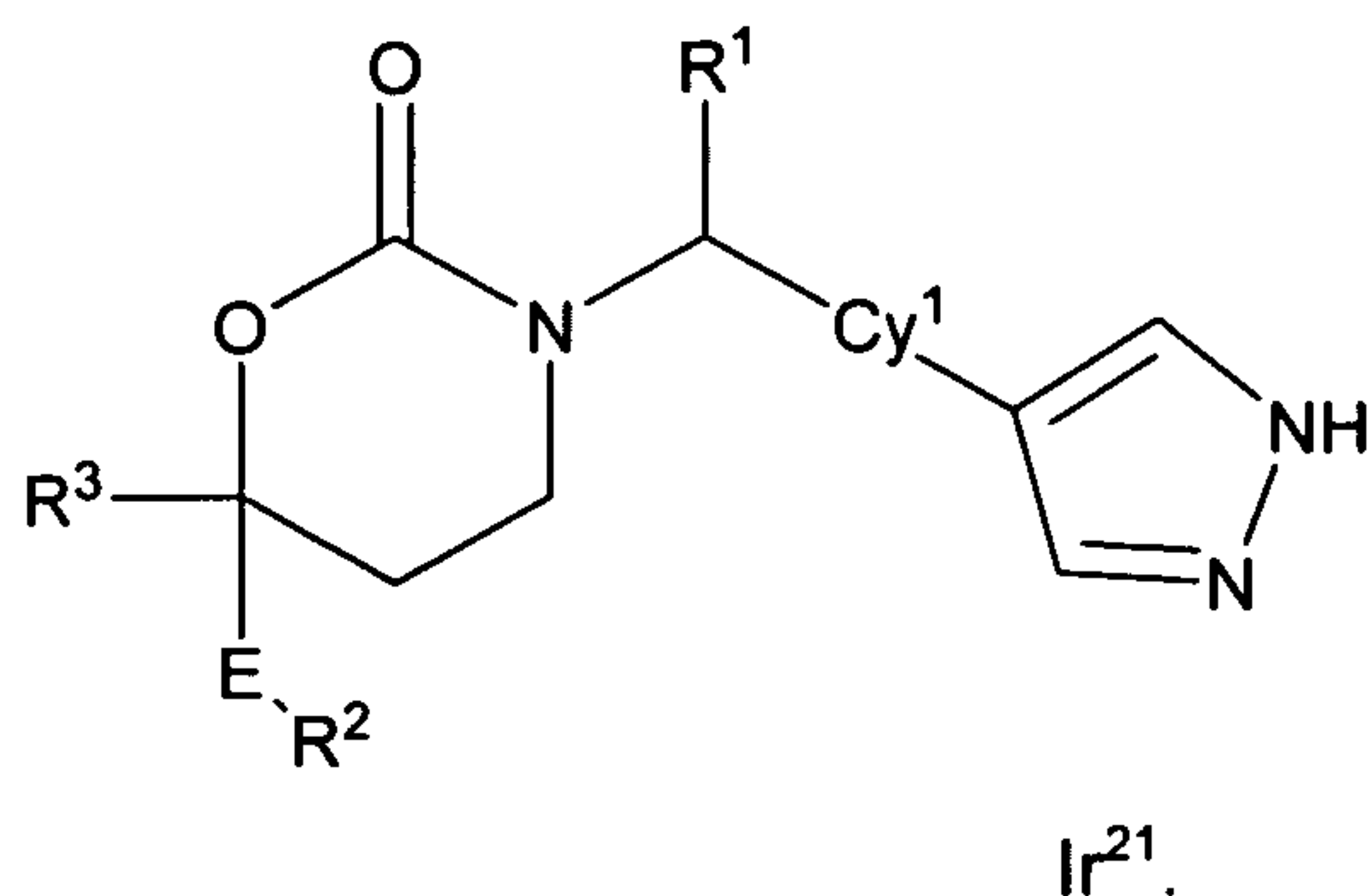
- 68 -

Ir¹¹Ir¹²Ir¹³Ir¹⁴Ir¹⁵Ir¹⁶Ir¹⁷Ir¹⁸Ir¹⁹Ir²⁰

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In Formulas Ir^{1-21} , the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Ir^{1-21} are optionally substituted (substitution at ring carbons bonded to hydrogen and ring nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a “substitutable ring nitrogen atom”) with up to four substituents as described above for Cy^2 . Suitable substituents for Cy^2 and suitable values for R^1 , R^2 , R^3 , Cy^1 and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, suitable substituents for Cy^1 and the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Ir^{1-21} are as described for G^1 and G^2 , respectively, in Formula If, and values for R^1 , R^2 , R^3 , Cy^1 and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, suitable substituents for Cy^1 include (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom in the pyrazole rings in Formulas Ir^{18} , Ir^{20} and Ir^{21} include (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₄)haloalkyl; suitable substituents for a ring carbon atom in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Ir^{1-21} include fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl, (C₃-C₄)cycloalkylaminocarbonyl, {(C₁-C₄)alkyl}{(C₃-C₄)cycloalkyl}aminocarbonyl and (C₁-C₄)alkylcarbonylamino; the ring nitrogen in pyridines Ir^{1-4} is optionally substituted by oxo; and suitable values for R^1 , R^2 , R^3 , Cy^1 and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. In another alternative, the embodiments described in this paragraph exclude the compound exemplified in Example 205, Example 211, Example 214, Example 222, Example 226, Example 235, Example 236, Example 281, Example 292, Example 295, Example 298, Example 300, Example 302, Example 305, Example 304, Example 306, Example

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307, Example 210, Example 296, Example 311, Example 230, Example 244, Example 258 and Example 291 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

For each of the embodiment described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiment described in the paragraph immediately following Formulas Ir¹⁻²¹, R¹ is preferably methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas Ir¹⁻²¹, R¹ is preferably methyl or ethyl; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas Ir¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas Ir¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas Ir¹⁻²¹, R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

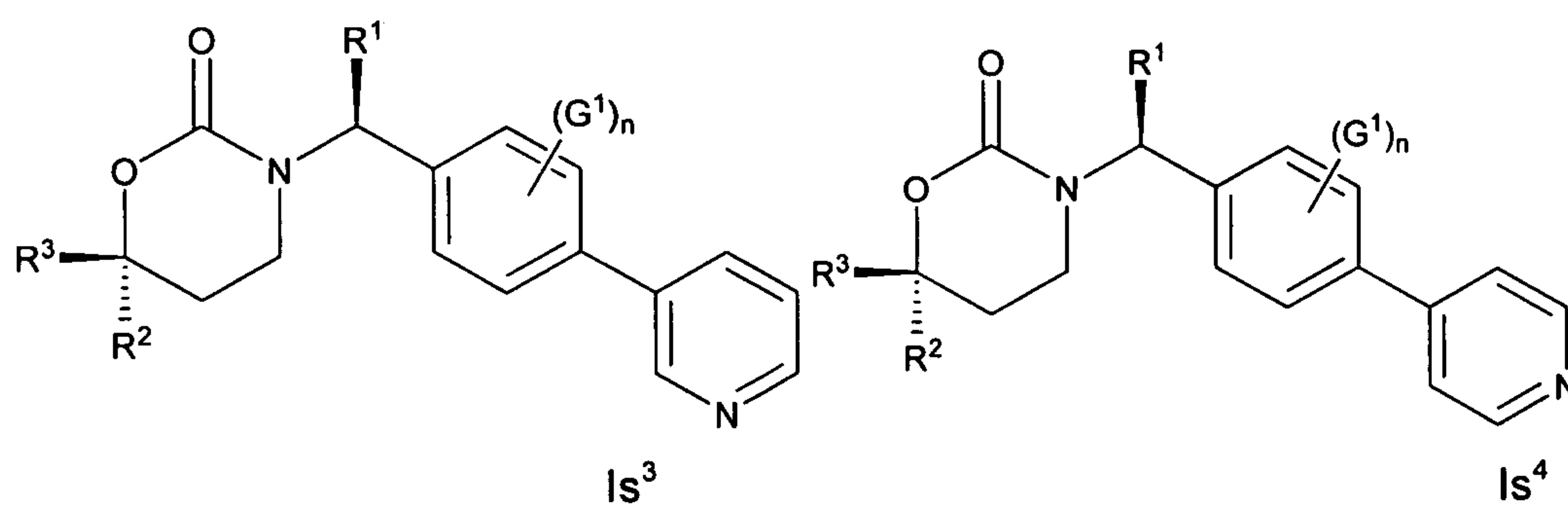
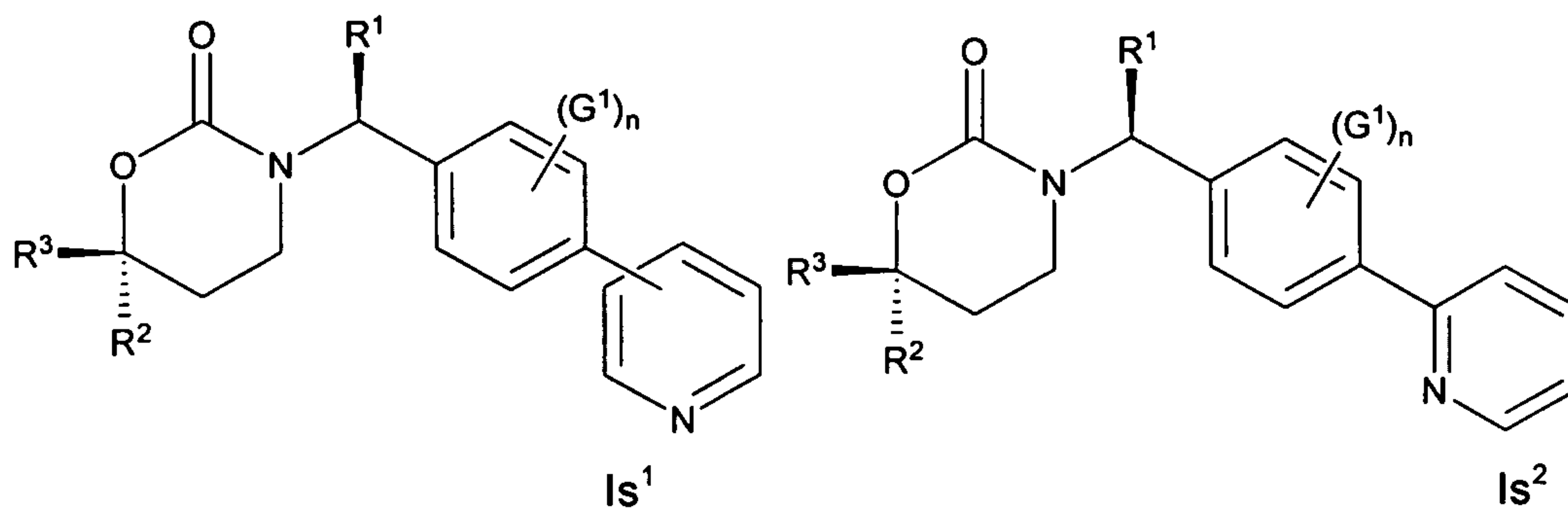
For each of the embodiment described in the paragraph immediately following Formulas Ir¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas Ir¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; one or two ring carbon atoms in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Ir¹⁻²¹ are optionally substituted with fluoro, chloro, cyano, CONH₂, CONHMe, CONMe₂, CONHc-Pr, methoxy, ethoxy, methyl, ethyl or CF₃. the substitutable ring nitrogen atom in the pyrazole rings in Formulas Ir¹⁸, Ir²⁰ and Ir²¹ are

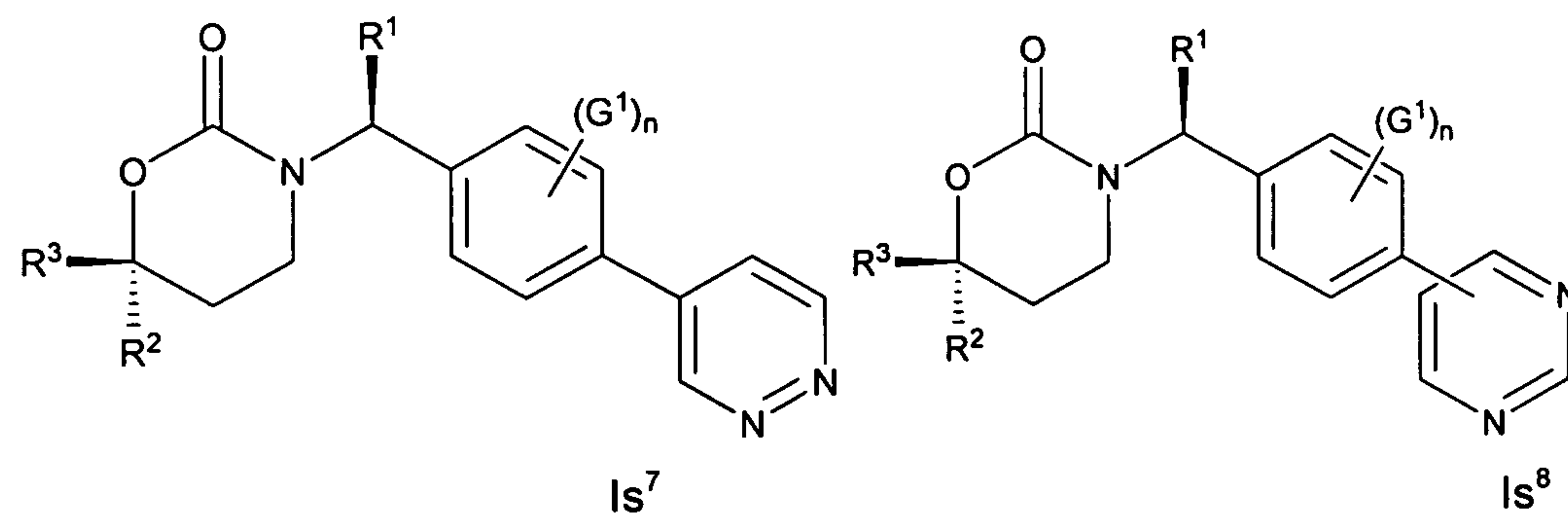
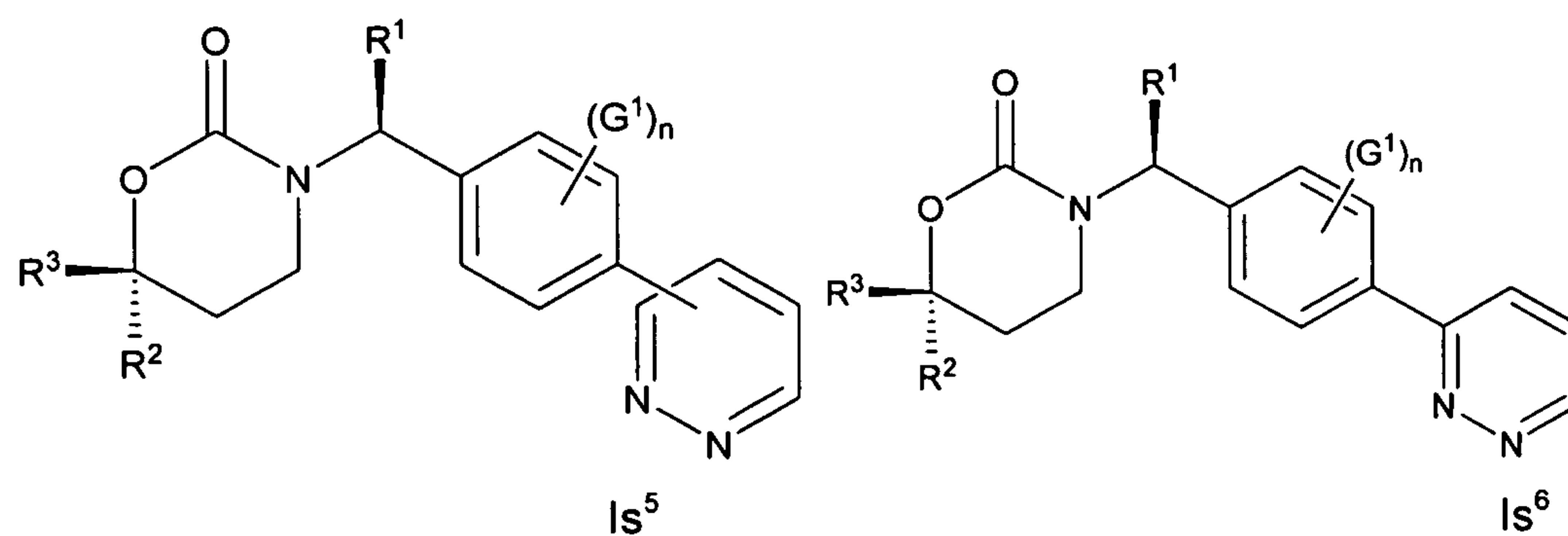
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optionally substituted with (C₁-C₄) alkyl, (C₃-C₄) cycloalkyl, (C₃-C₄) cycloalkyl(C₁-C₂) alkyl, or (C₁-C₂) haloalkyl, the ring nitrogen in the pyridine rings in Formulas Ir¹⁻⁴ is optionally substituted by oxo.

Another embodiment of the invention is a compound of any one of Formulas Is¹⁻²¹, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof:

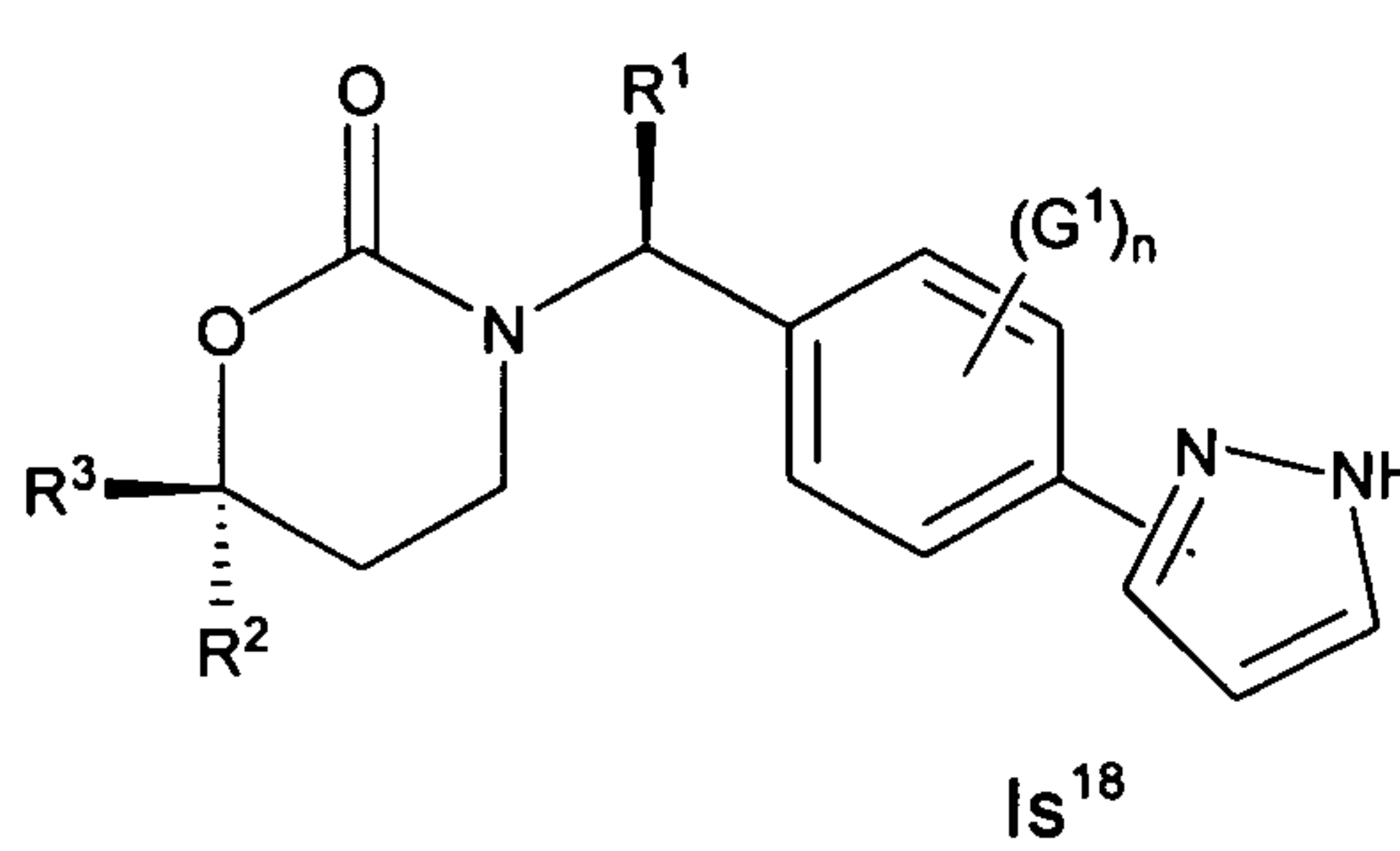
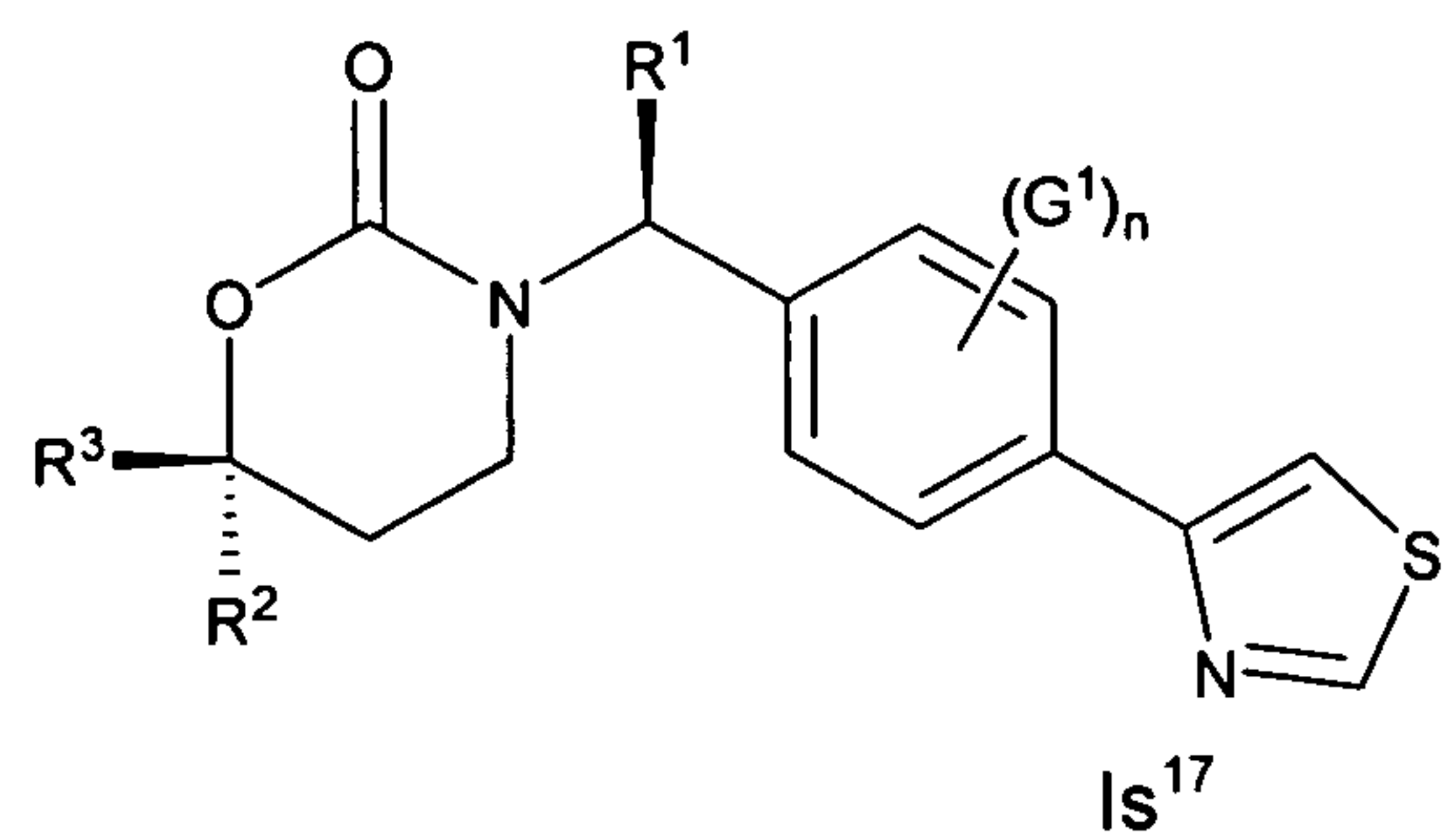
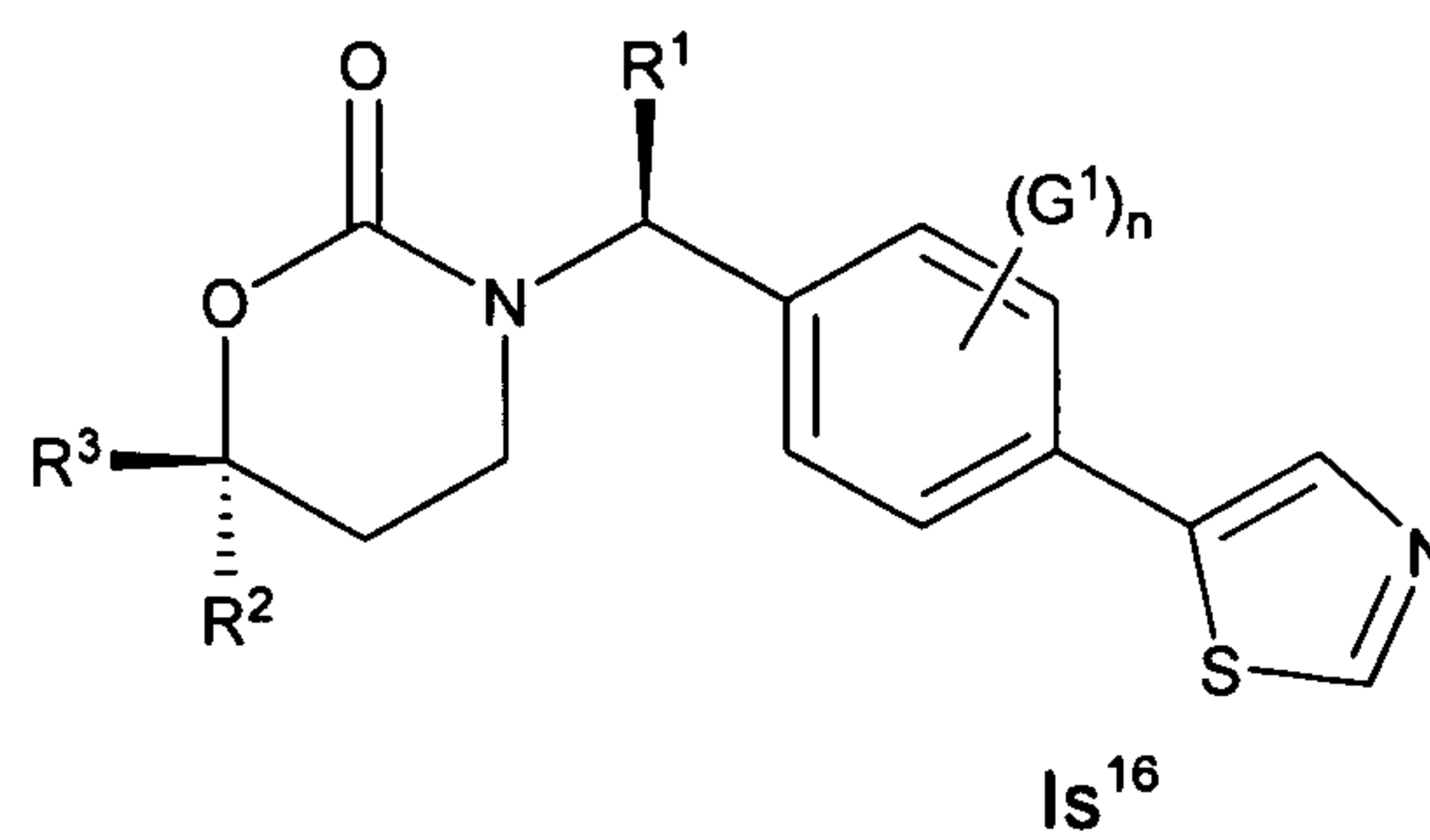
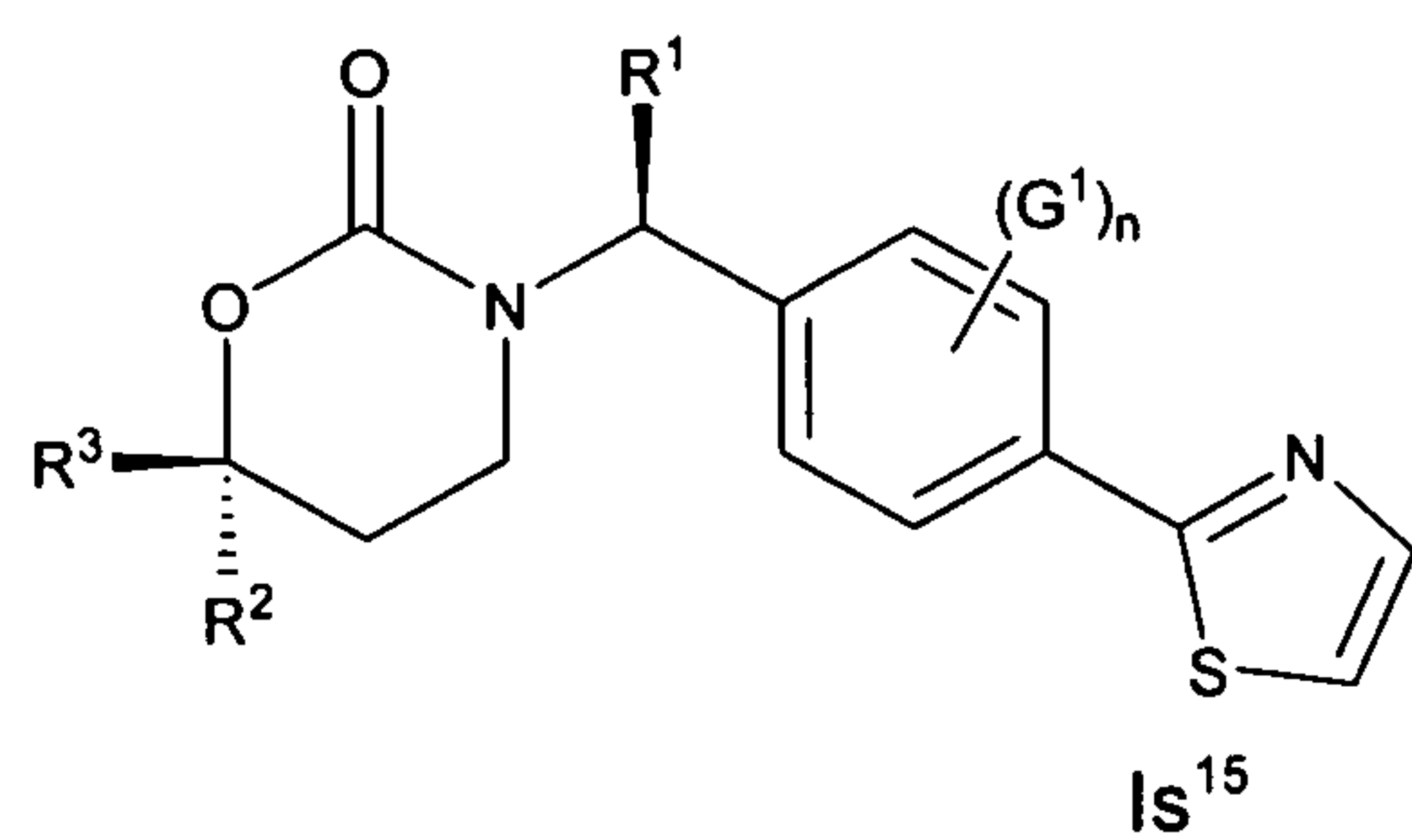
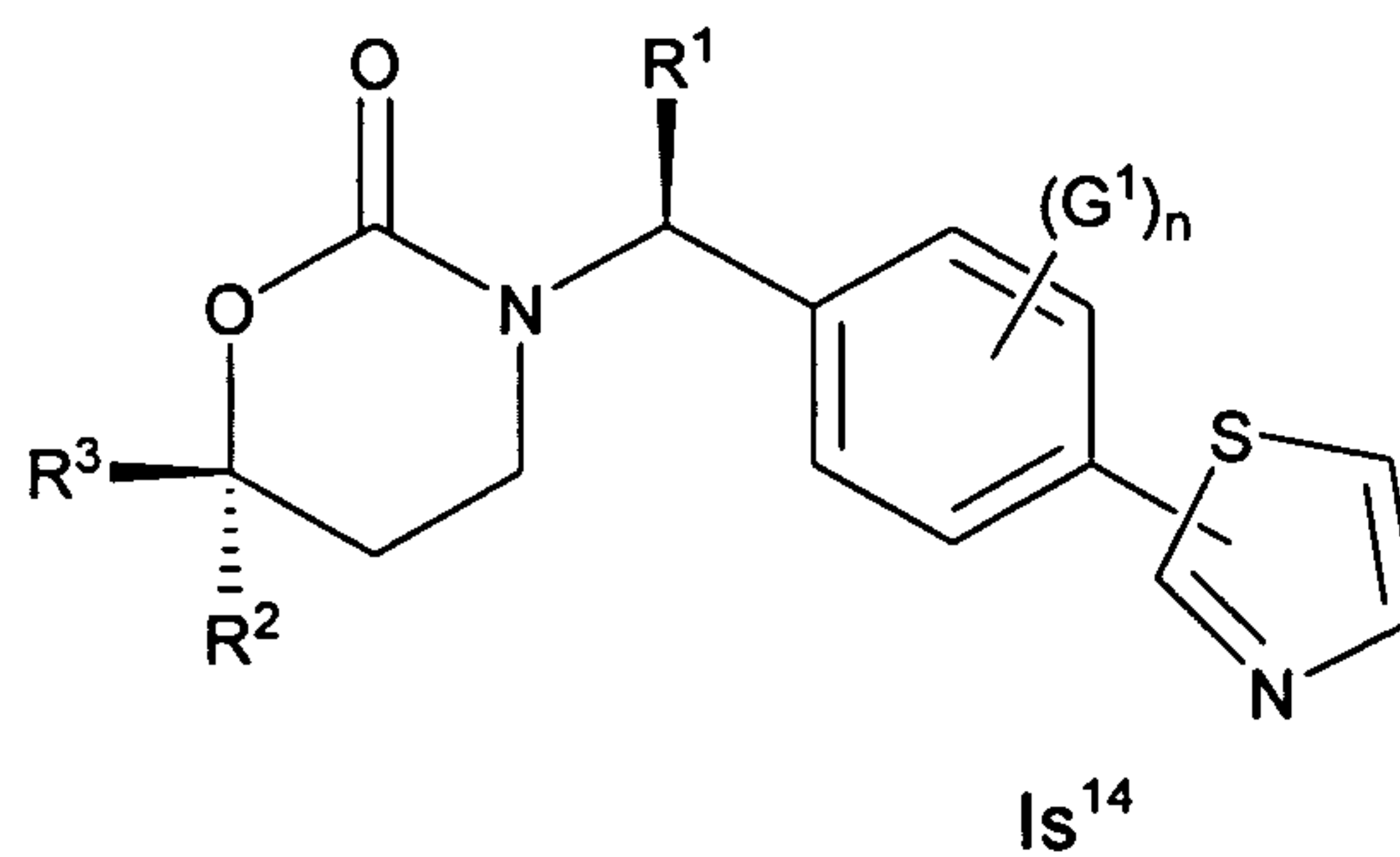
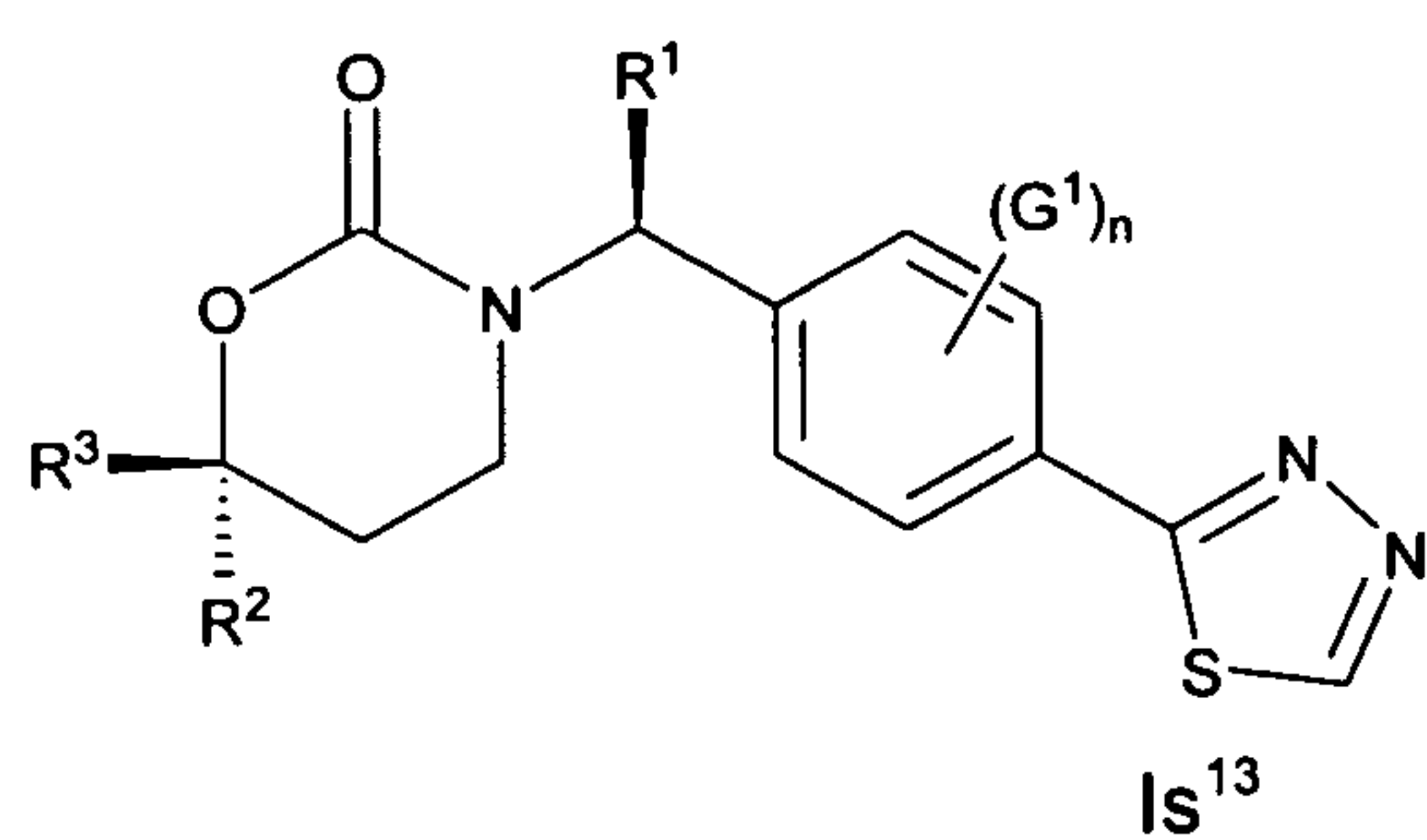
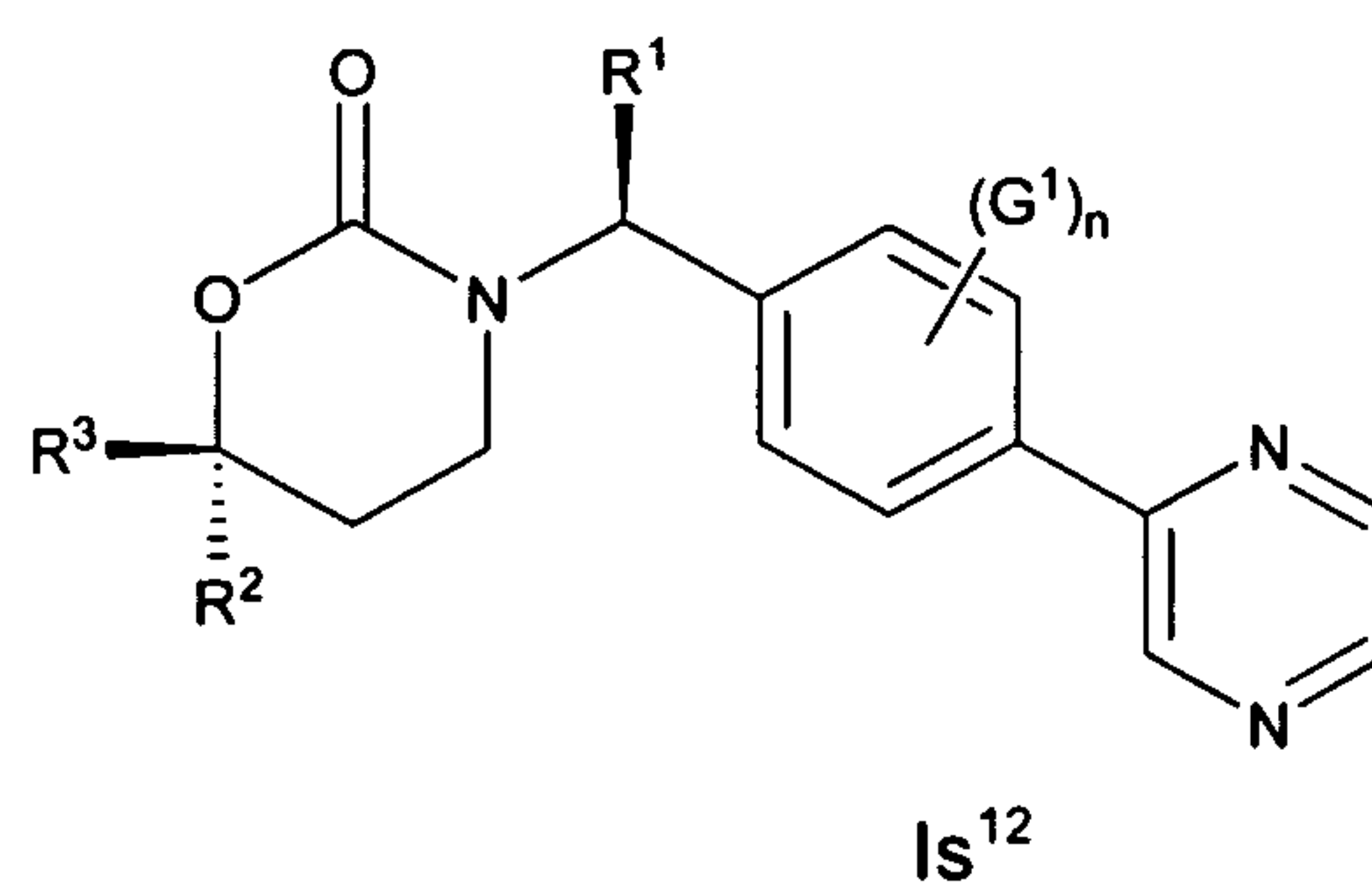
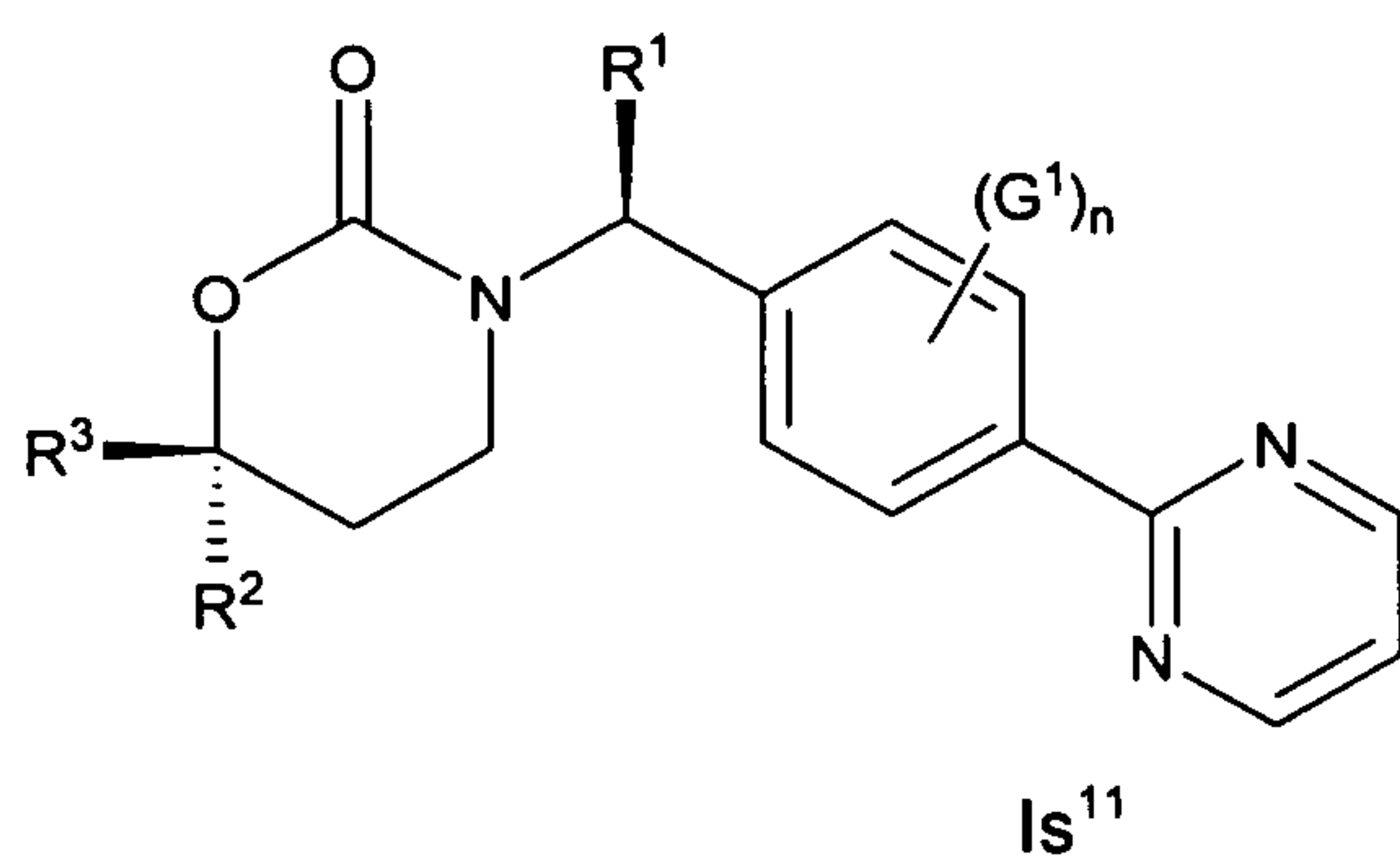
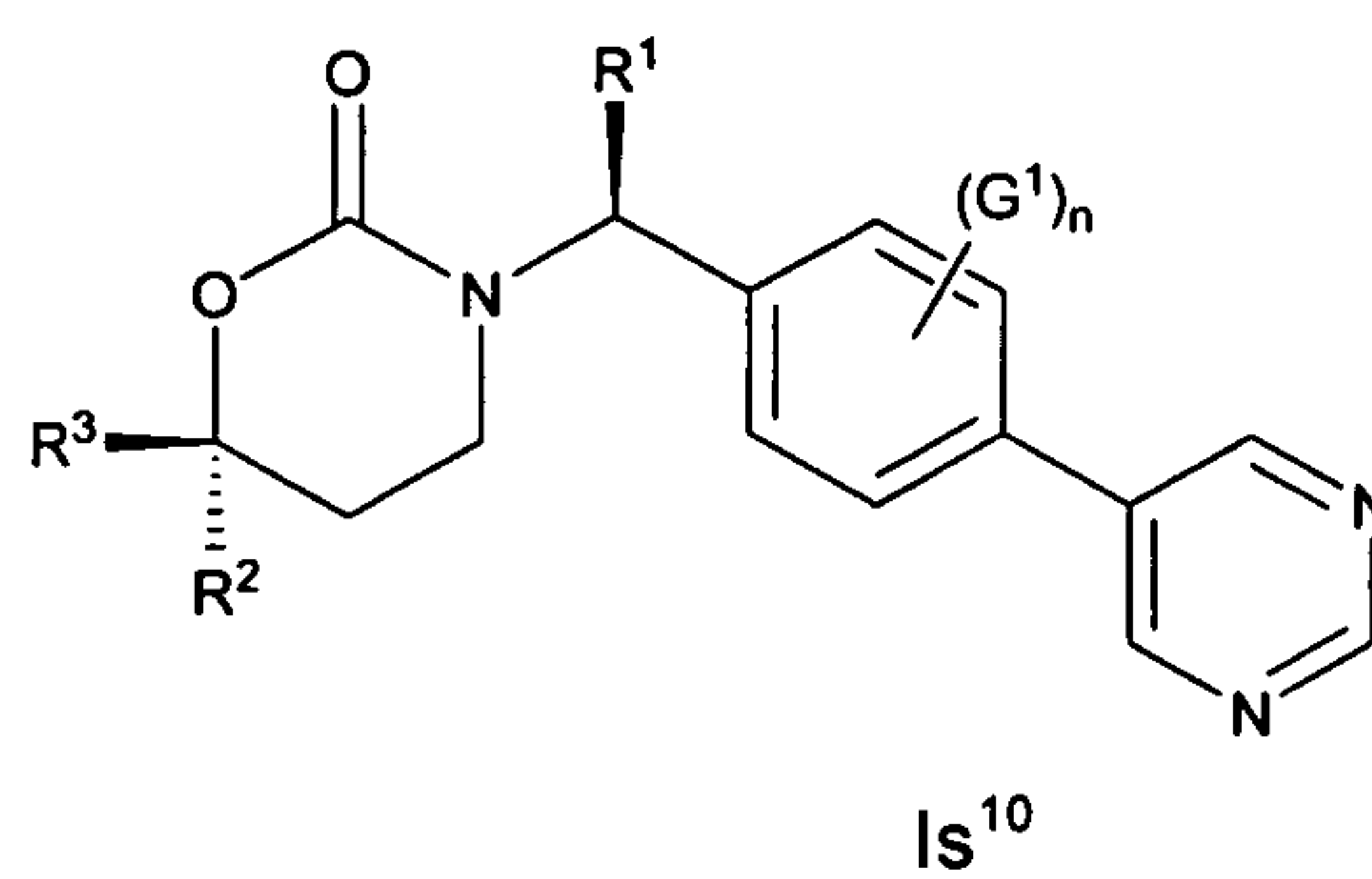
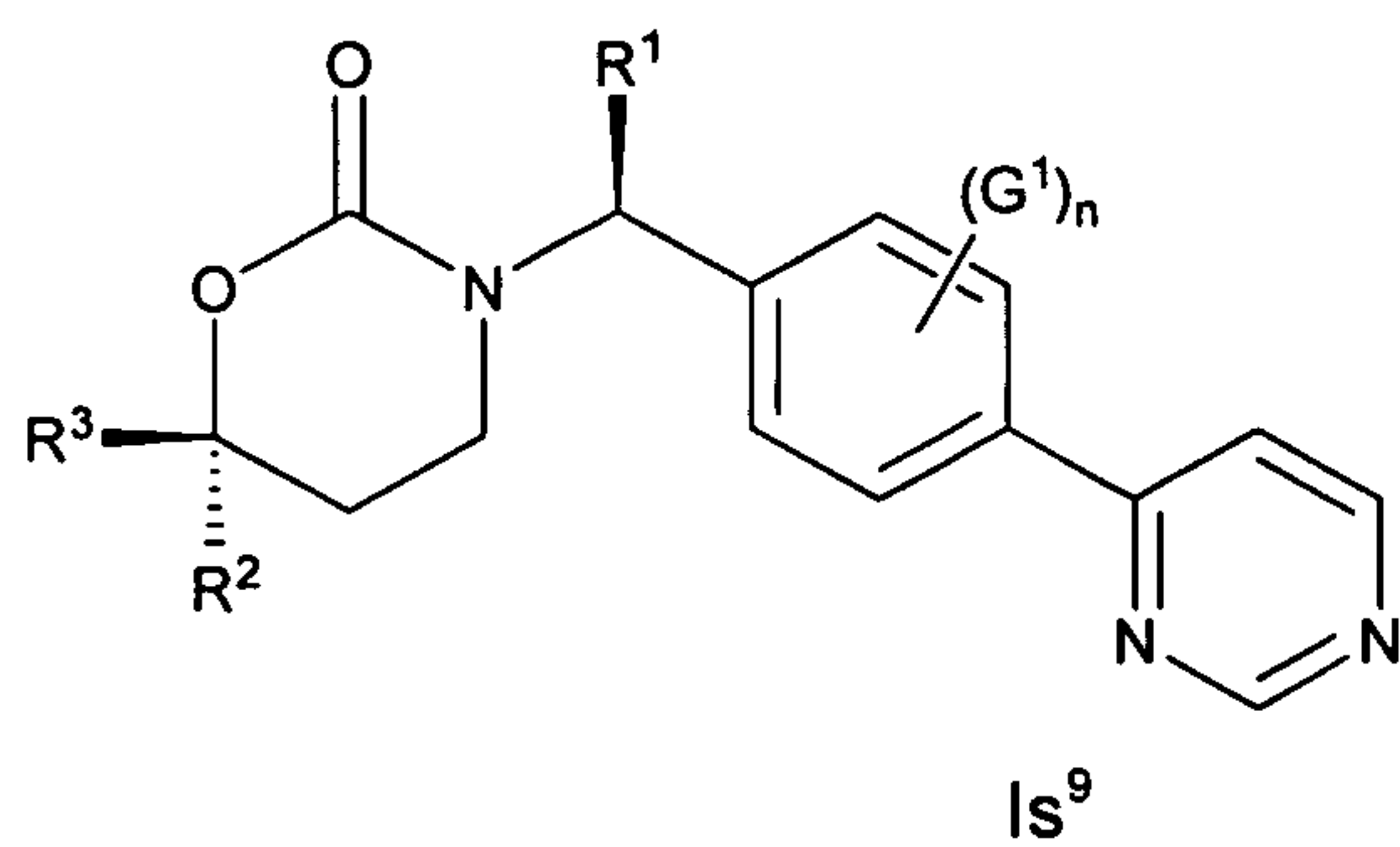


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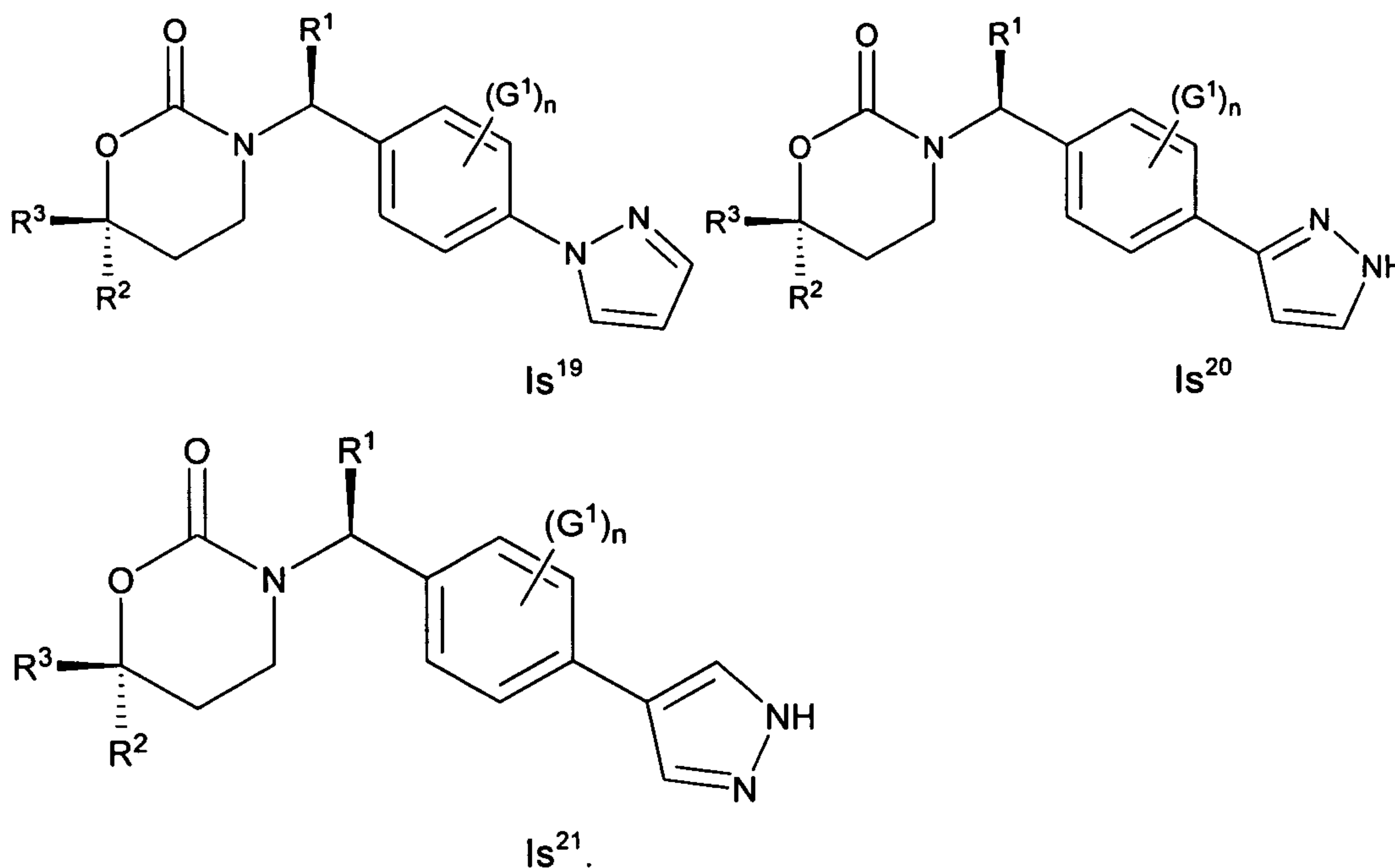
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- 5 In Formulas Is¹⁻²¹, the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Is¹⁻²¹ are optionally substituted (substitution at ring carbons bonded to hydrogen and ring nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a "substitutable ring nitrogen atom") with up to four substituents as described above for Cy². Suitable values for G¹ are as described in Formula If; n
- 10 is 0, 1 or 2; substituents for Cy² and suitable values for R¹, R² and R³ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, n is 0, 1 or 2, suitable values for G¹ in Formulas Is¹⁻²¹ and suitable substituents for the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Is¹⁻²¹ are as described
- 15 for G¹ and G², respectively, in Formula If, and values for R¹, R², R³ and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, n is 0, 1 or 2; suitable values for G¹ include (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom
- 20 in the pyrazole rings in Formulas Is¹⁸, Is²⁰ and Is²¹ include (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₄)haloalkyl; suitable substituents for a ring carbon atom in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Is¹⁻²¹ include fluorine, chlorine, cyano, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl, (C₃-C₄)cycloalkylaminocarbonyl, {(C₁-C₄)alkyl}{(C₃-C₄)cycloalkyl}aminocarbonyl and (C₁-C₄)alkylcarbonylamino; the ring nitrogen in
- 25

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pyridines Is¹⁻⁴ is optionally substituted by oxo; and suitable values for R¹, R² and R³ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. In another alternative, the embodiments described in this paragraph exclude the compound exemplified in

5 Example 205, Example 211, Example 214, Example 222, Example 226, Example 235, Example 236, Example 281, Example 292, Example 295, Example 298, Example 300, Example 302, Example 305, Example 304, Example 306, Example 307, Example 210, Example 296, Example 311, Example 230, Example 244, Example 258 and Example 291, or a pharmaceutically acceptable salt, enantiomer or

10 diastereomer thereof.

For each of the embodiment described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiment described in the paragraph immediately following Formulas Is¹⁻²¹, R¹ is preferably methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂,
15 H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas Is¹⁻²¹, R¹ is preferably methyl or ethyl; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

20 For each of the embodiment described in the paragraph immediately following Formulas Is¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

25

For each of the embodiment described in the paragraph immediately following Formulas Is¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

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For each of the embodiment described in the paragraph immediately following Formulas Is¹⁻²¹, R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

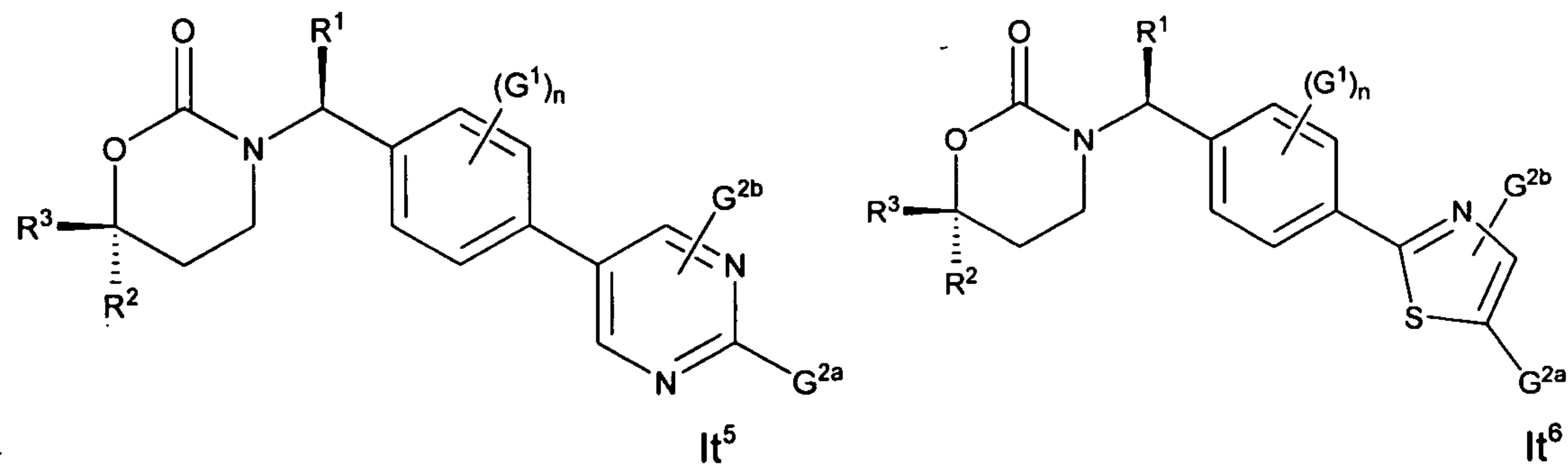
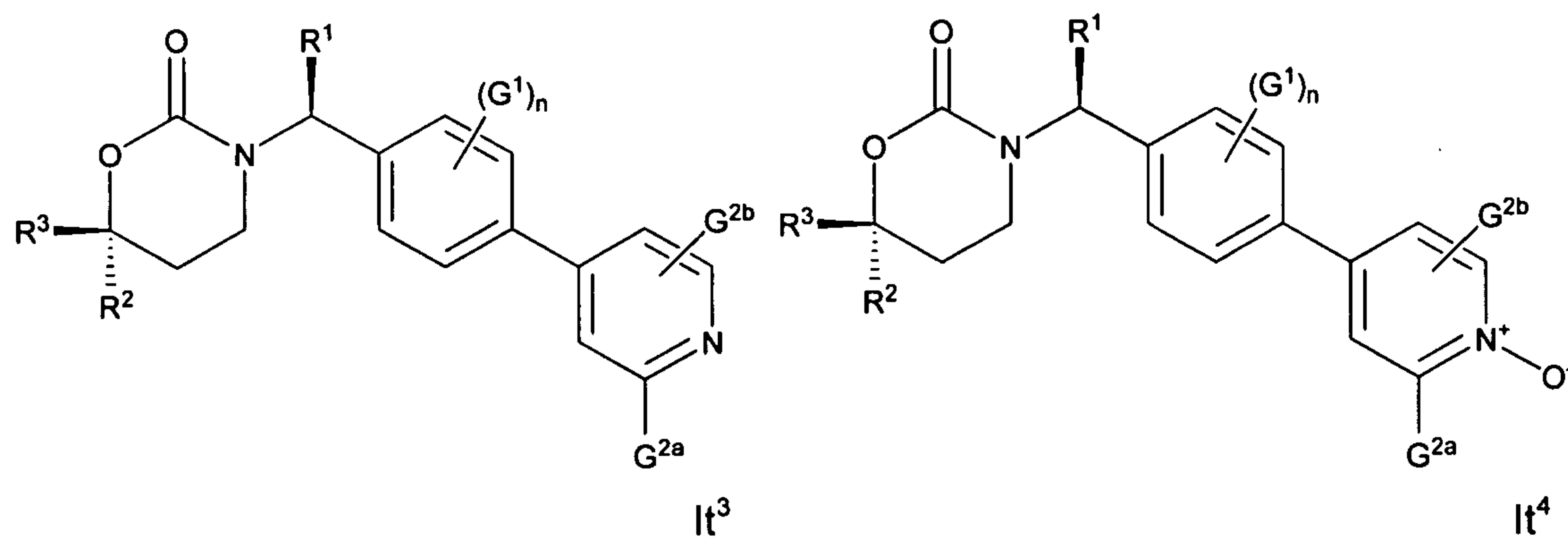
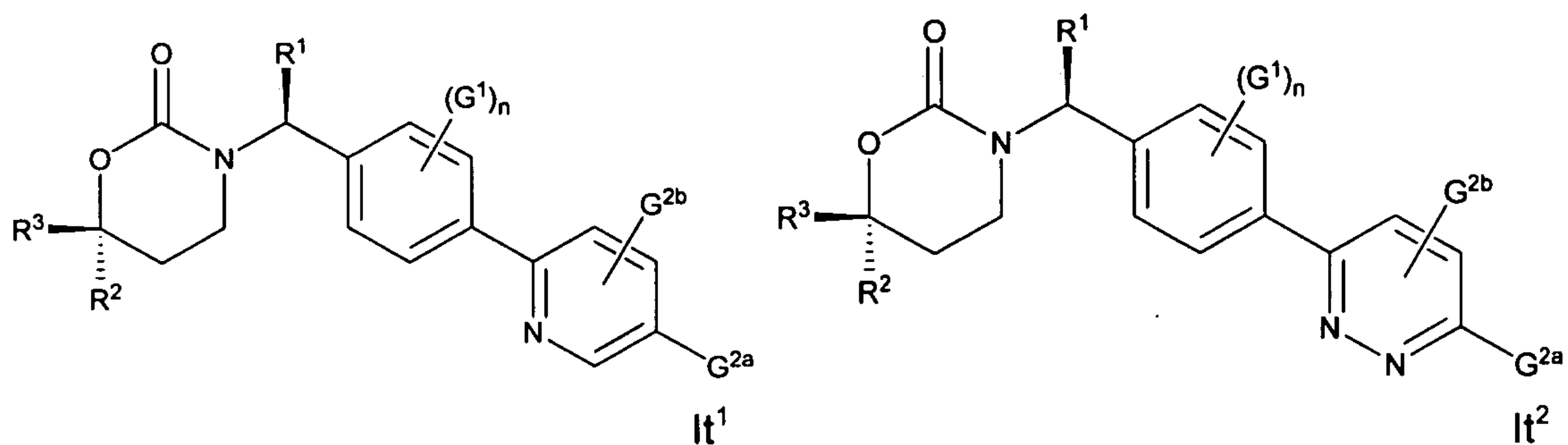
For each of the embodiment described in the paragraph immediately following Formulas Is¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

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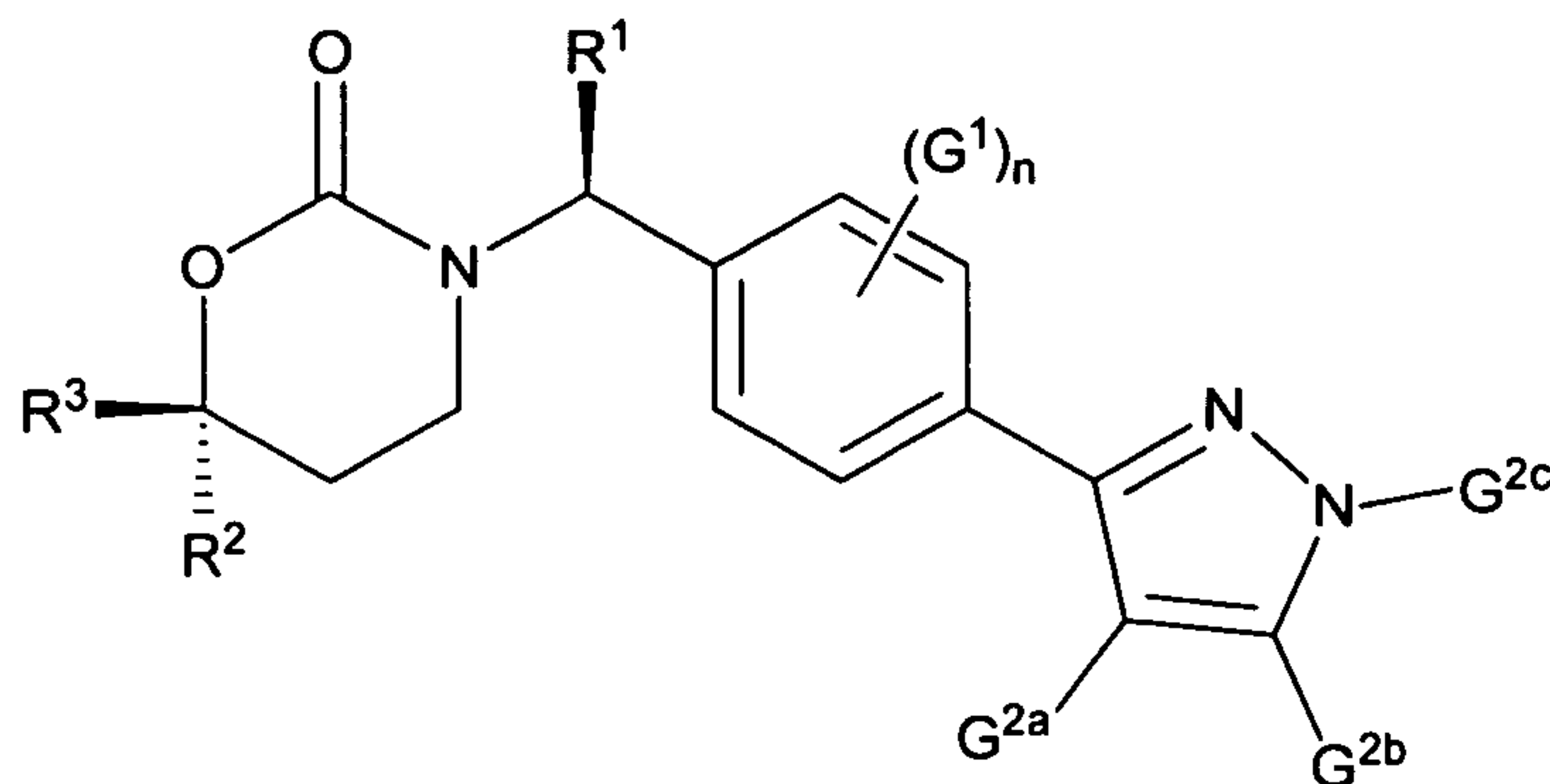
- 75 -

For each of the embodiment described in the paragraph immediately following Formulas Is¹⁻²¹, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; one or two ring carbon atoms in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Is¹⁻²¹ are optionally substituted with fluoro, chloro, cyano, CONH₂, CONHMe, CONMe₂, CONHc-Pr, methyl, ethyl or CF₃; the substitutable ring nitrogen atom in the pyrazole rings in Formulas Is¹⁸, Is²⁰ and Is²¹ is optionally substituted with (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, or (C₁-C₂)haloalkyl, the ring nitrogen in the pyridine rings in Formulas Is¹⁻⁴ is optionally substituted by oxo.

Another embodiment of the invention is a compound represented by any one of Formulas It¹⁻⁶, or a pharmaceutically acceptable salt thereof:



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It⁷.

In Formulas It¹⁻⁷, G¹ is (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; n is 0, 1 or 2; G^{2a} and G^{2b} are independently selected from hydrogen, fluorine, chlorine, cyano, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl, (C₃-C₄)cycloalkylaminocarbonyl, {(C₁-C₄)alkyl}{(C₃-C₄)cycloalkyl}aminocarbonyl and (C₁-C₄)alkylcarbonylamino; G^{2c} is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl or (C₁-C₄)haloalkyl; and suitable values for R¹, R² and R³ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. In another alternative, the embodiments in this paragraph exclude the compound exemplified in Example 205, Example 211, Example 214, Example 222, Example 226, Example 235, Example 236, Example 281, Example 292, Example 295, Example 298, Example 300, Example 302, Example 305, Example 304, Example 306, Example 307, Example 210, Example 296, Example 311, Example 230, Example 244, Example 258, and Example 291, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

For each of the embodiment described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiment described in the paragraph immediately following Formulas It¹⁻⁷, R¹ is preferably methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas It¹⁻⁷, R¹ is preferably methyl or ethyl; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas It¹⁻⁷, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-

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C₄)haloalkyl and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

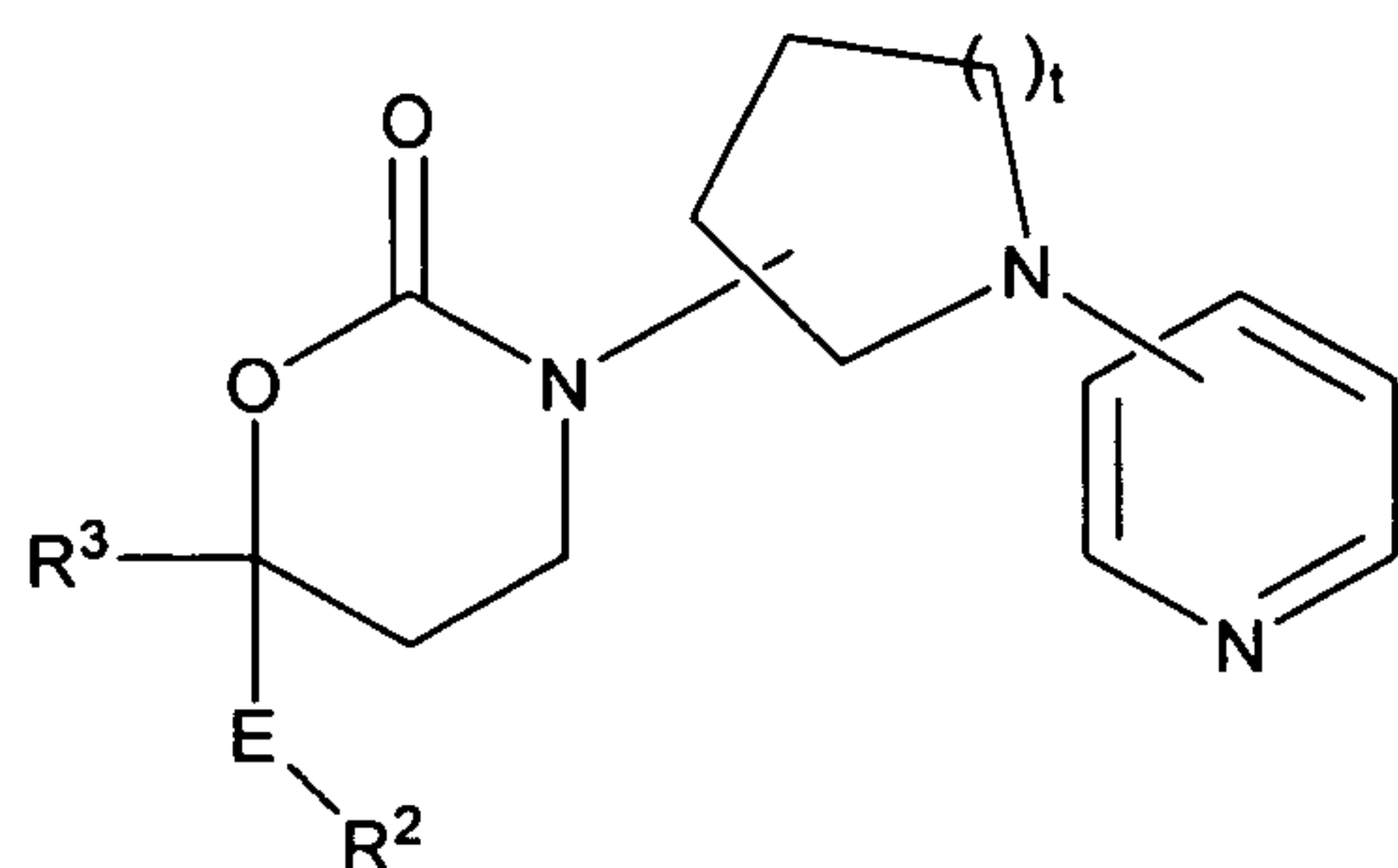
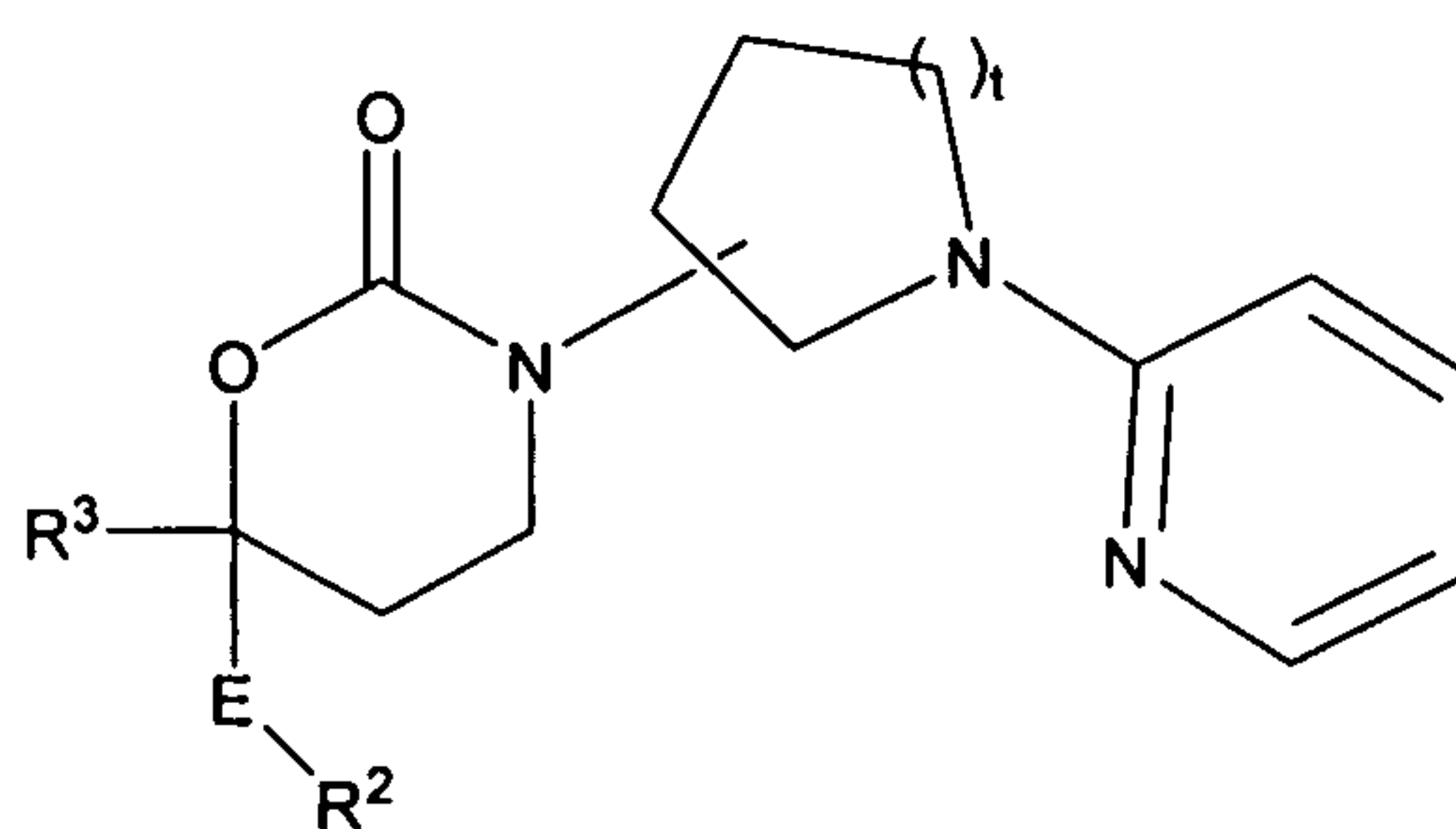
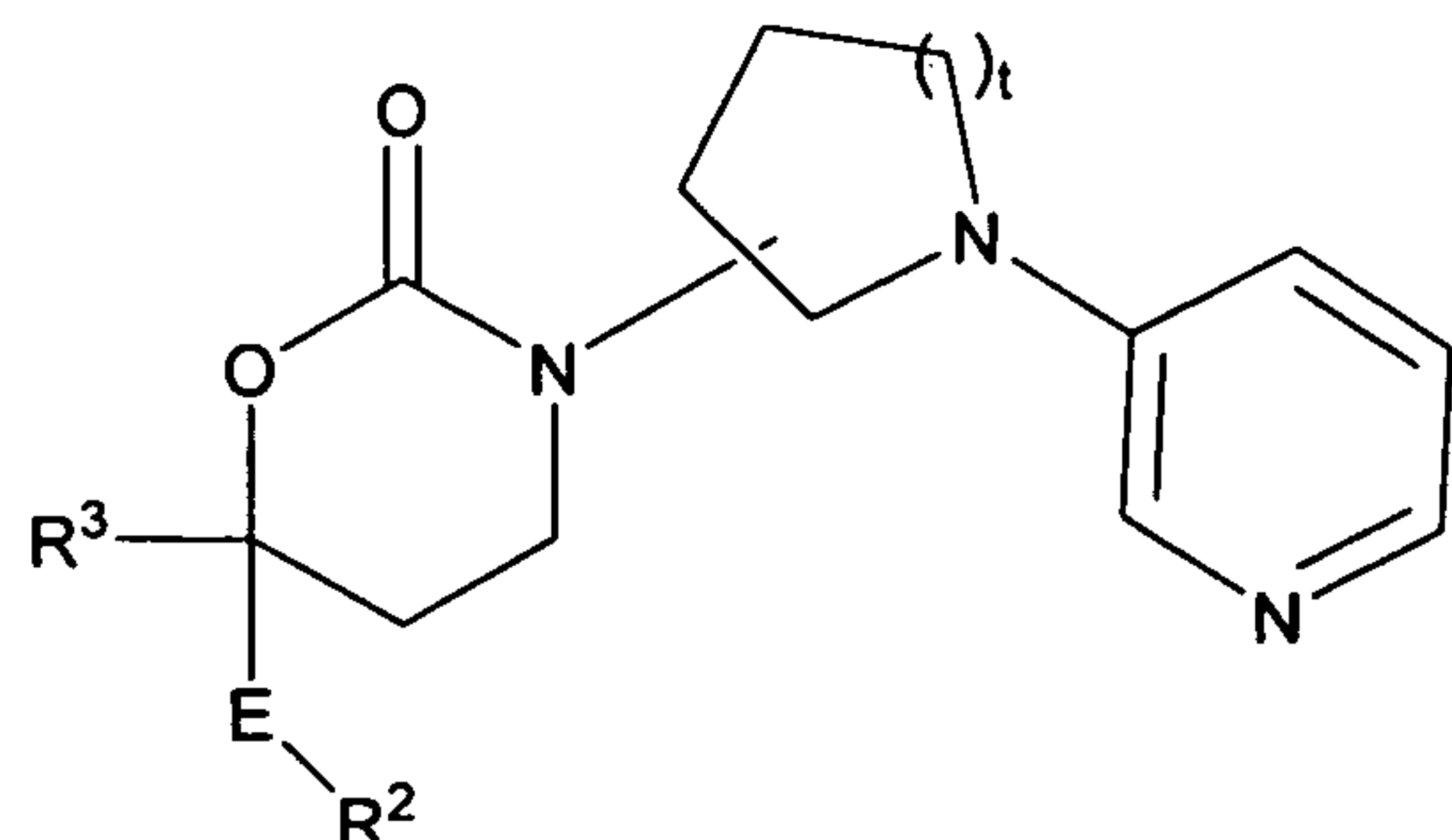
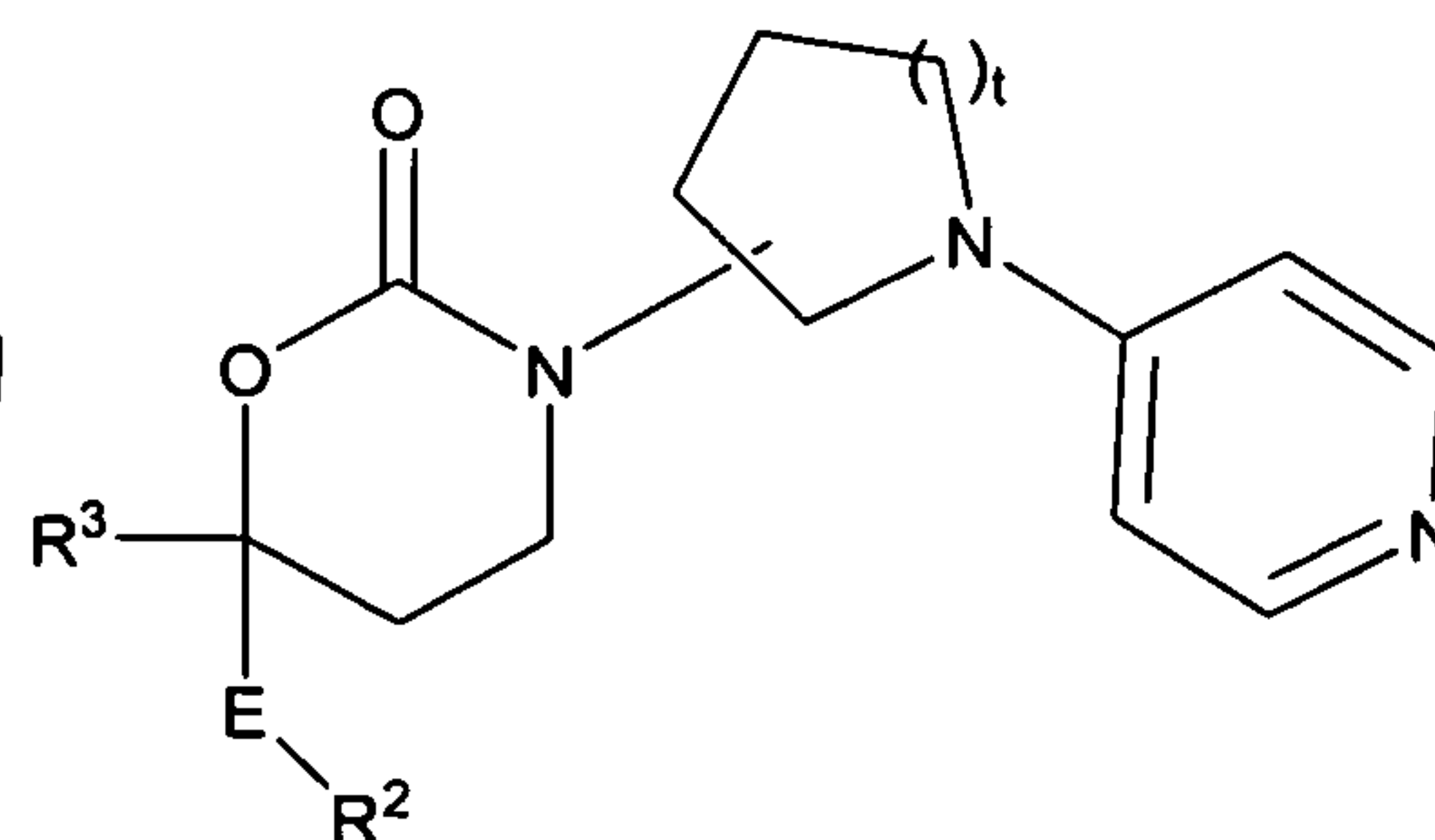
For each of the embodiment described in the paragraph immediately following Formulas It¹⁻⁷, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas It¹⁻⁷, R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas It¹⁻⁷, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

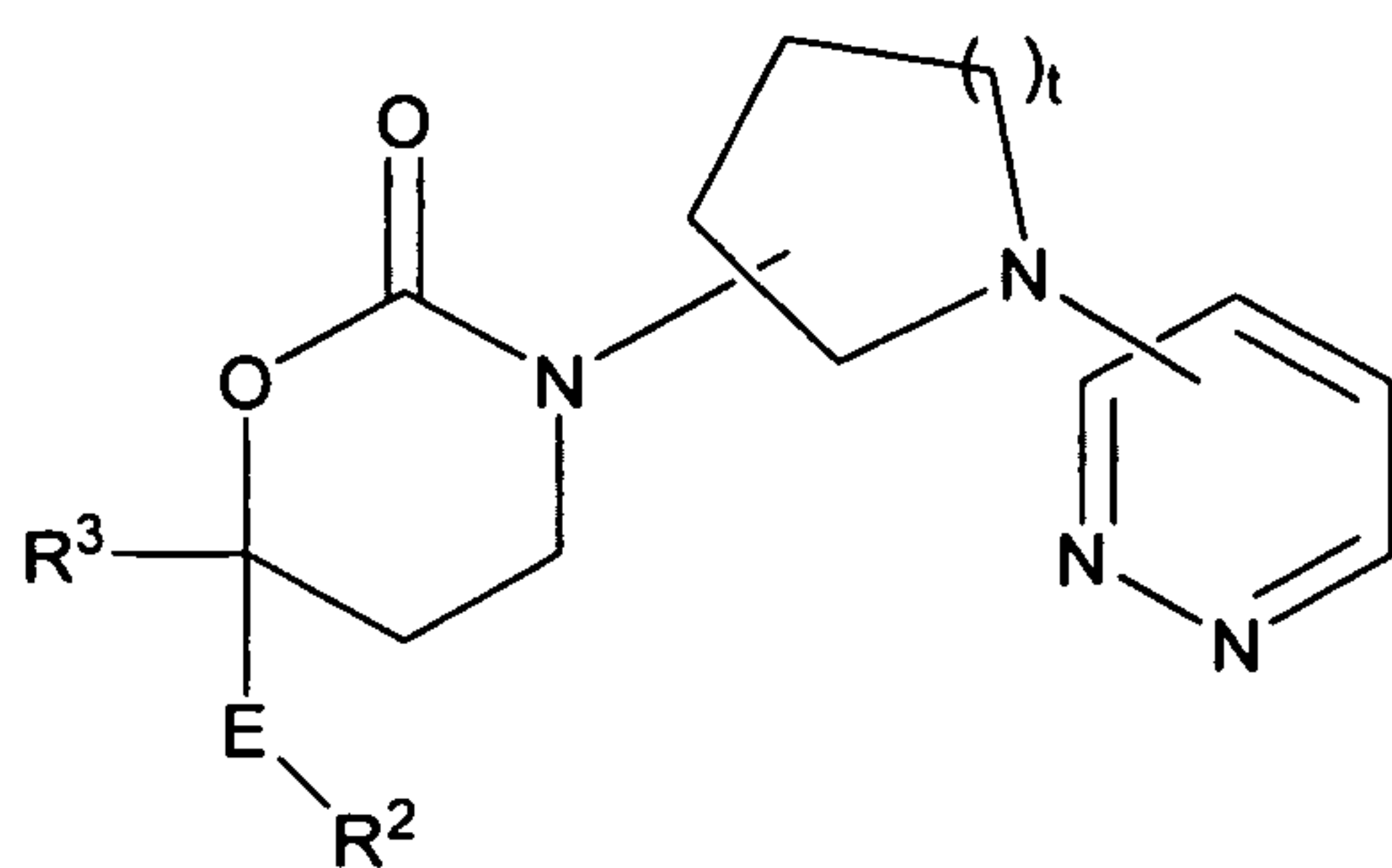
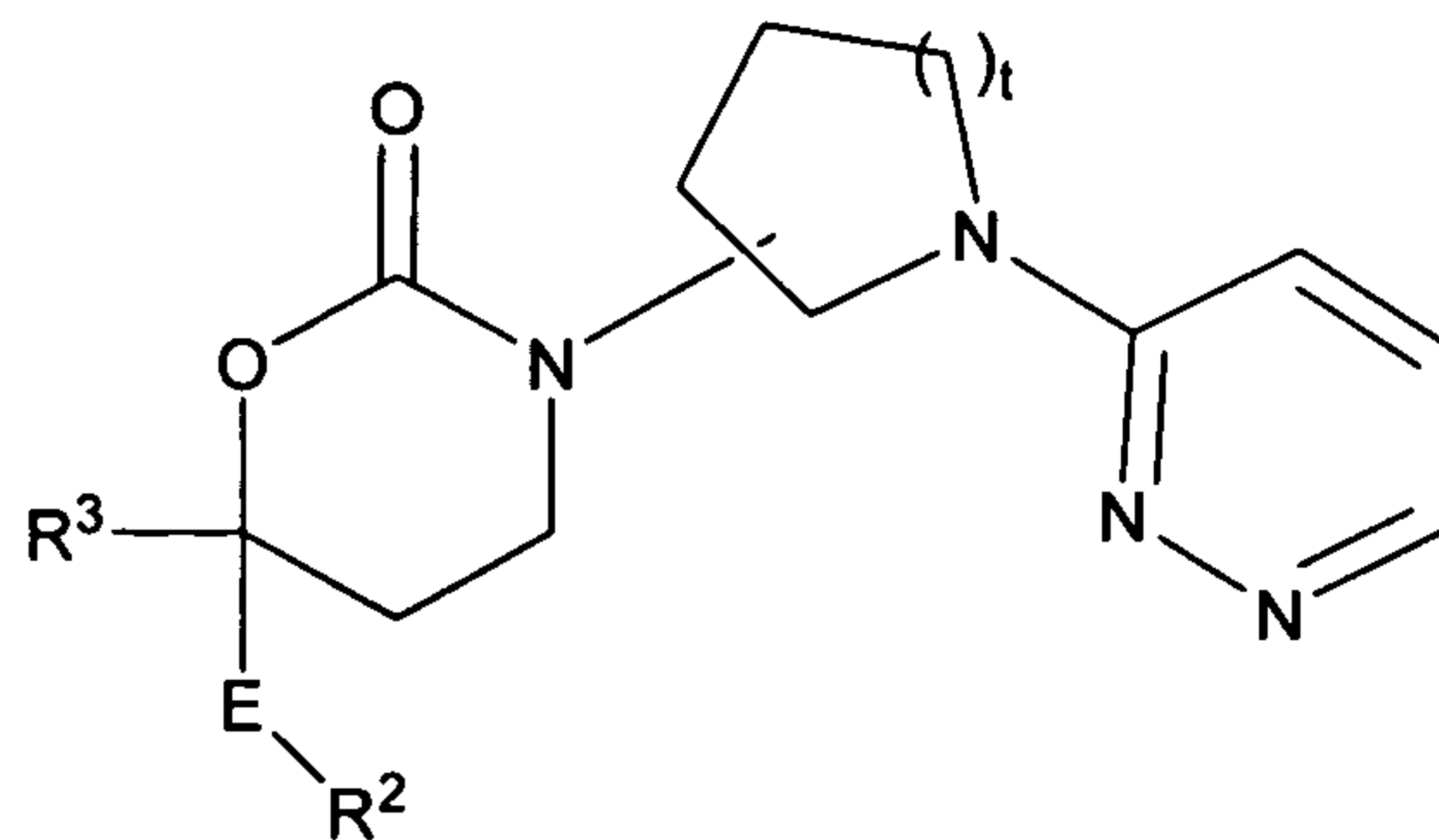
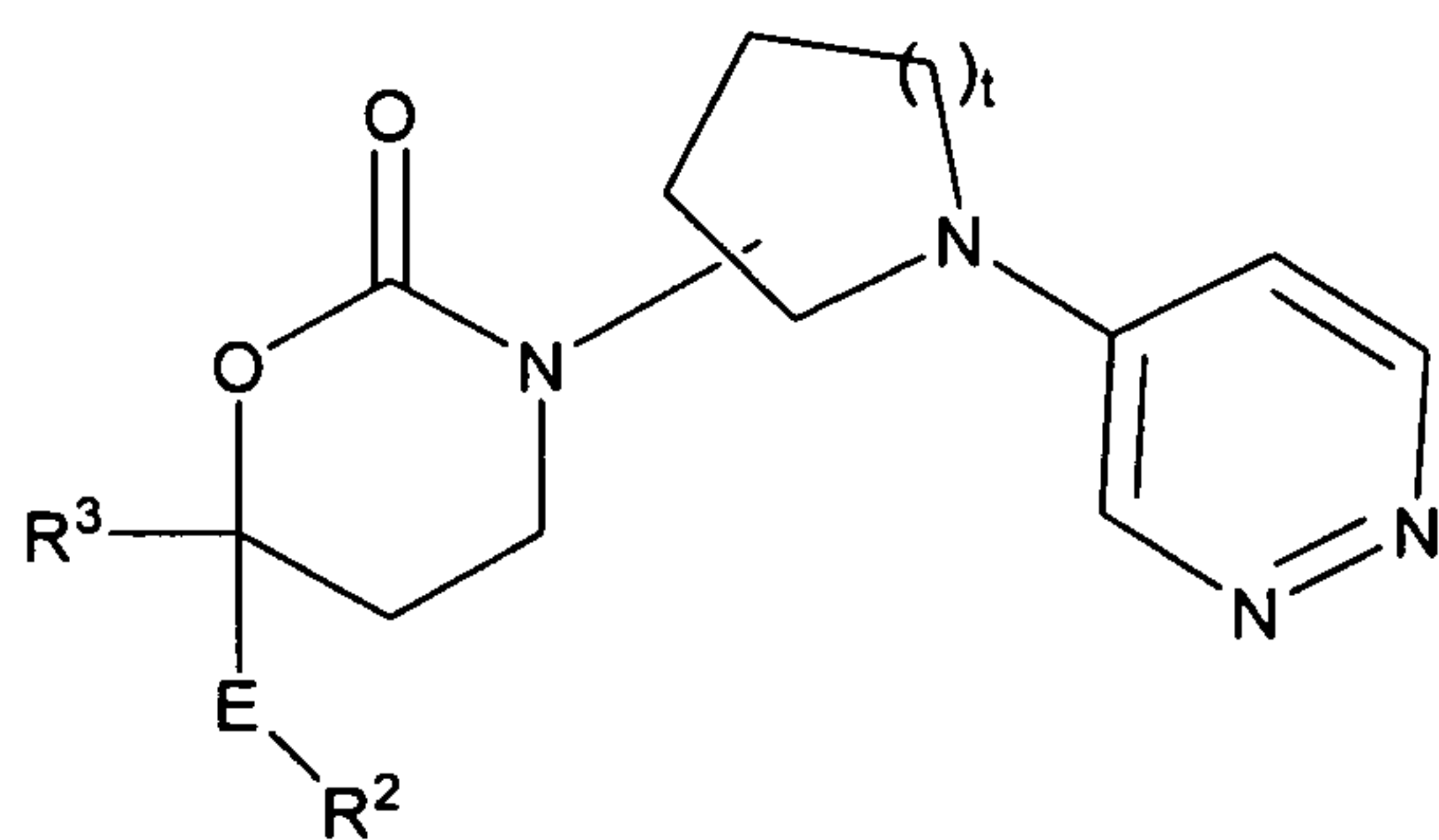
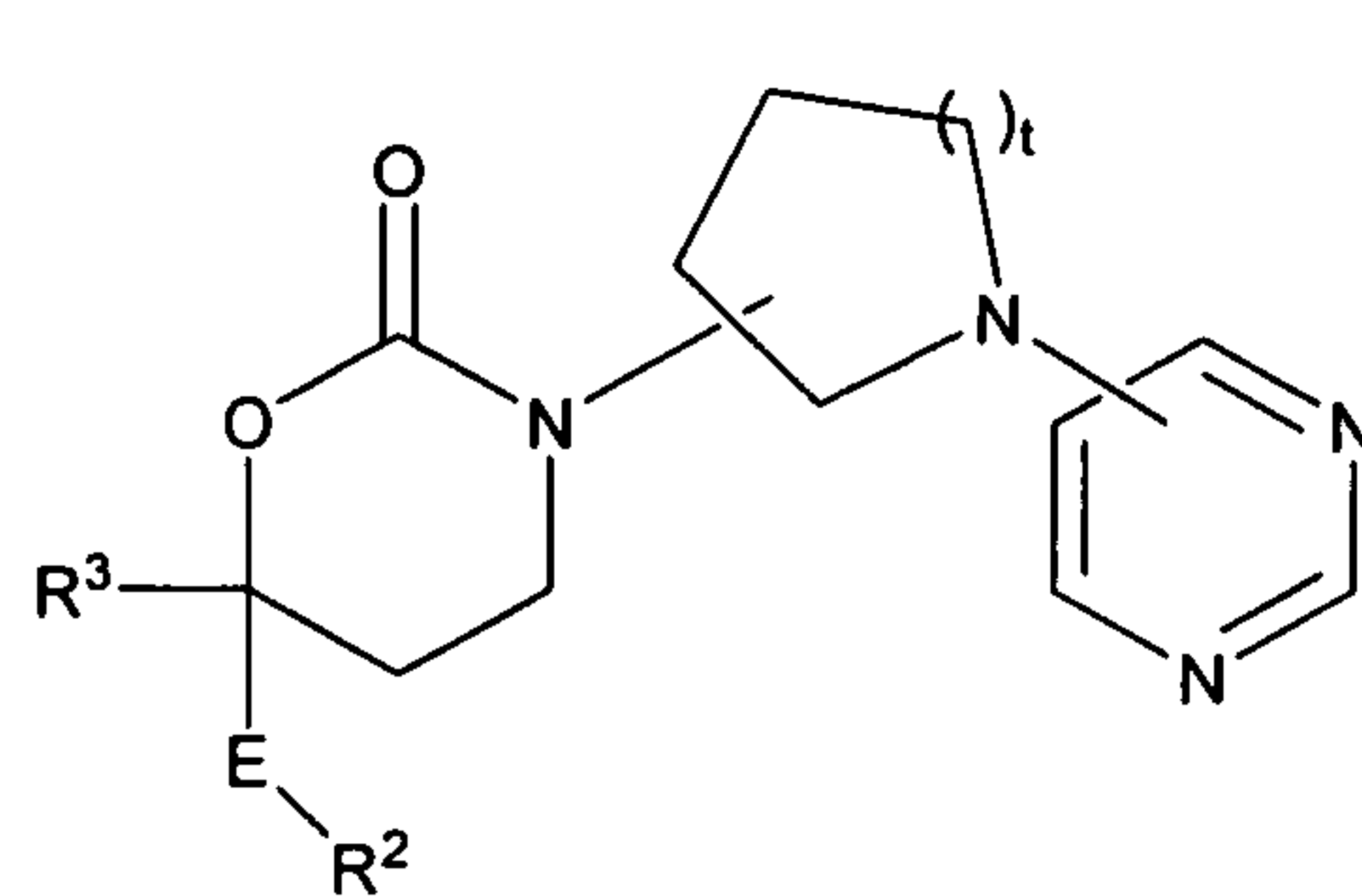
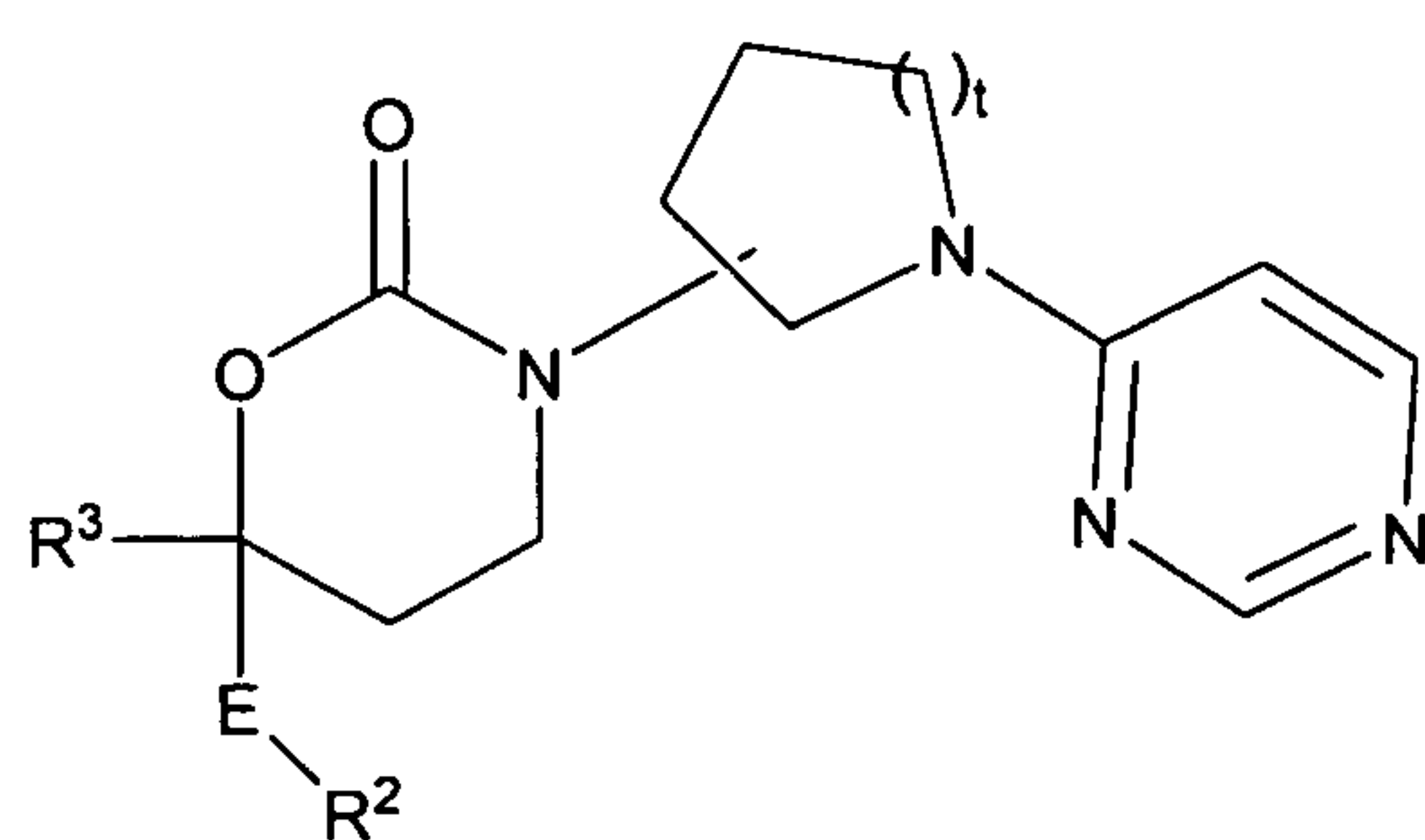
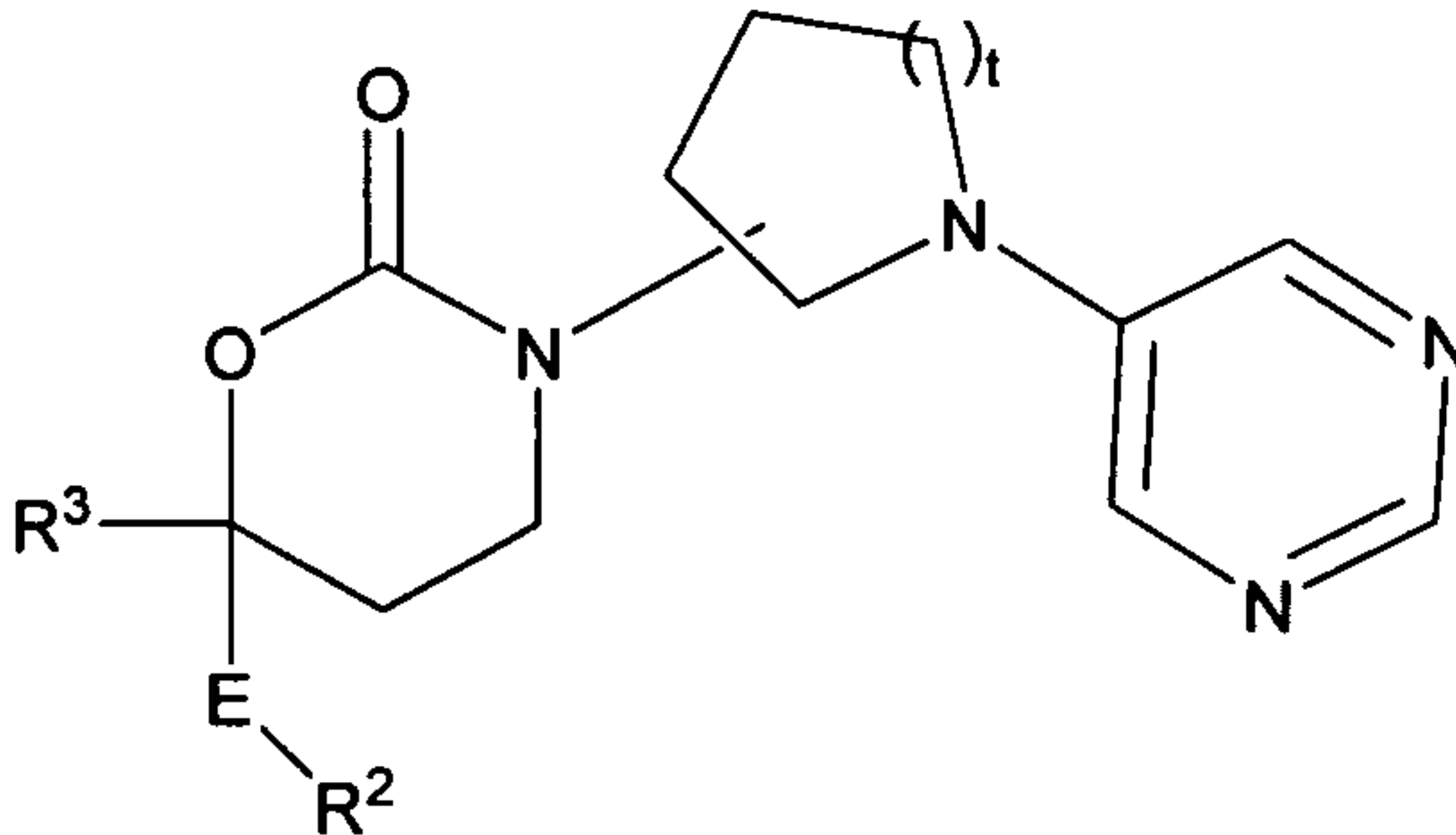
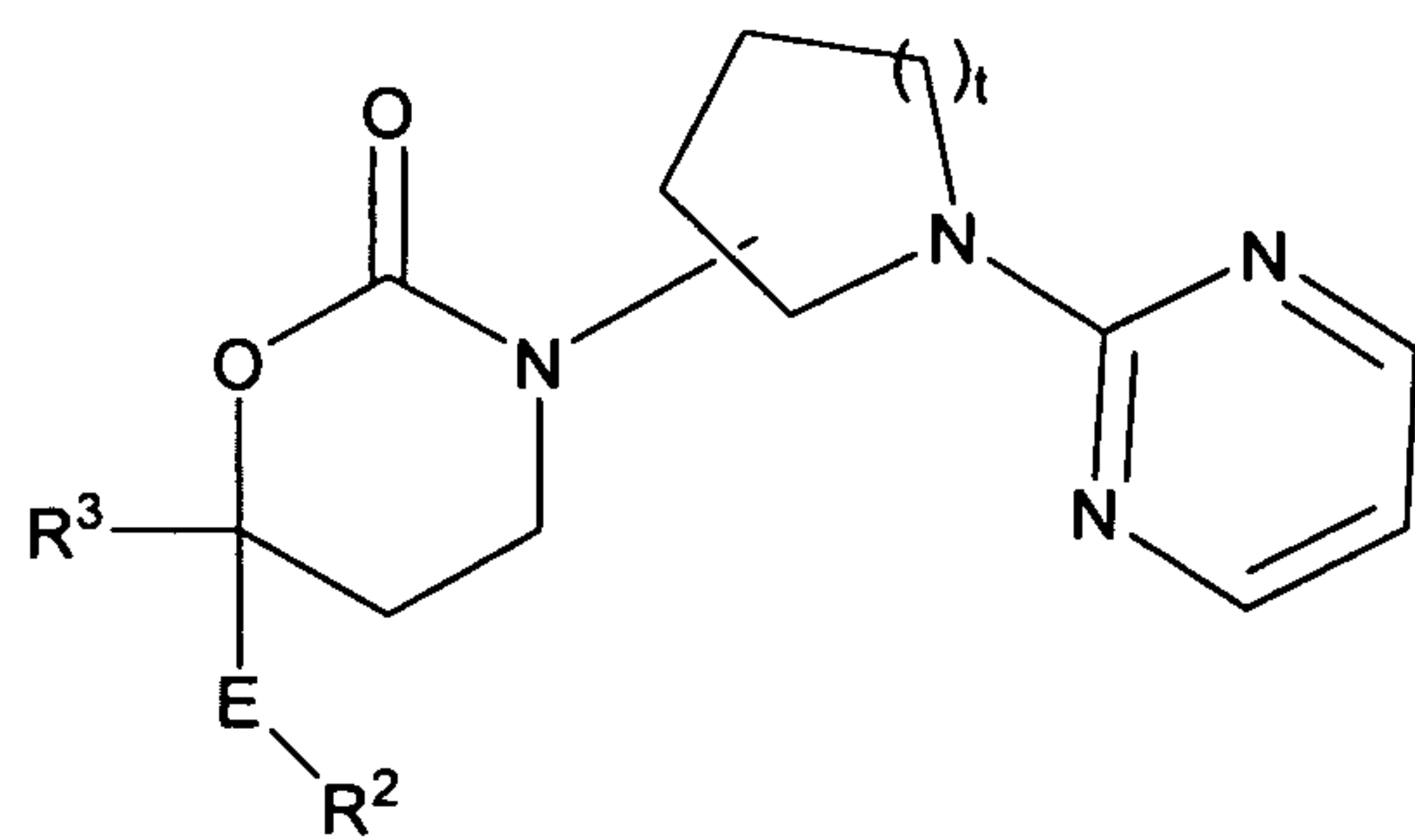
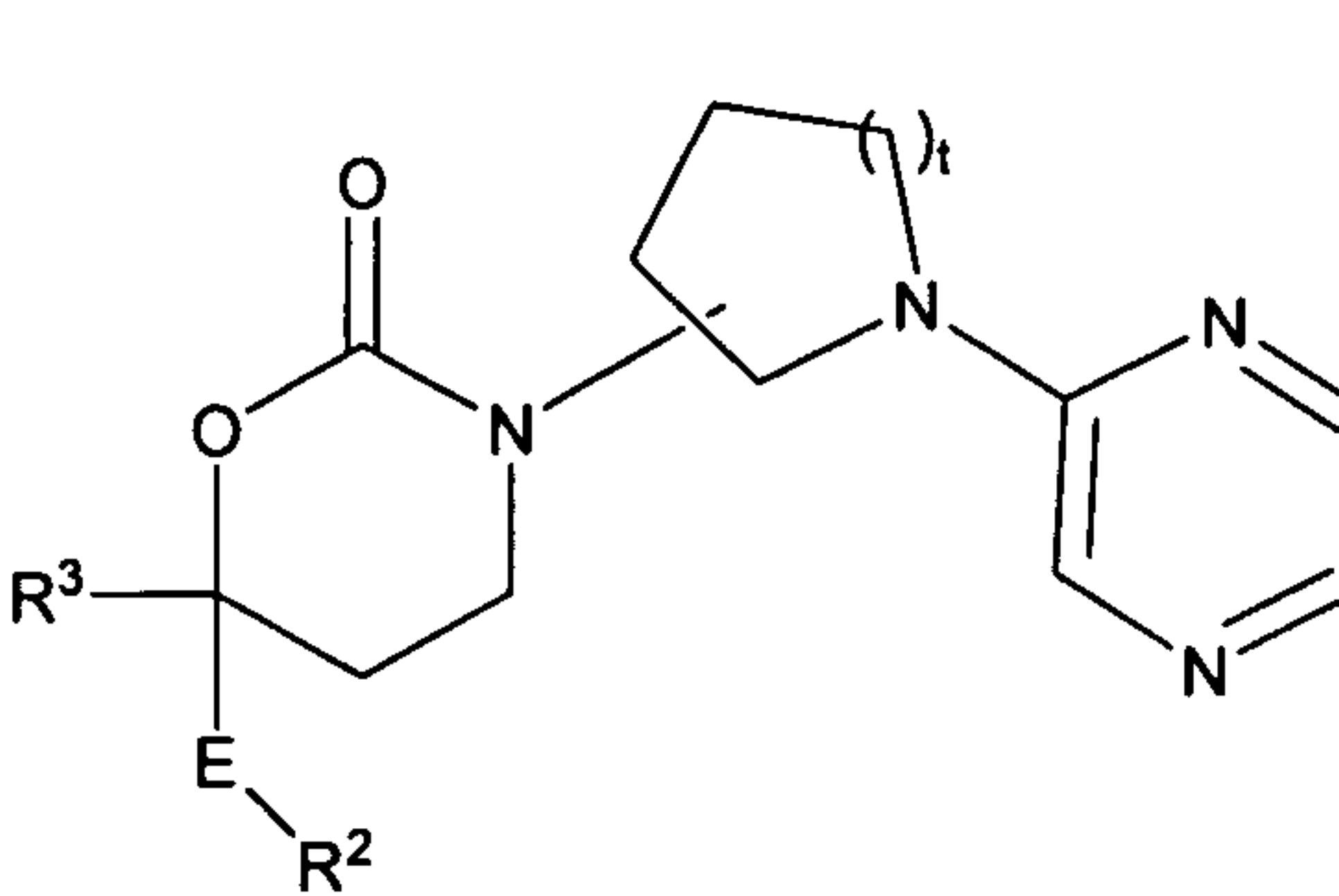
Alternatively, -CHO, NH₂, -SO₂NH₂, -COOH, and -CONH₂ are excluded as permissible substituents for the pyridine and thiazole rings at the position corresponding to Cy² for all of the specific embodiments described above for Formulas Iq¹⁻²¹, Ip¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, and It¹⁻⁷.

Another embodiment of the invention is a compound of any one of Formulas Iu¹⁻²⁰ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof:

Iu¹Iu²Iu³Iu⁴

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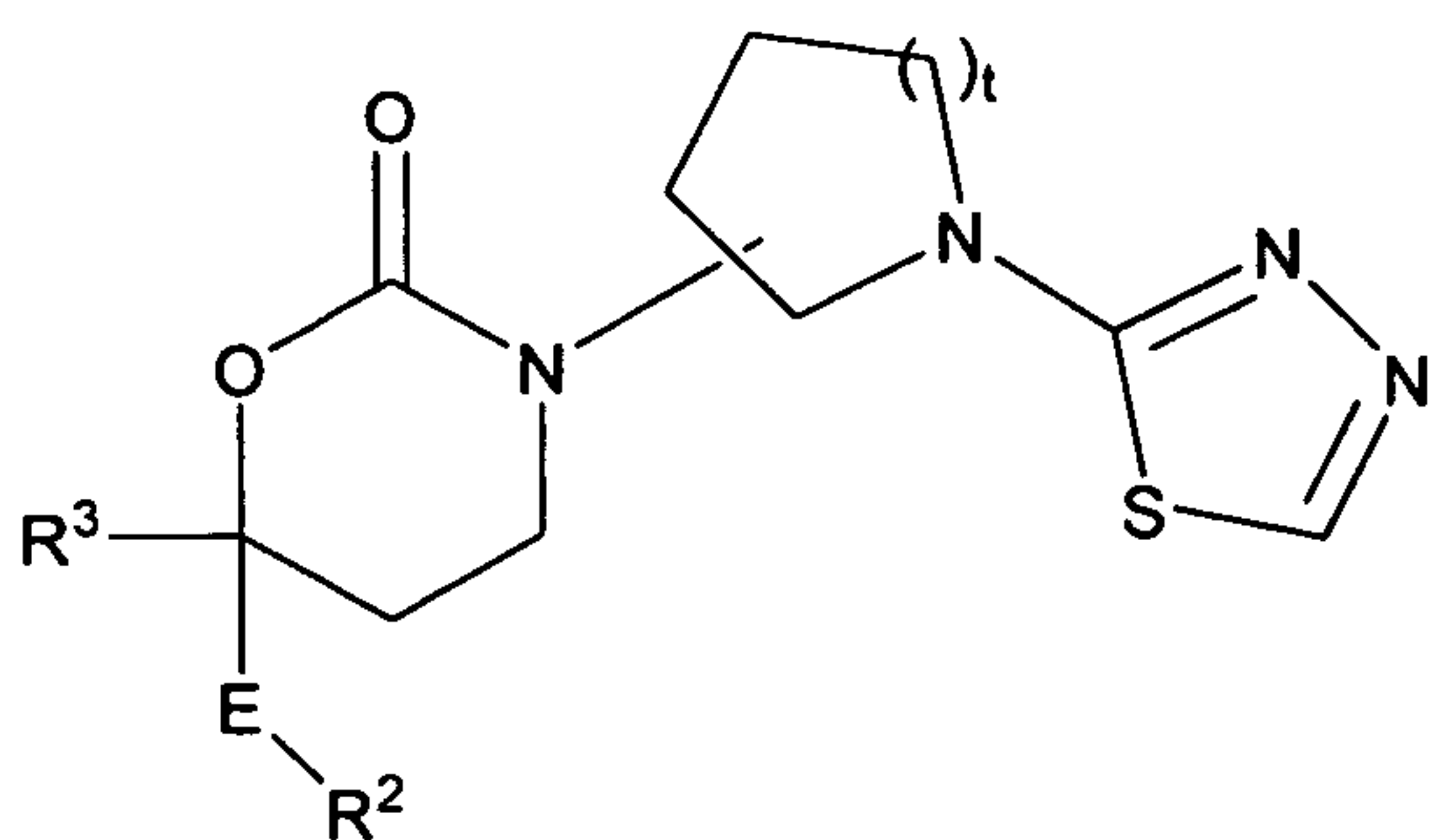
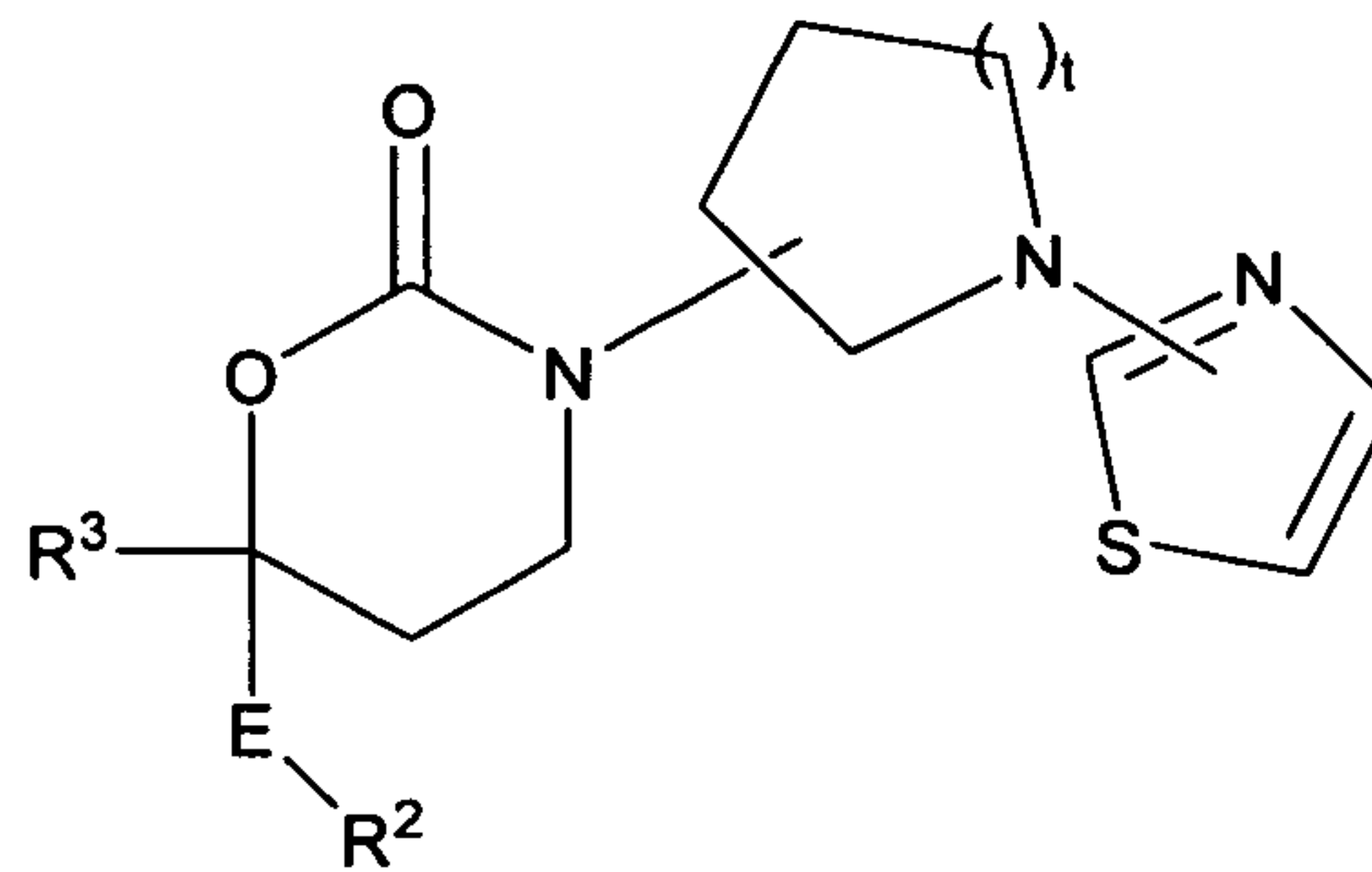
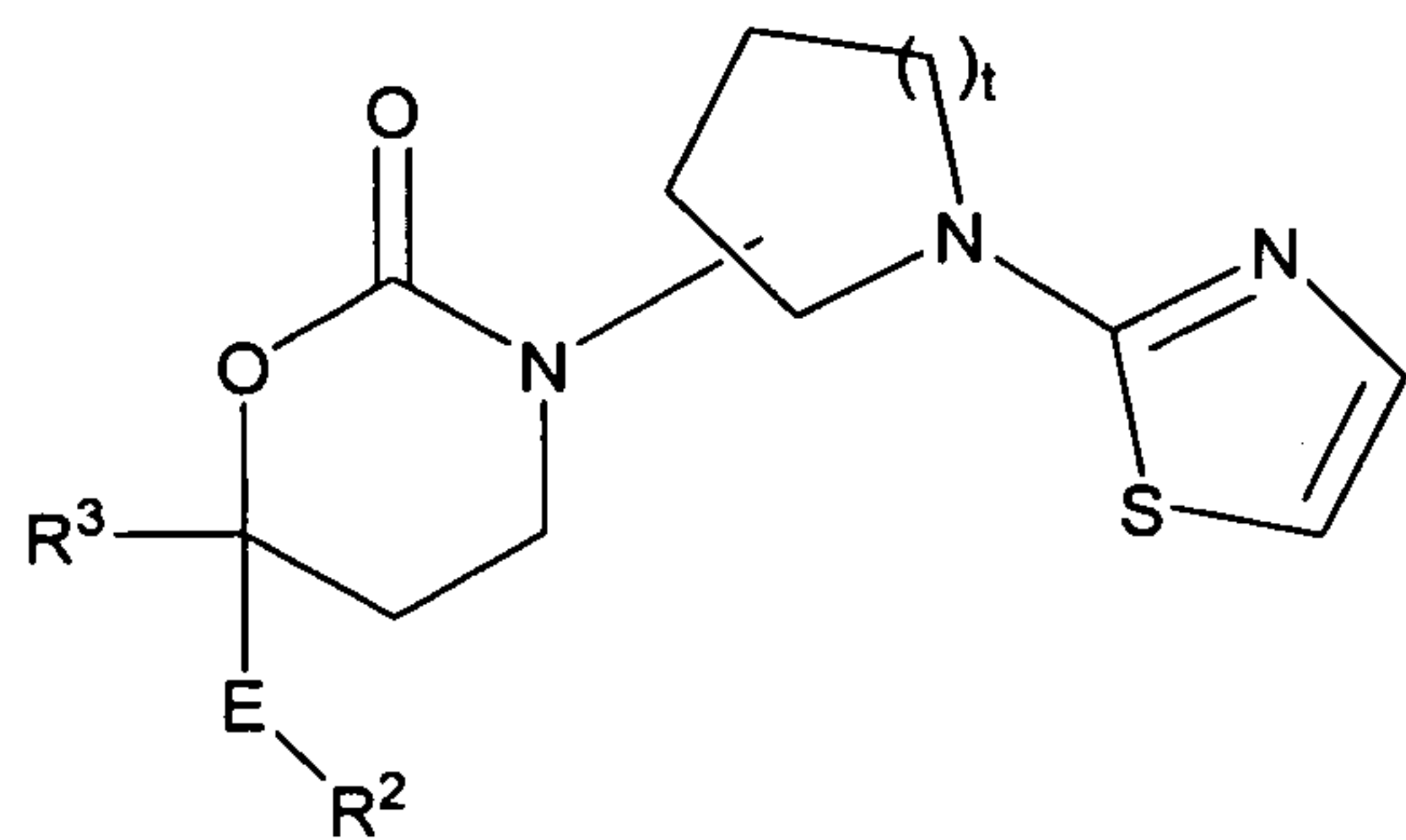
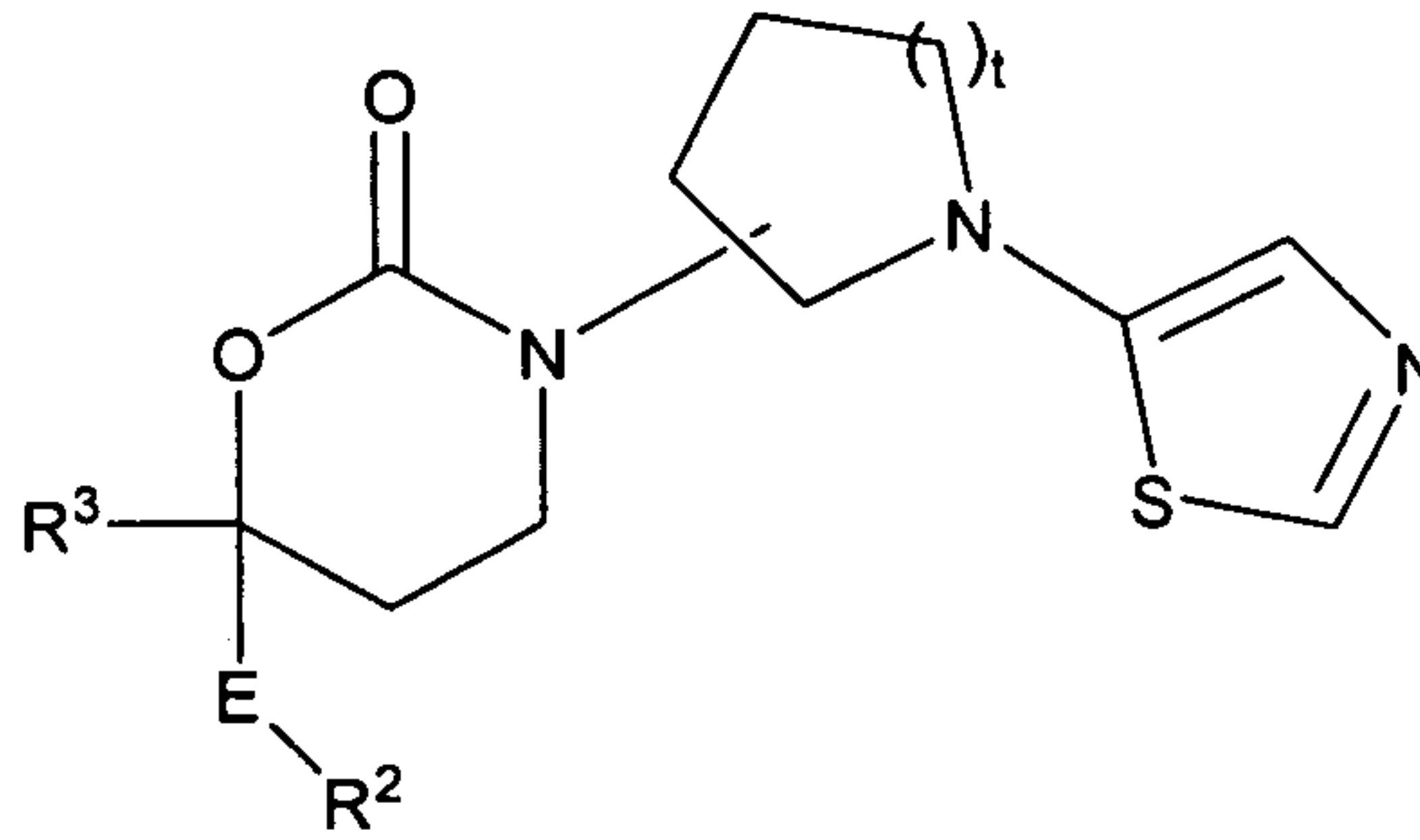
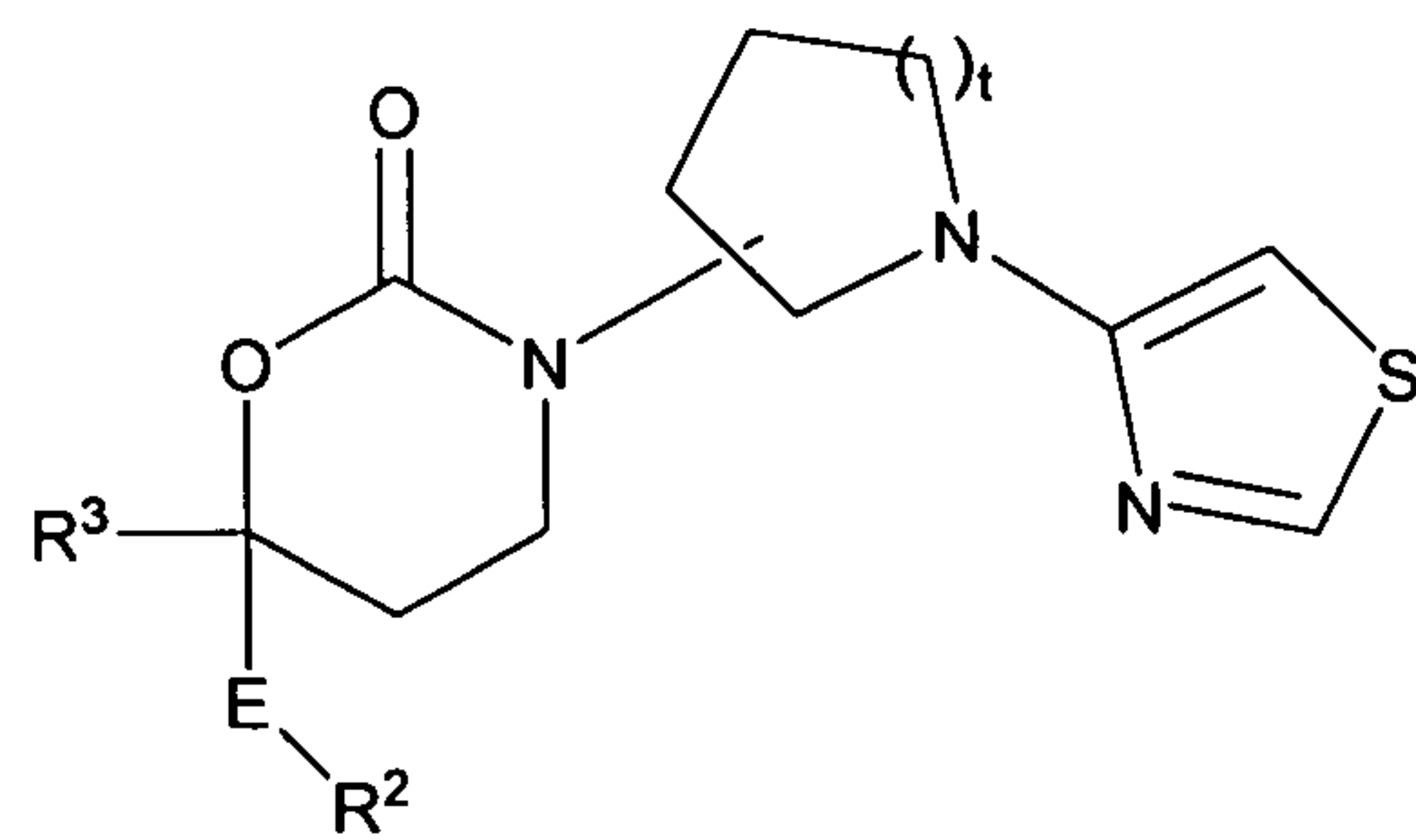
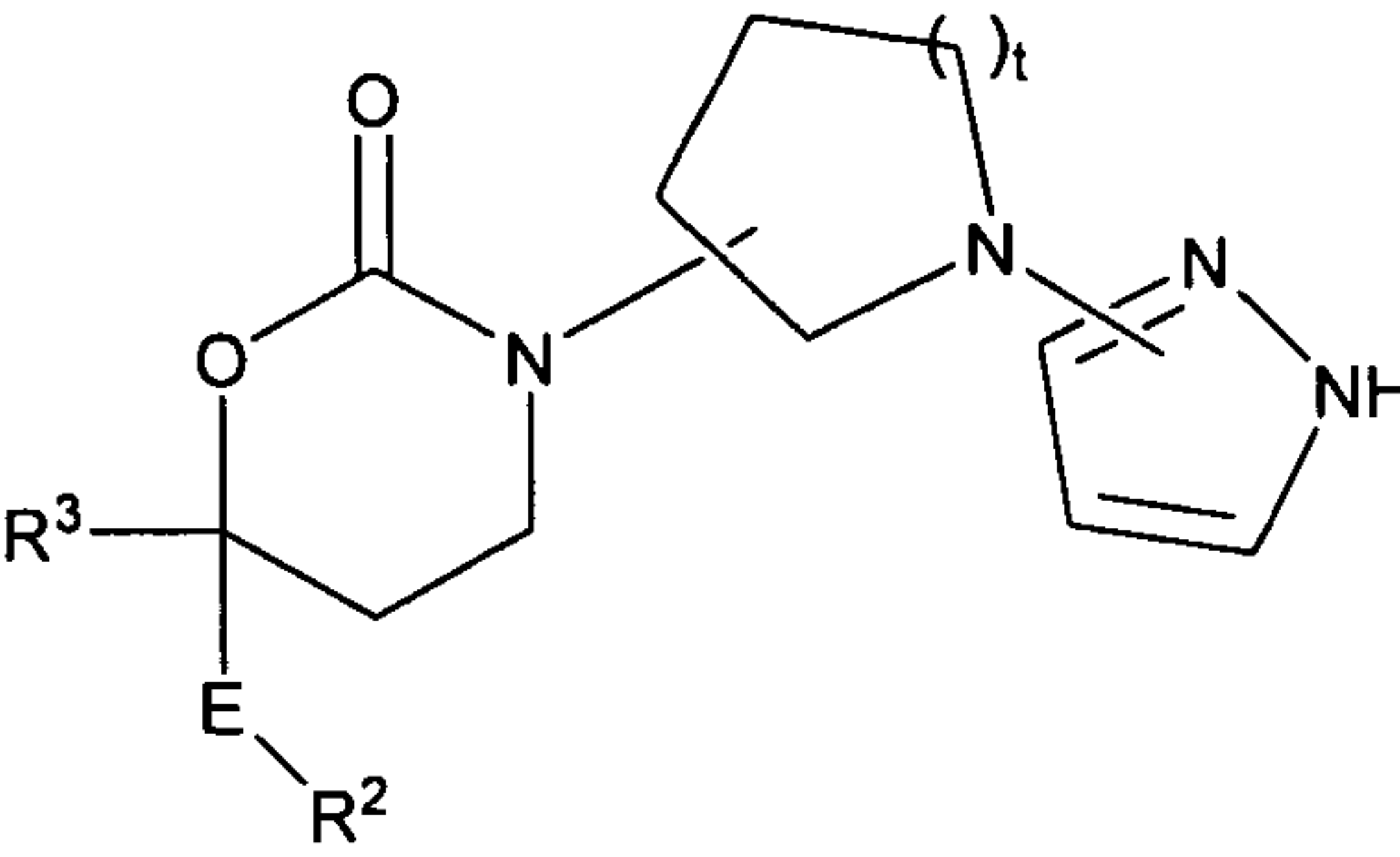
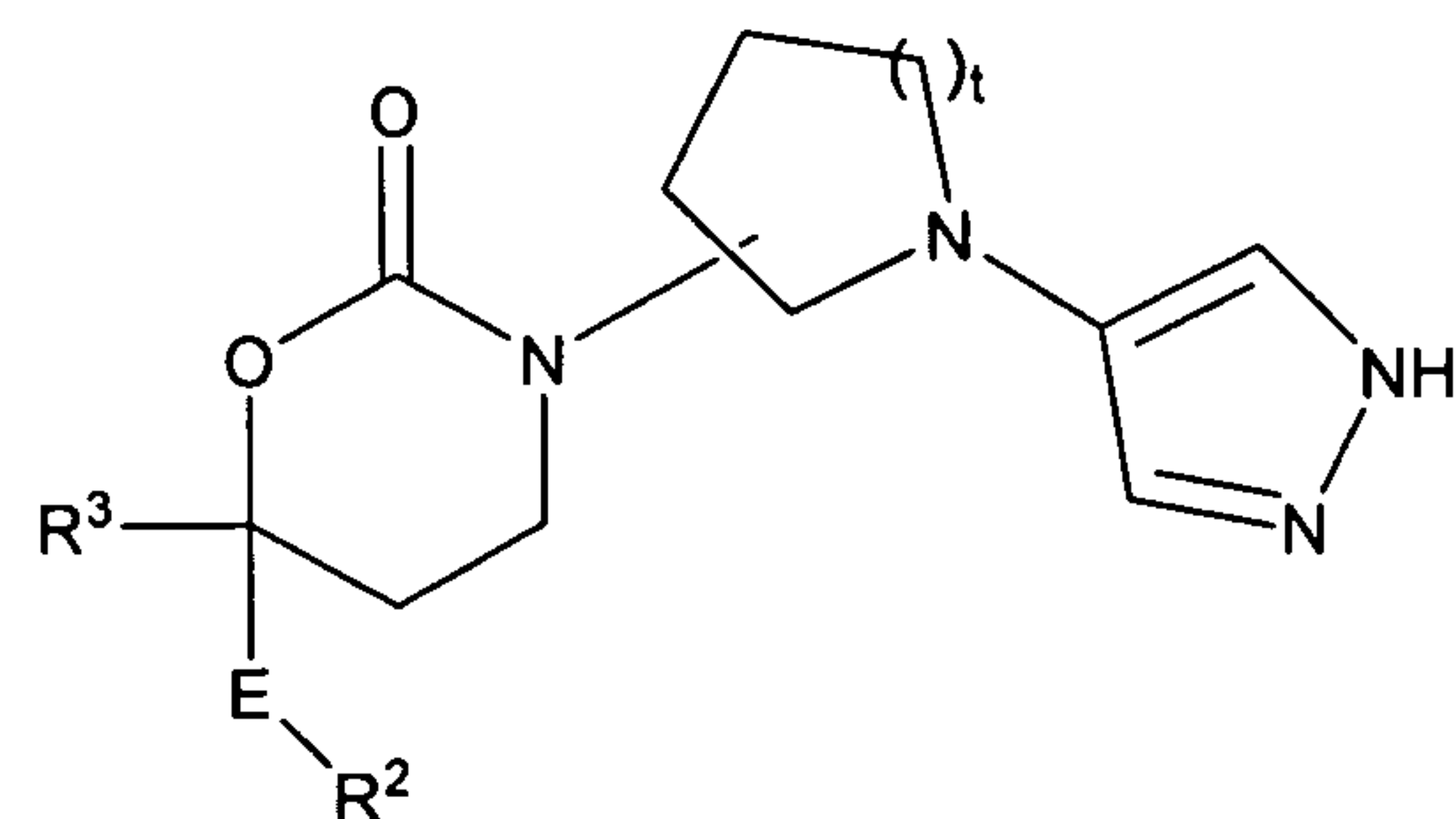
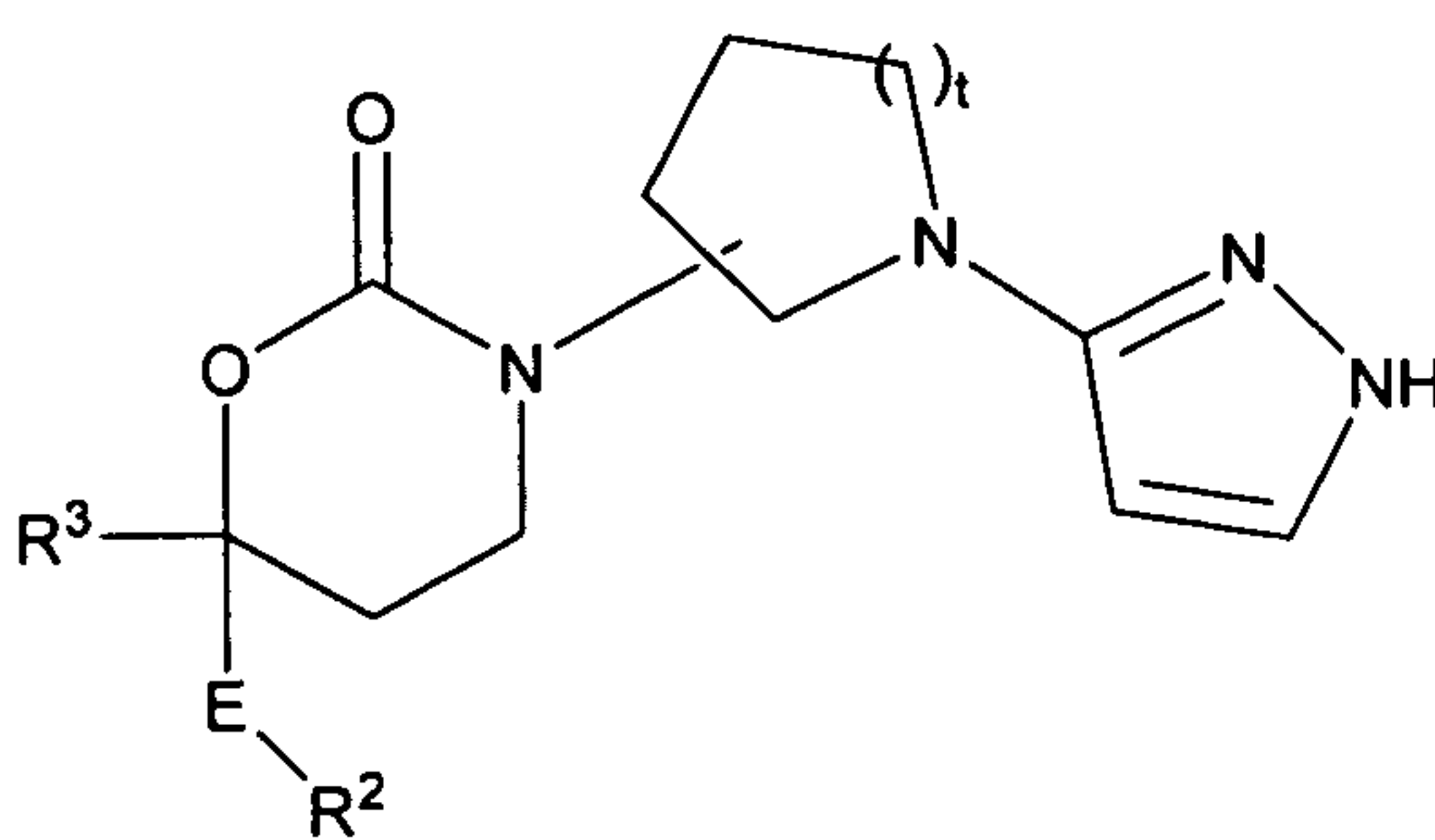
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Lu⁵Lu⁶Lu⁷Lu⁸Lu⁹Lu¹⁰Lu¹¹Lu¹²

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Lu¹³Lu¹⁴Lu¹⁵Lu¹⁶Lu¹⁷Lu¹⁸Lu¹⁹Lu²⁰

In Formulas Lu¹⁻²⁰, the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Lu¹⁻²⁰ are optionally substituted (substitution at ring carbons bonded to hydrogen and ring nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a "substitutable ring nitrogen atom") with up to four substituents as described above for Cy²; and the pyrrolidine, piperidine and azepane rings are optionally substituted with 0, 1 or 2 substituents as described above for Cy¹. Suitable substituents for Cy¹ and Cy² and suitable values for R², R³ and E are as defined in

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any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments; and t is 1, 2 or 3. Alternatively, suitable substituents for the pyrrolidine, piperidine and azepane rings and the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas lu^{1-20} are as described for G^1 and G^2 , respectively, in Formula If; values for R^2 , R^3 and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments; and t is 1, 2 or 3. Alternatively, suitable substituents for the pyrrolidine, piperidine and azepane rings include oxo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom in the pyrazole rings in Formulas lu^{18-20} include (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₄)haloalkyl; suitable substituents for a ring carbon atom in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas lu^{1-20} include fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl, (C₃-C₄)cycloalkylaminocarbonyl, {(C₁-C₄)alkyl}{(C₃-C₄)cycloalkyl}aminocarbonyl and (C₁-C₄)alkylcarbonylamino; the ring nitrogen in the pyridine rings in Formulas lu^{1-4} is optionally substituted by oxo; t is 1, 2 or 3; and suitable values for R^2 , R^3 and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments.

Alternatively, for each of the embodiments described in the paragraph immediately following Formulas lu^{1-20} , R^3 is preferably MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

Alternatively, for each of the embodiments described in the paragraph immediately following Formulas lu^{1-20} , R^3 is preferably H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

Alternatively, for each of the embodiments described in the paragraph immediately following Formulas lu^{1-20} , R^2 is preferably phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R^3 is preferably MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

Alternatively, for each of the embodiments described in the paragraph immediately following Formulas lu^{1-20} , R^2 is preferably phenyl optionally substituted

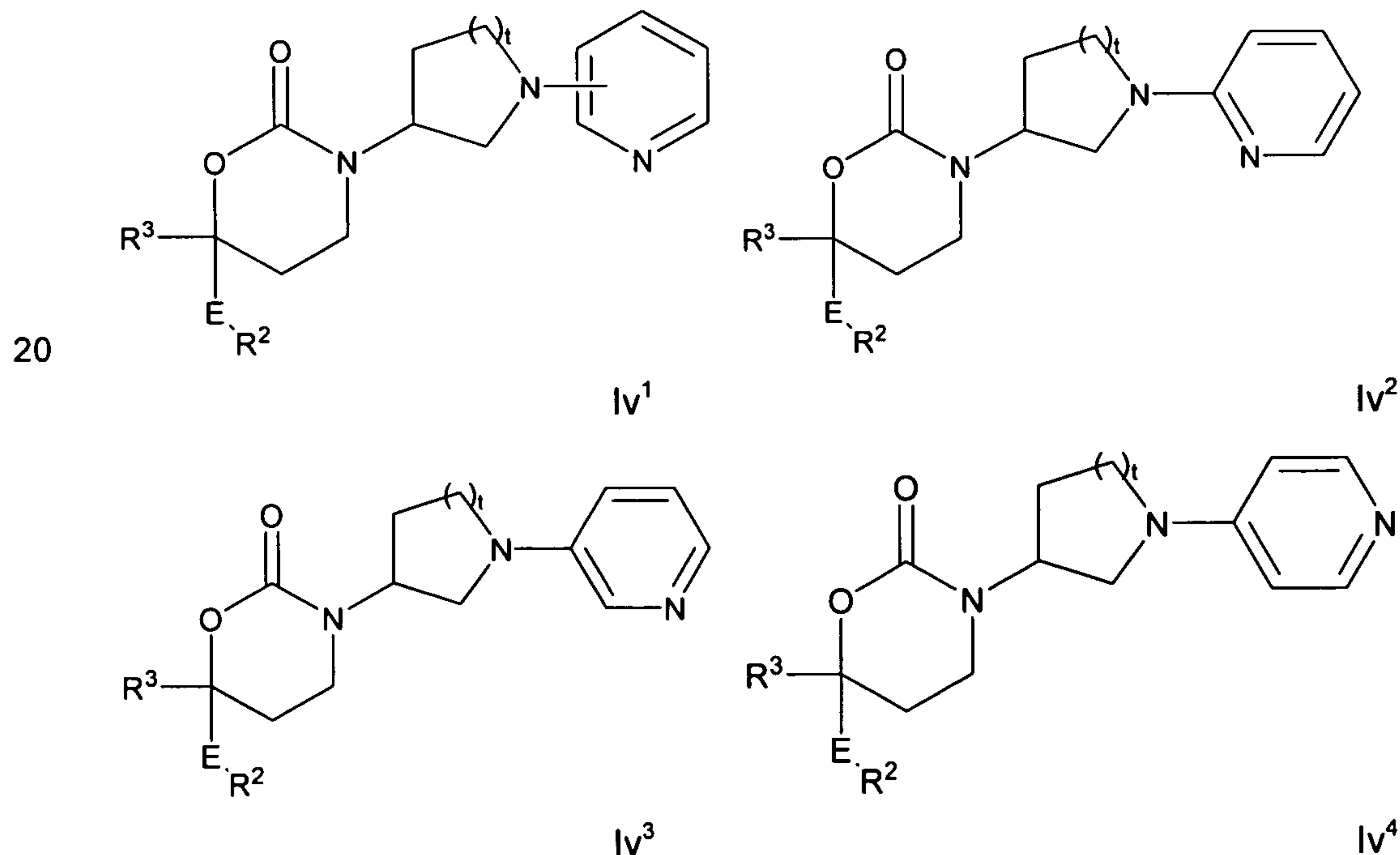
- 81 -

with 1, 2 or 3 substituents selected from halo, cyano, CONH_2 , $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$ and SO_2Me ; and R^3 is preferably $\text{H}_2\text{NC(=O)CMe}_2\text{CH}_2$, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

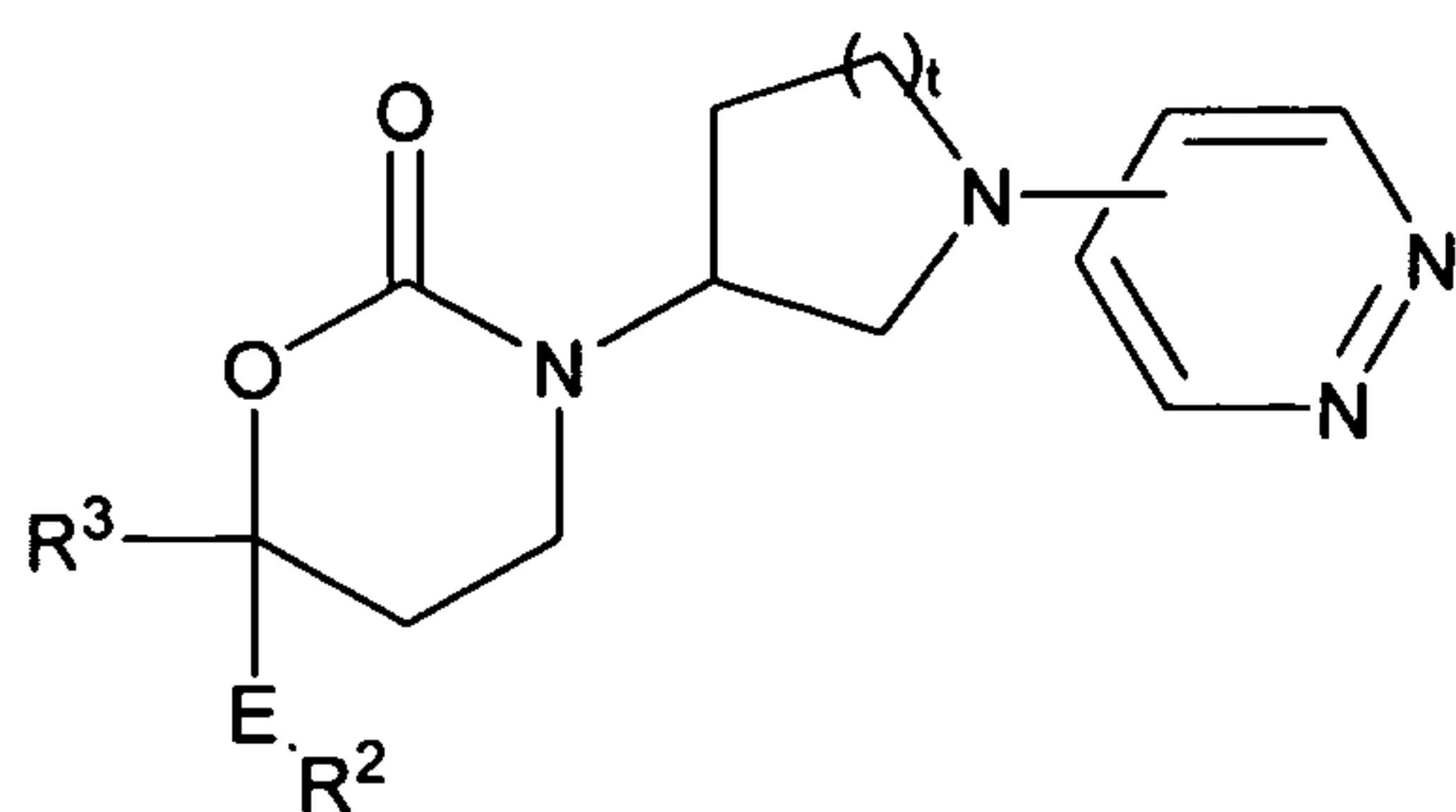
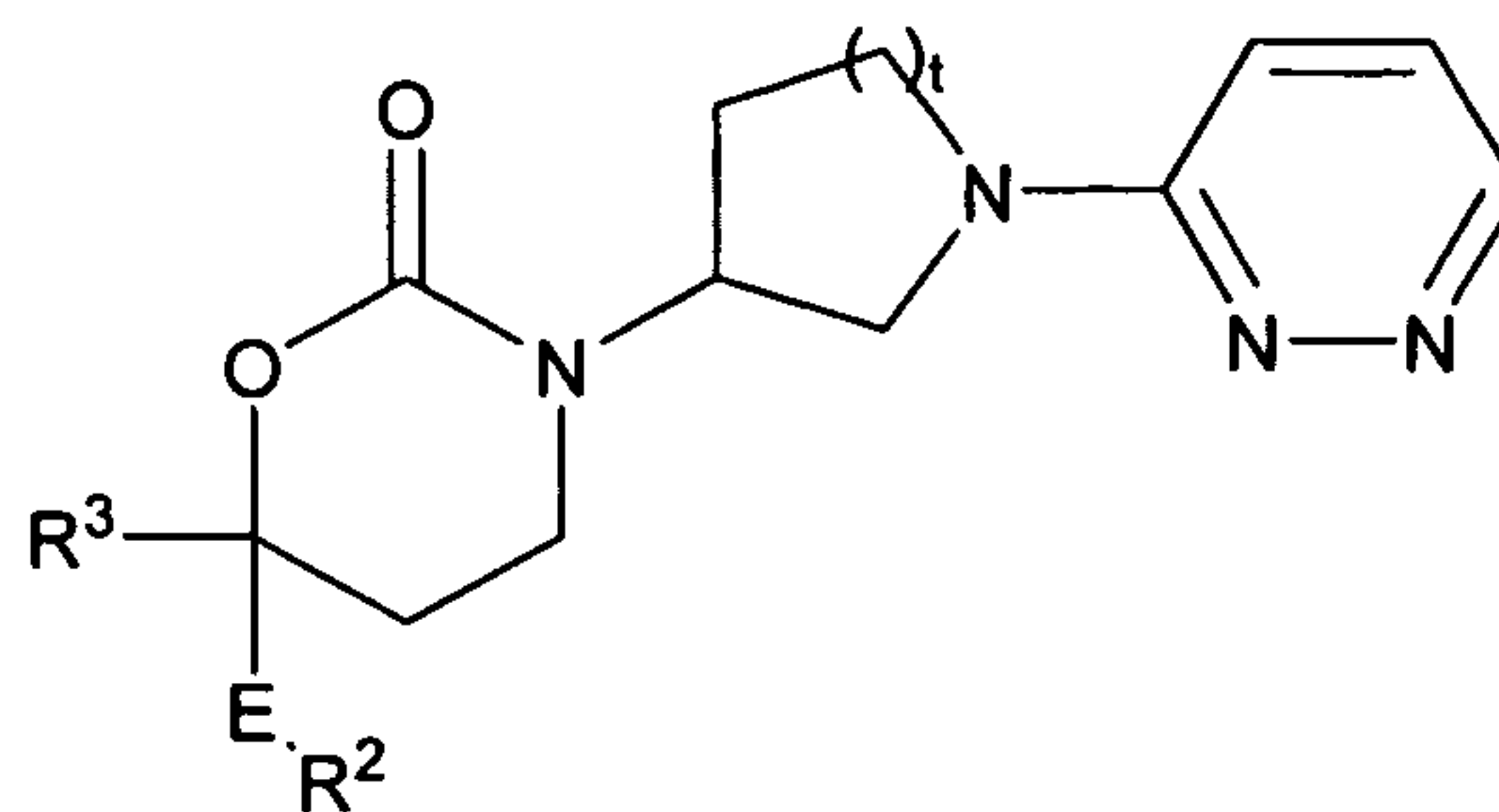
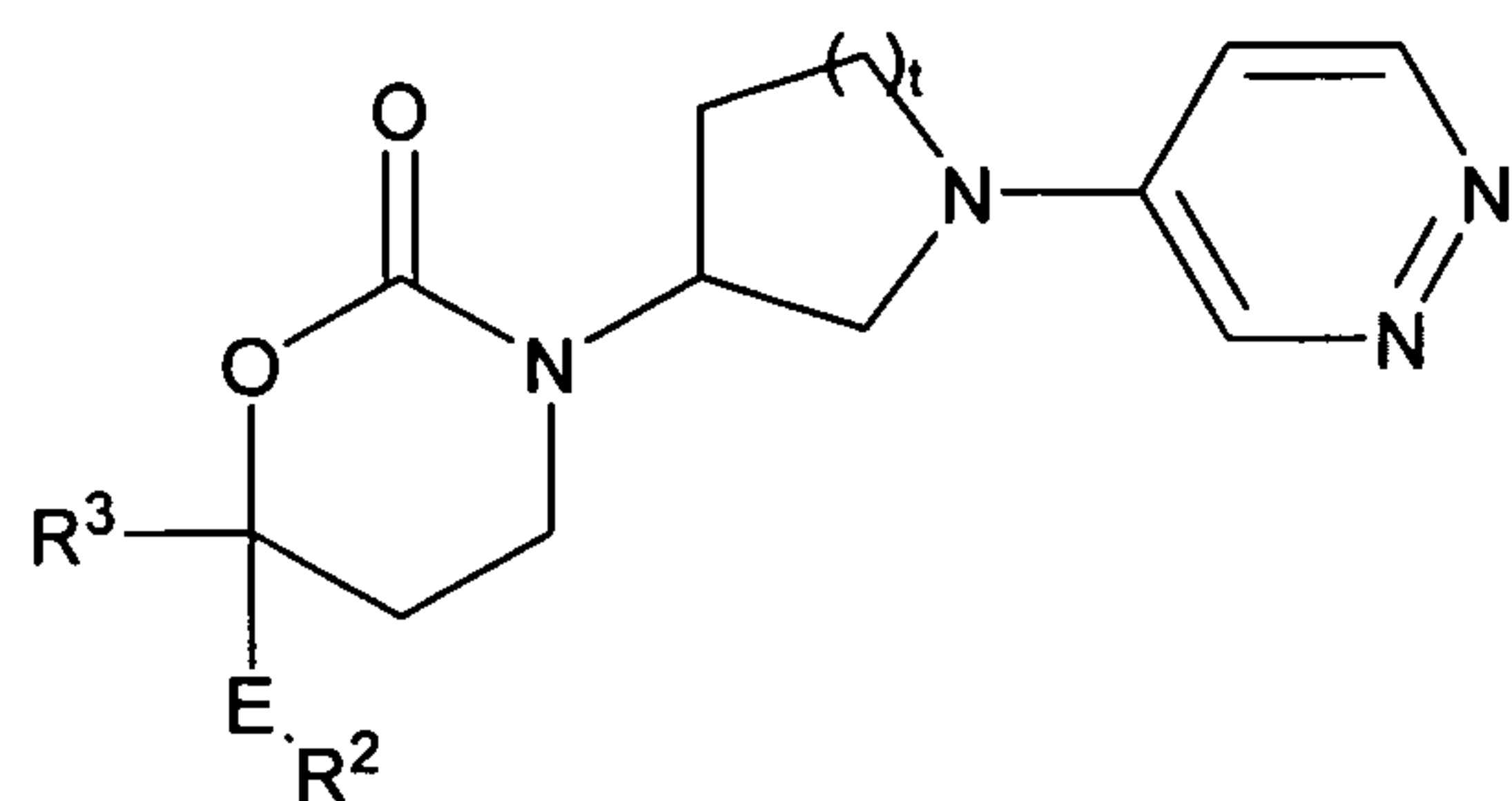
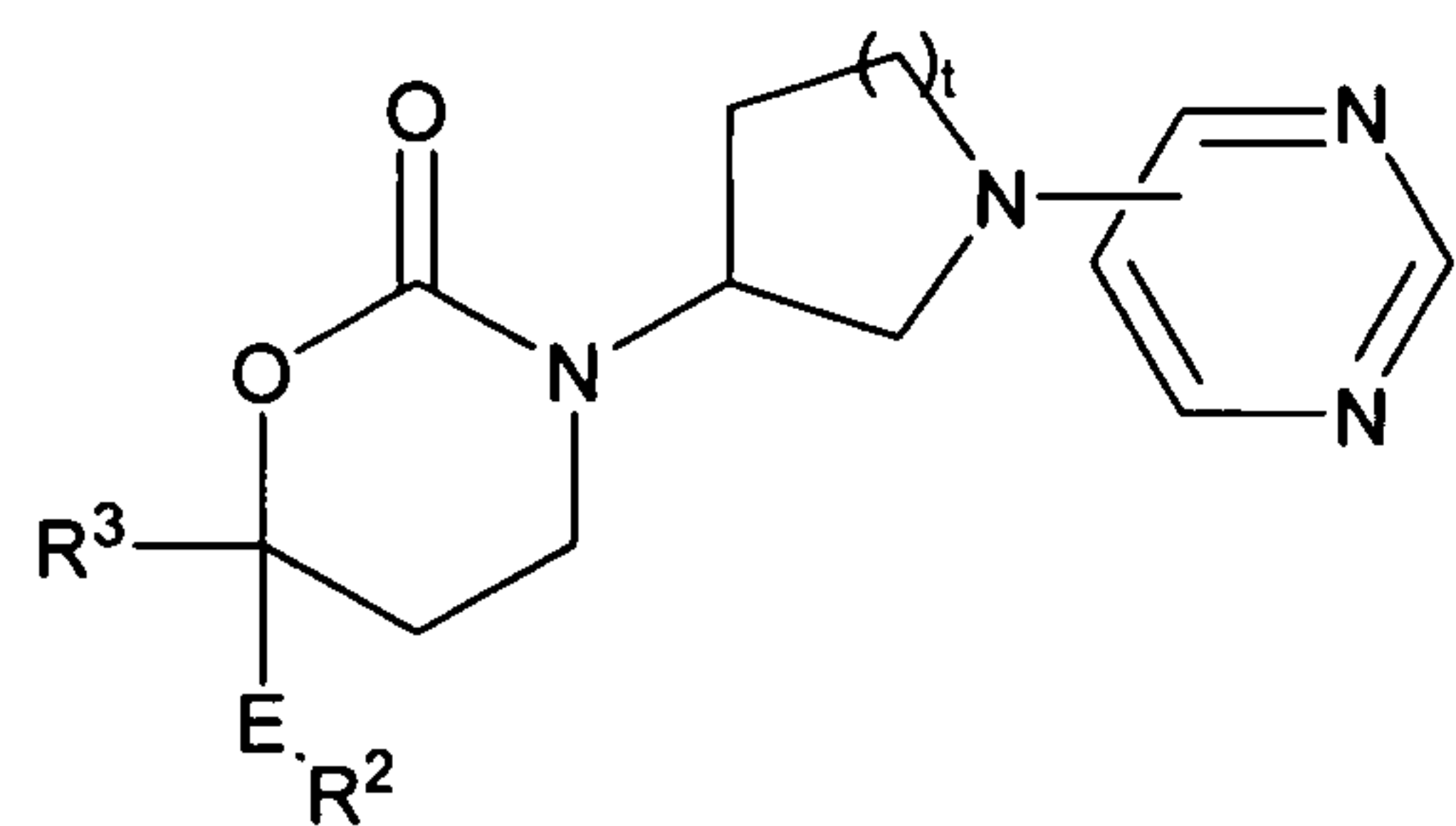
Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Iv^{1-20} , t is preferably 2; R^2 is preferably phenyl or fluorophenyl; and R^3 is preferably 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

Alternatively, for each of the embodiment described in the paragraph immediately following Formulas Iv^{1-20} , wherein t is 2; R^2 is preferably phenyl or fluorophenyl; R^3 preferably is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; one or two ring carbon atoms in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iv^{1-20} are optionally substituted with fluoro, chloro, cyano, CONH_2 , CONHMe , CONMe_2 , CONHc-Pr , methyl, ethyl or CF_3 ; the substitutable ring nitrogen atom in the pyrazole rings in Formulas Iv^{18-20} are optionally substituted with $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_3\text{-C}_4)\text{cycloalkyl}$, $(\text{C}_3\text{-C}_4)\text{cycloalkyl}(\text{C}_1\text{-C}_2)\text{alkyl}$, and $(\text{C}_1\text{C}_2)\text{haloalkyl}$; the ring nitrogen in the pyridine rings in Formulas Iv^{1-4} are optionally substituted by oxo.

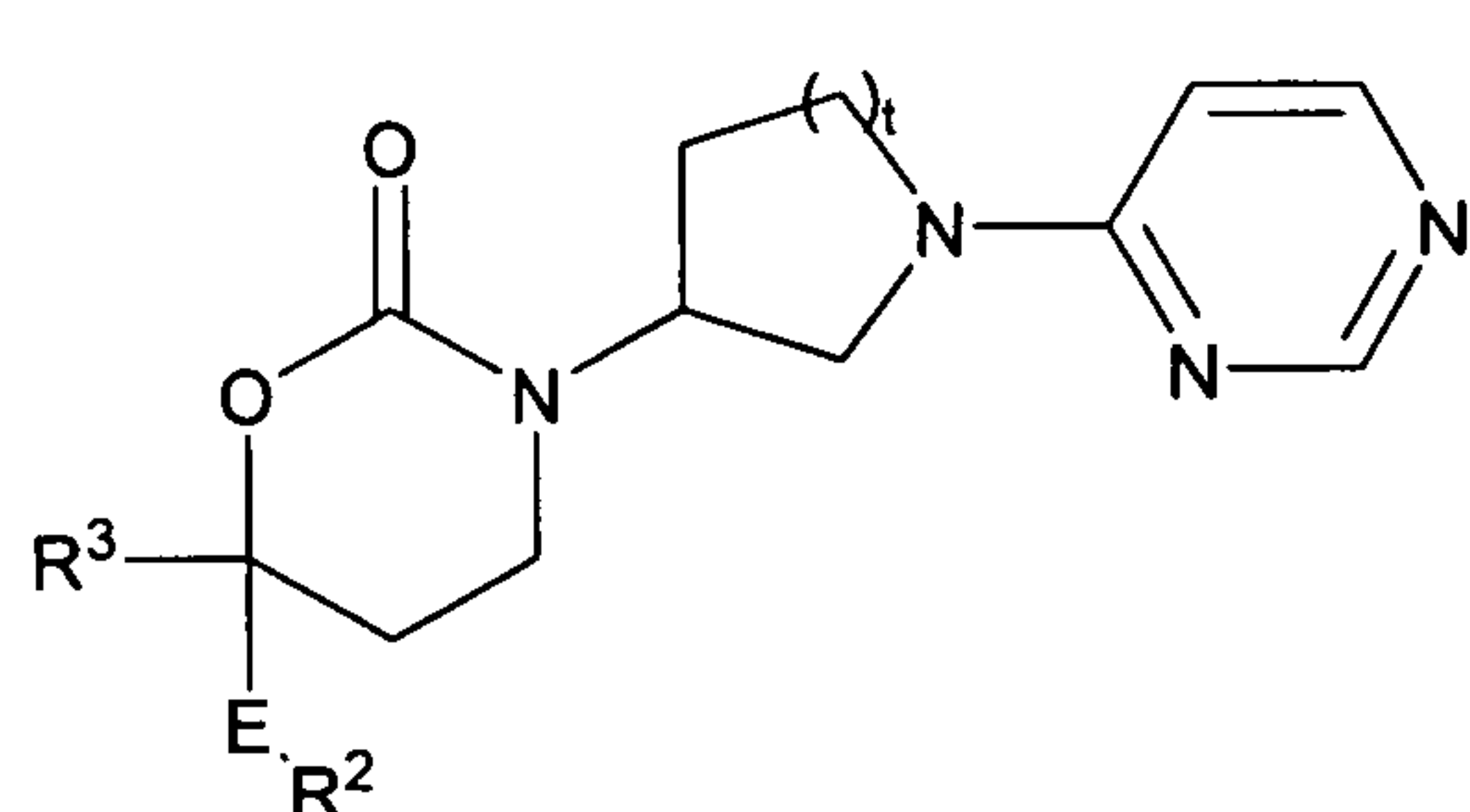
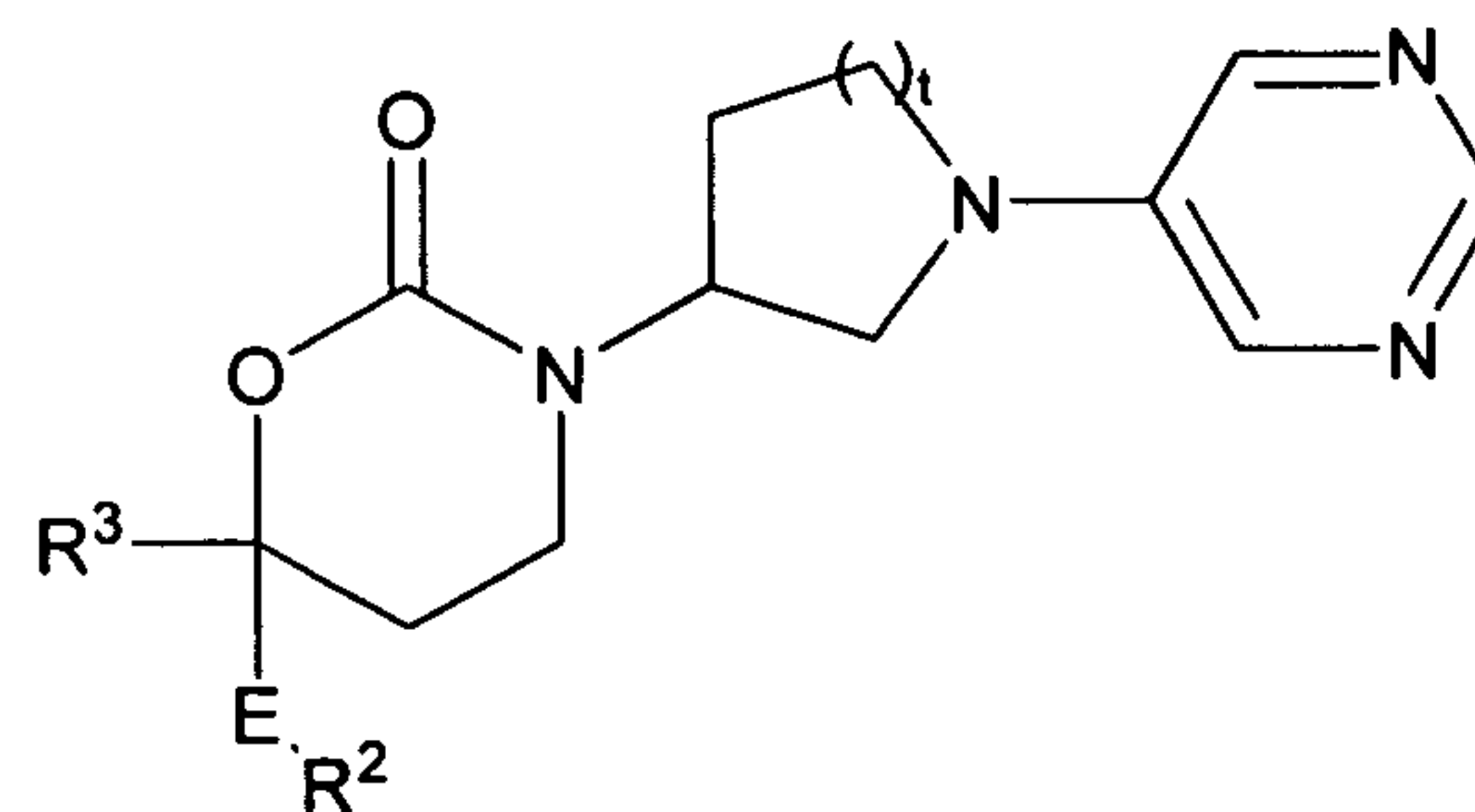
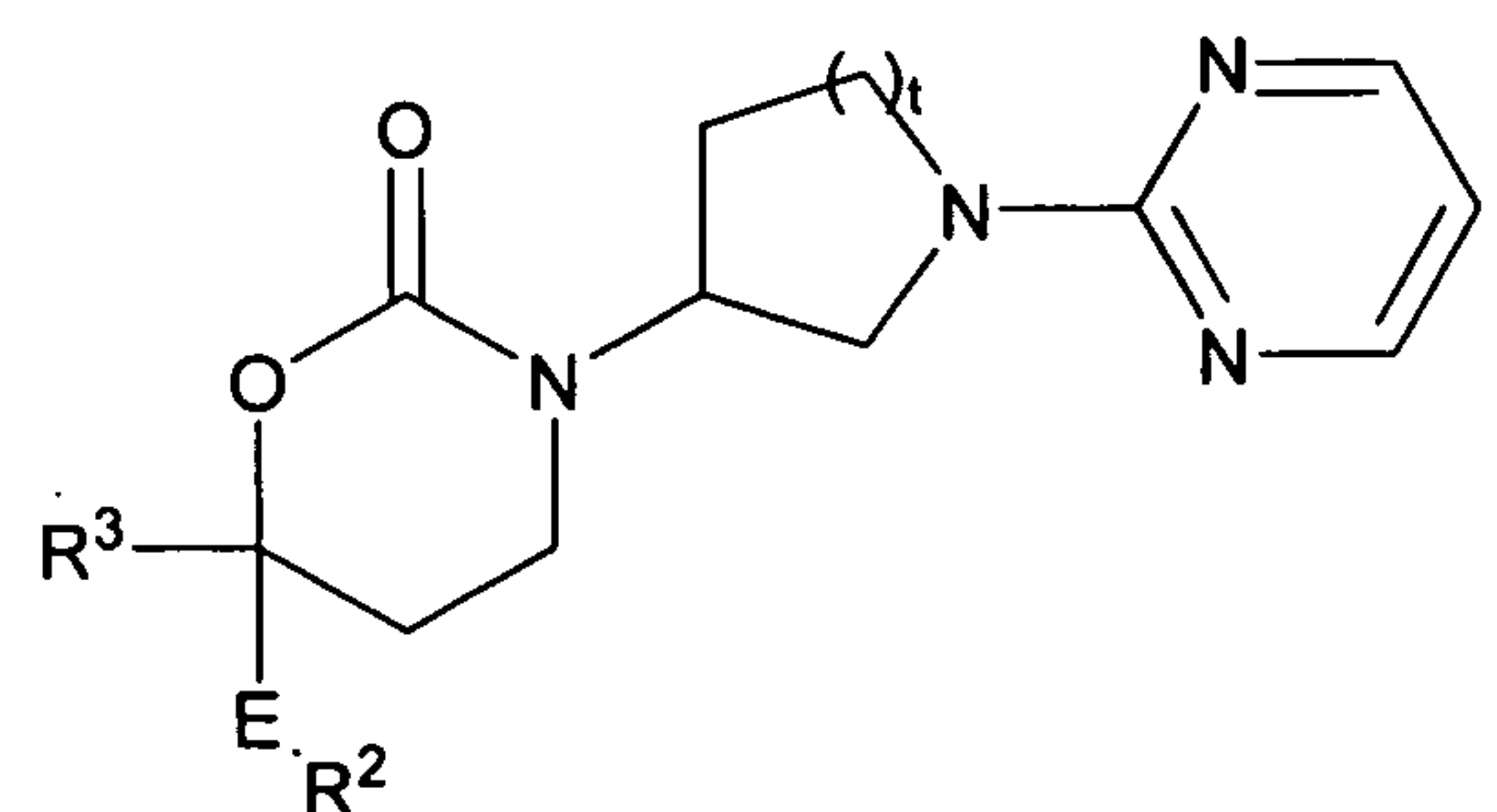
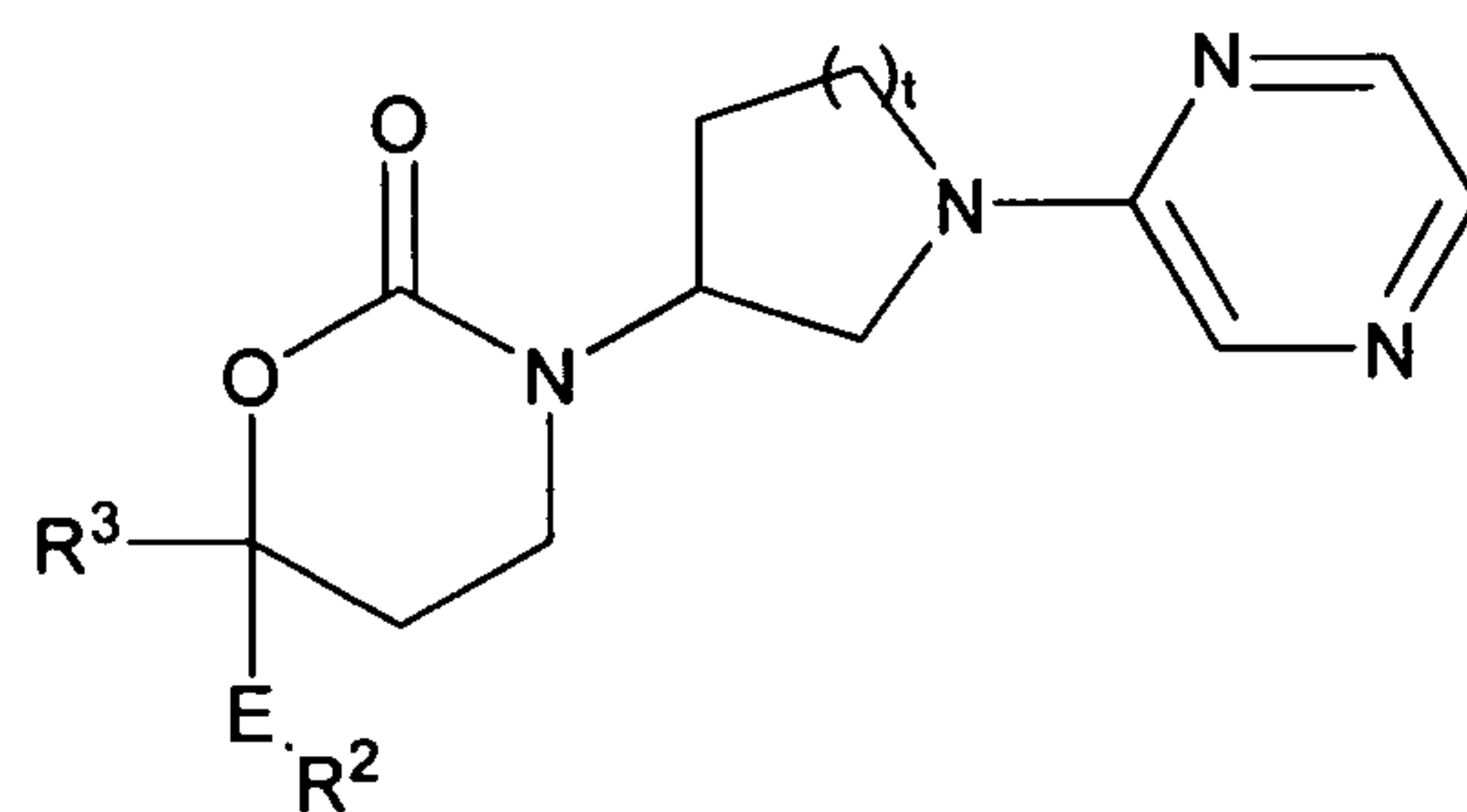
Another embodiment of the invention is a compound of any one of Formulas Iv^{1-20} , or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof:



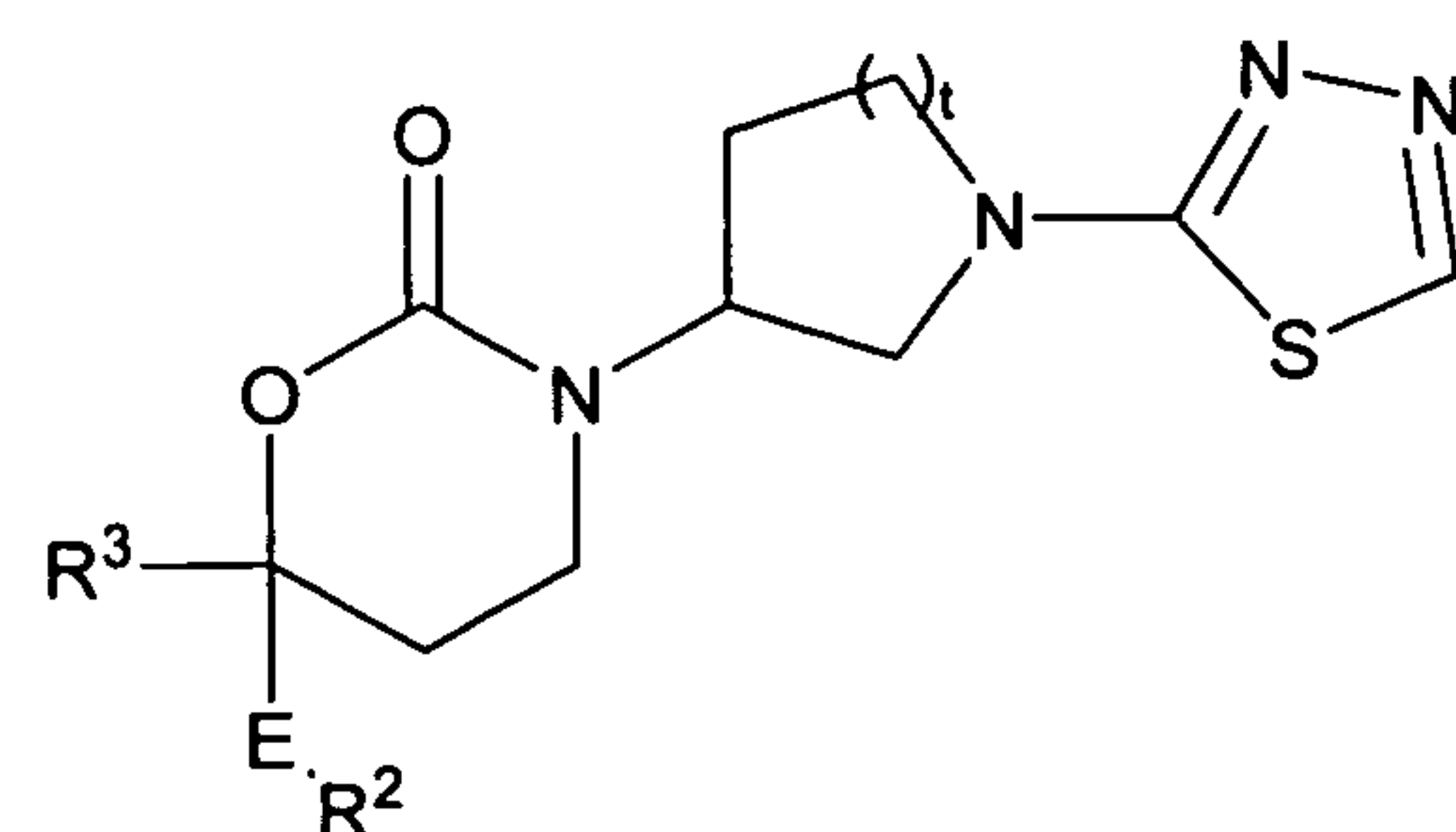
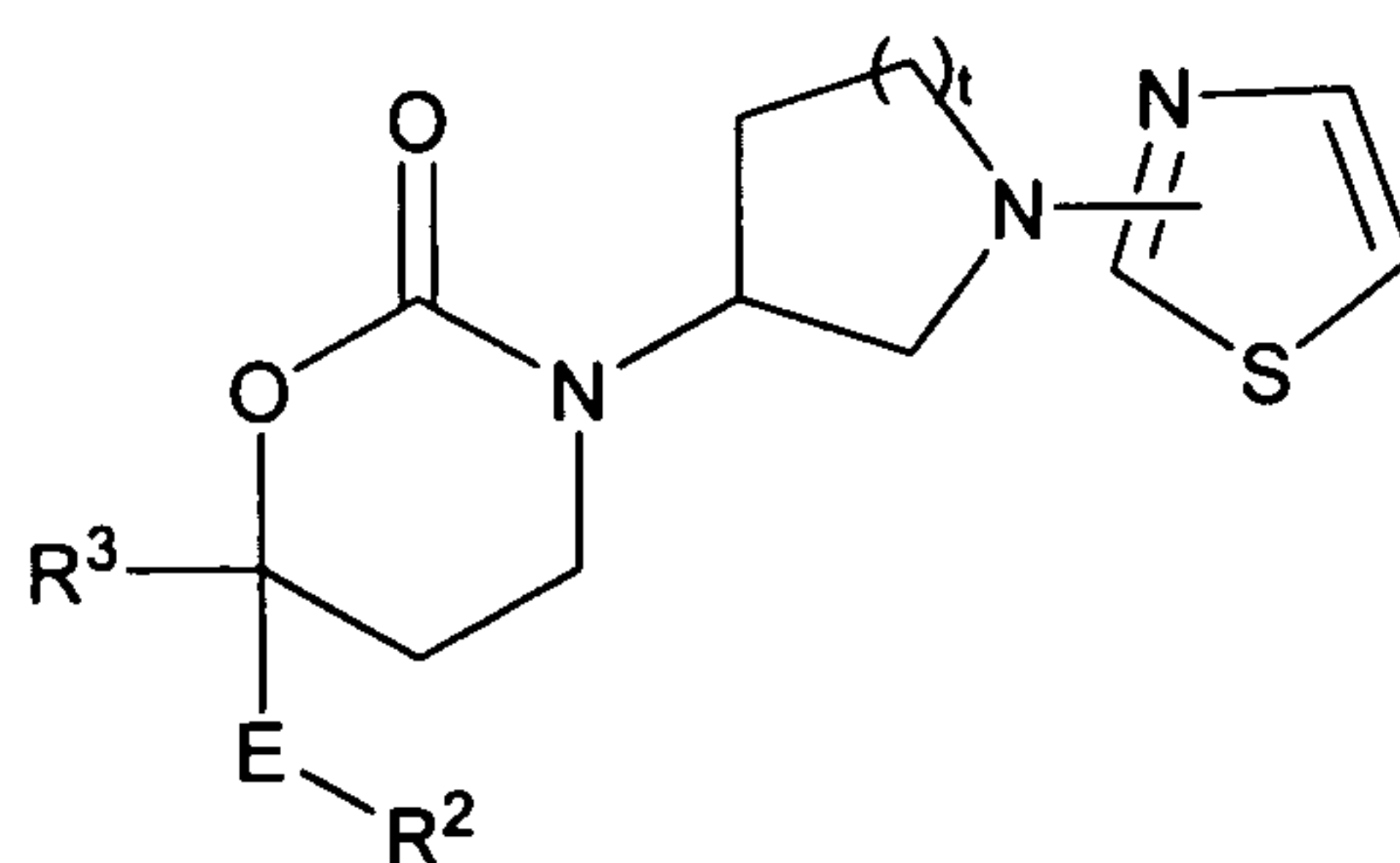
- 82 -

IV⁵IV⁶IV⁷IV⁸

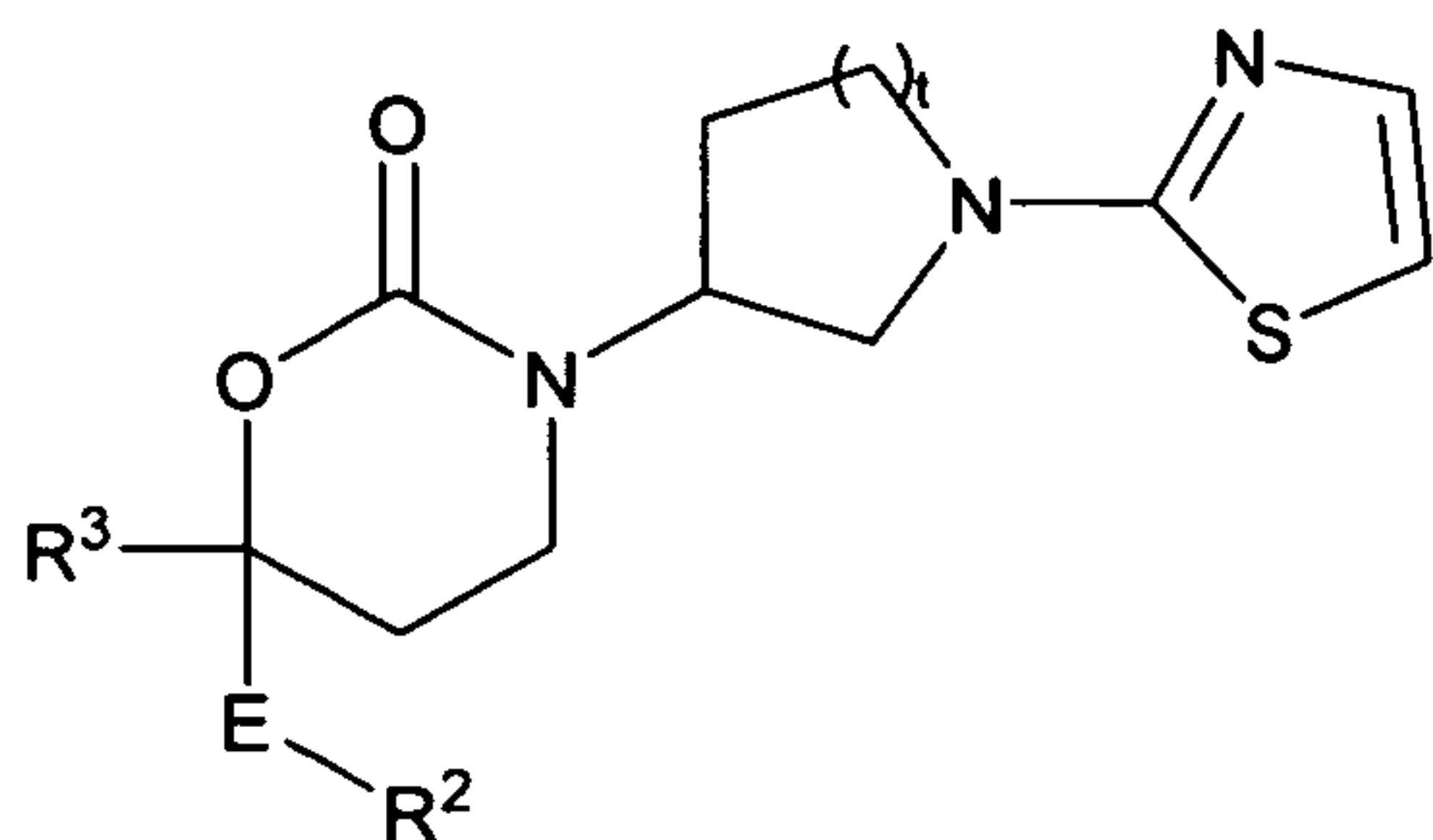
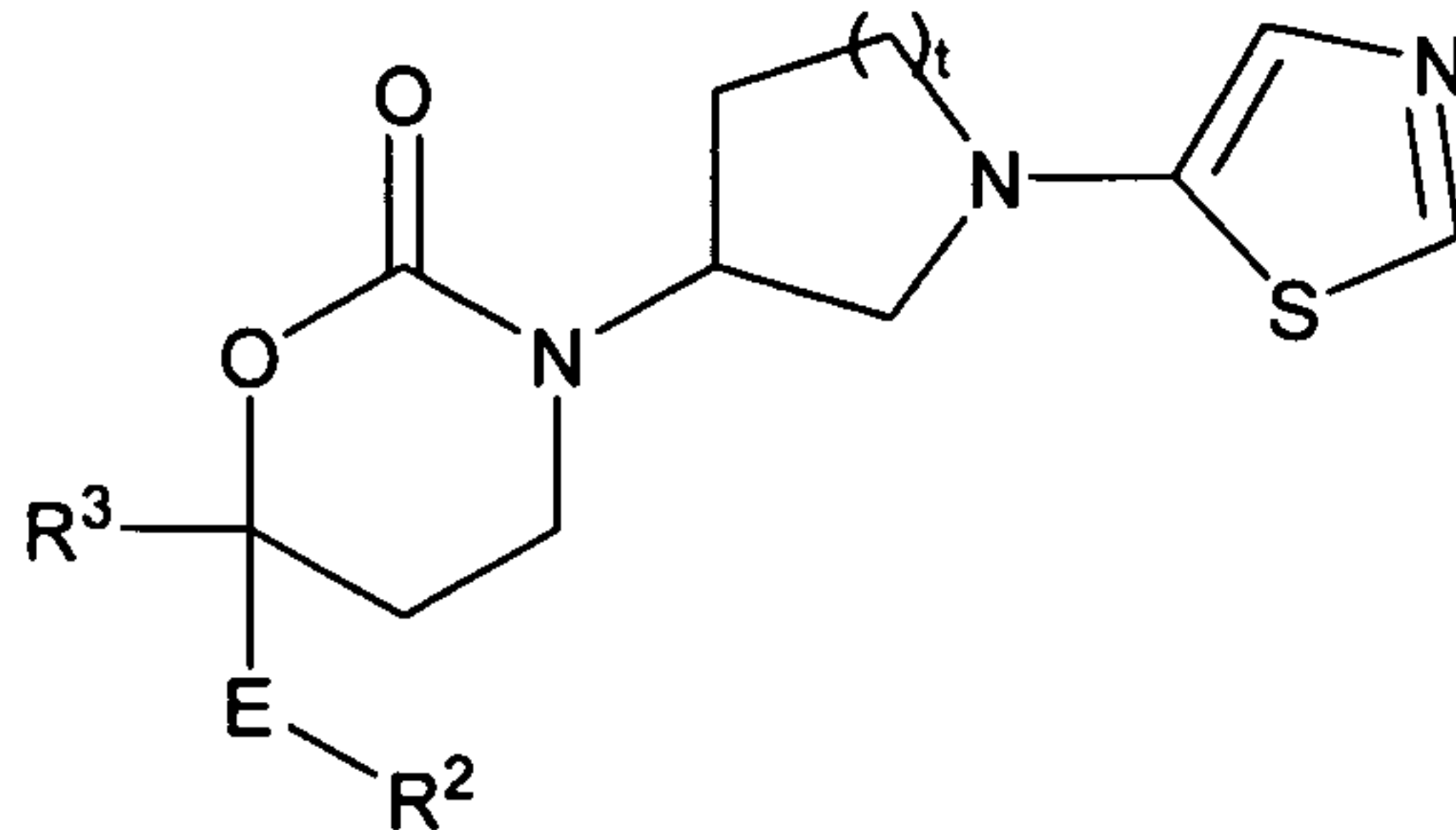
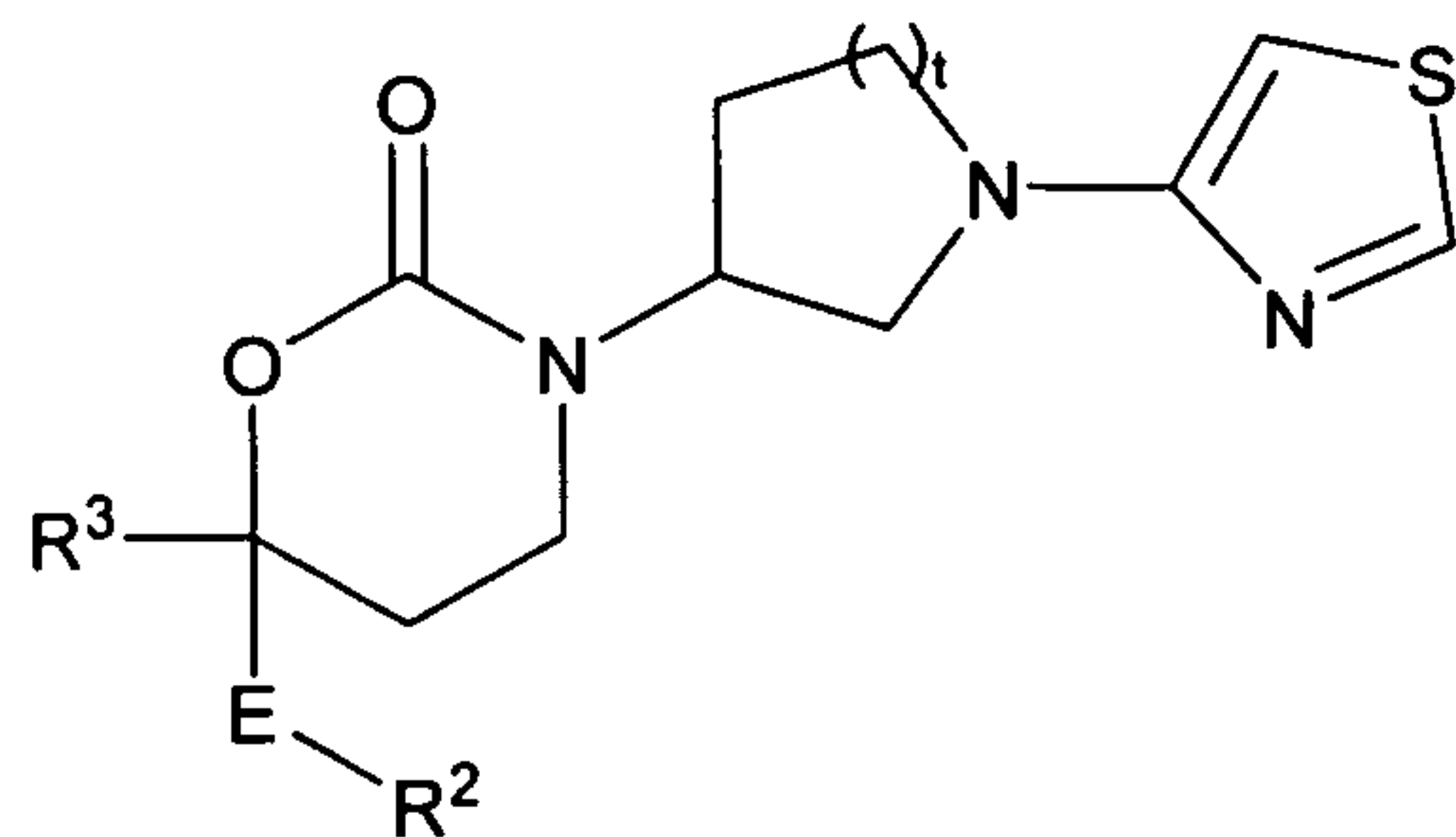
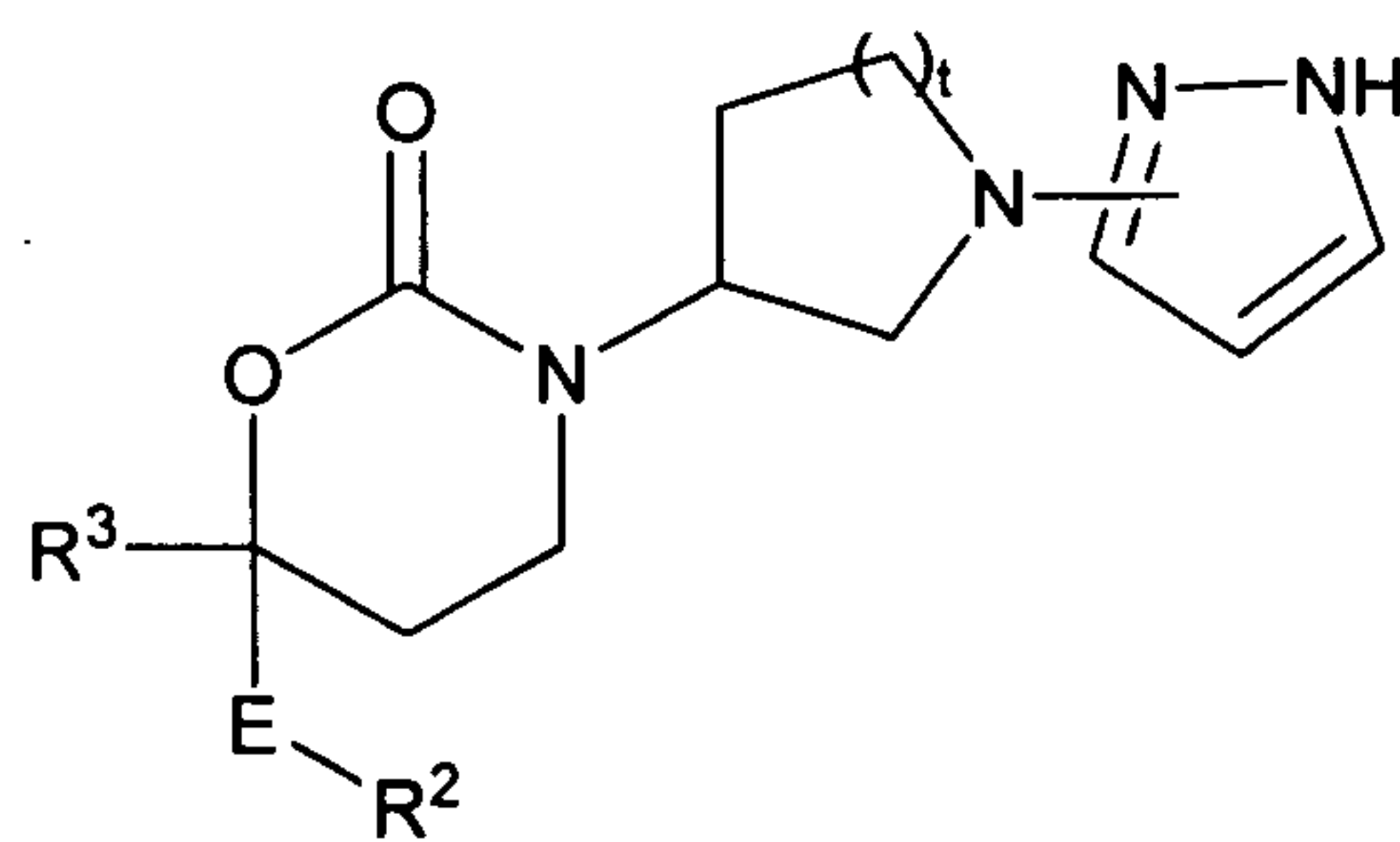
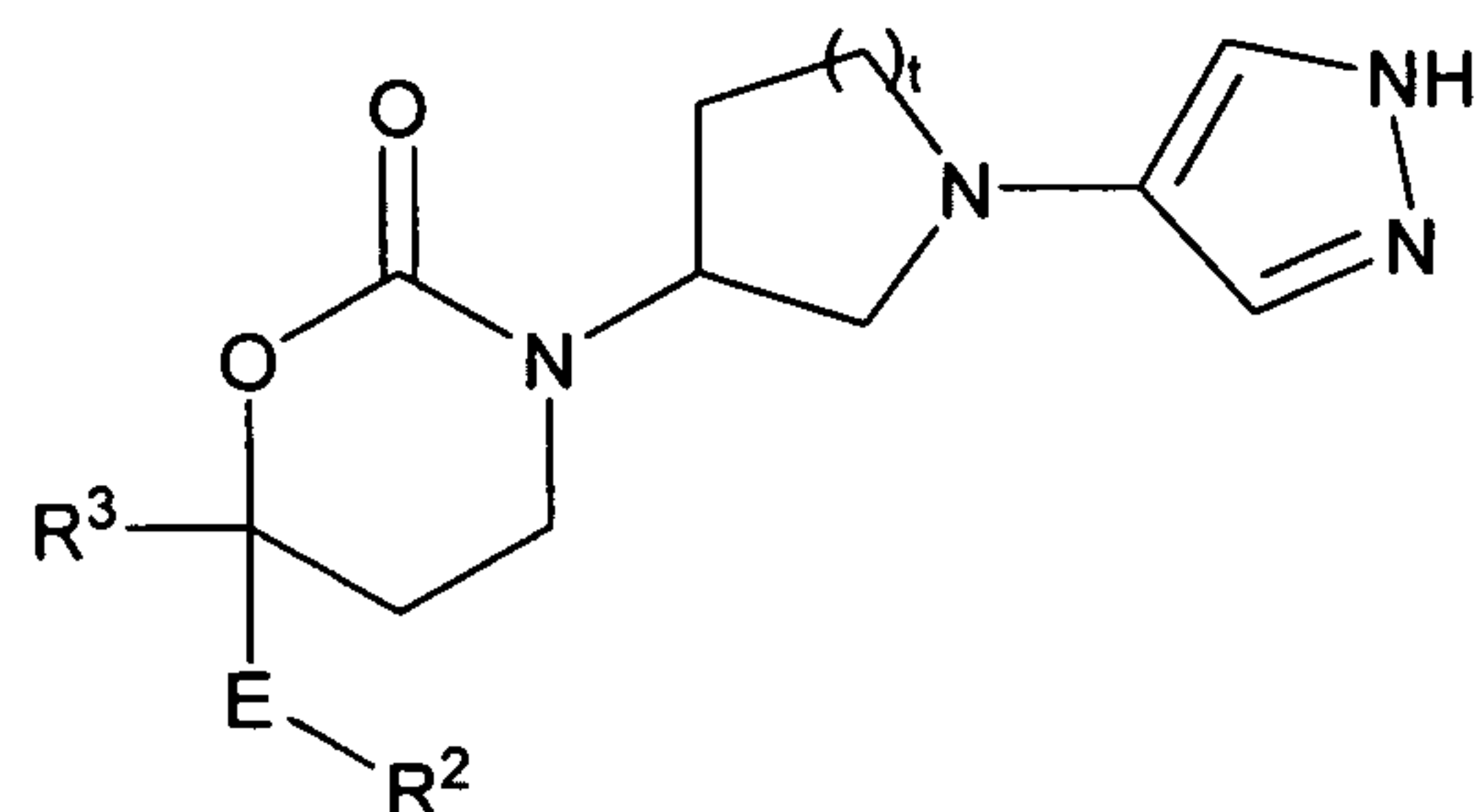
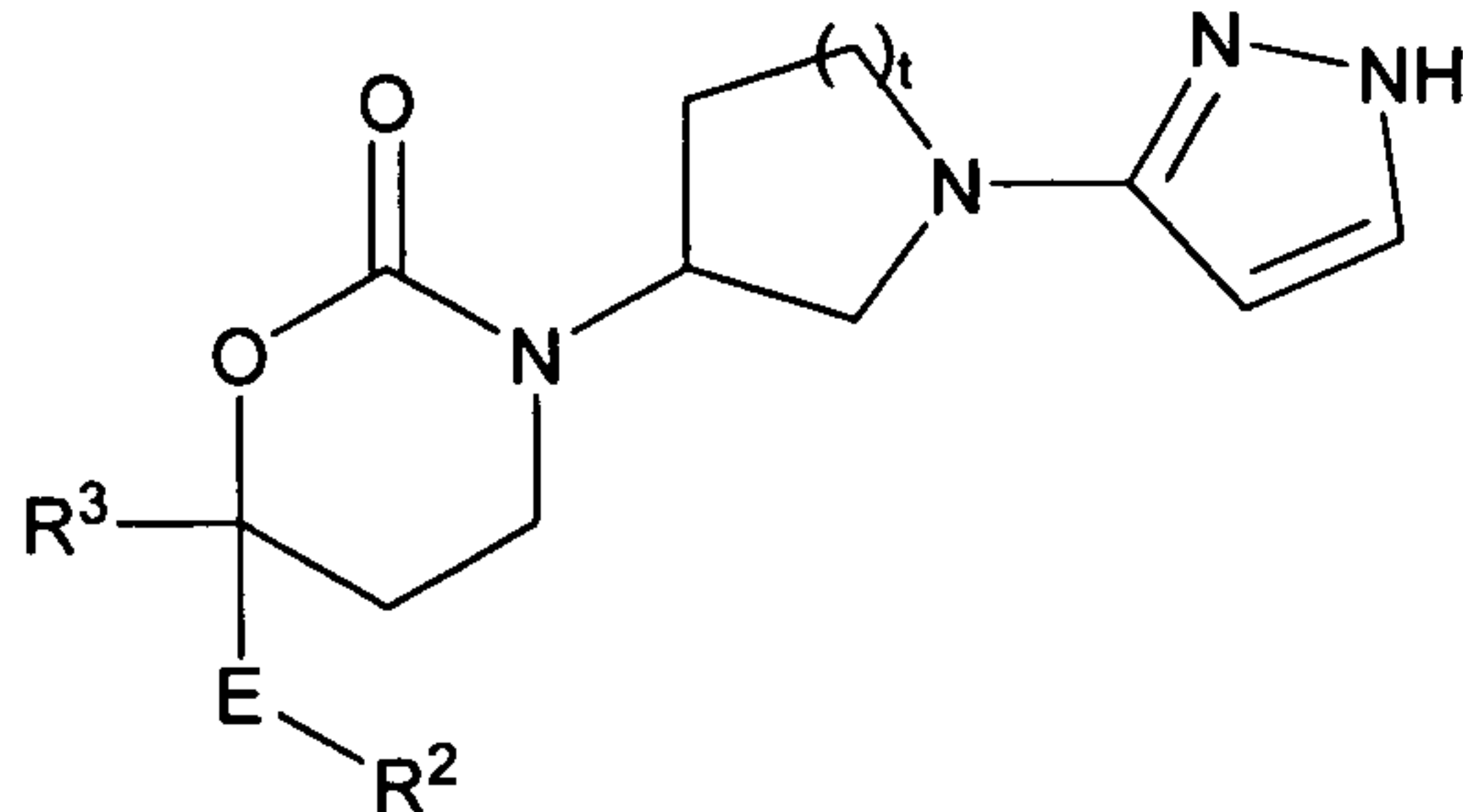
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IV⁹IV¹⁰IV¹¹IV¹²

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IV¹³IV¹⁴

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Iv¹⁵Iv¹⁶Iv¹⁷Iv¹⁸Iv¹⁹Iv²⁰

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In Formulas Iv¹⁻²⁰, the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iv¹⁻²⁰ are optionally substituted (substitution at ring carbons bonded to hydrogen and ring nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a "substitutable ring nitrogen atom") with up to four substituents as described above for Cy². Suitable substituents for Cy² and suitable values for R², R³ and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. t is 1, 2 or 3.

10

Alternatively, suitable substituents for the pyrrolidine, piperidine and azepane rings and the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iv¹⁻²⁰ are as described for G¹ and G², respectively, in Formula If, t is 1, 2 or 3 and values for R², R³ and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, suitable substituents for the pyrrolidine, piperidine and azepane rings include oxo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring

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nitrogen atom in the pyrazole rings in Formulas Iv¹⁸⁻²⁰ include (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₄)haloalkyl; suitable substituents for a ring carbon atom in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iv¹⁻²⁰ include fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl, (C₃-C₄)cycloalkylaminocarbonyl, {(C₁-C₄)alkyl}{(C₃-C₄)cycloalkyl}aminocarbonyl and (C₁-C₄)alkylcarbonylamino; the ring nitrogen in the pyridine rings in Formulas Iv¹⁻⁴ is optionally substituted by oxo; t is 1, 2 or 3; and suitable values for R², R³ and E are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments.

For each of the embodiments described in the paragraph immediately following Formulas Iv¹⁻²⁰, R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Iv¹⁻²⁰, R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Iv¹⁻²⁰, R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

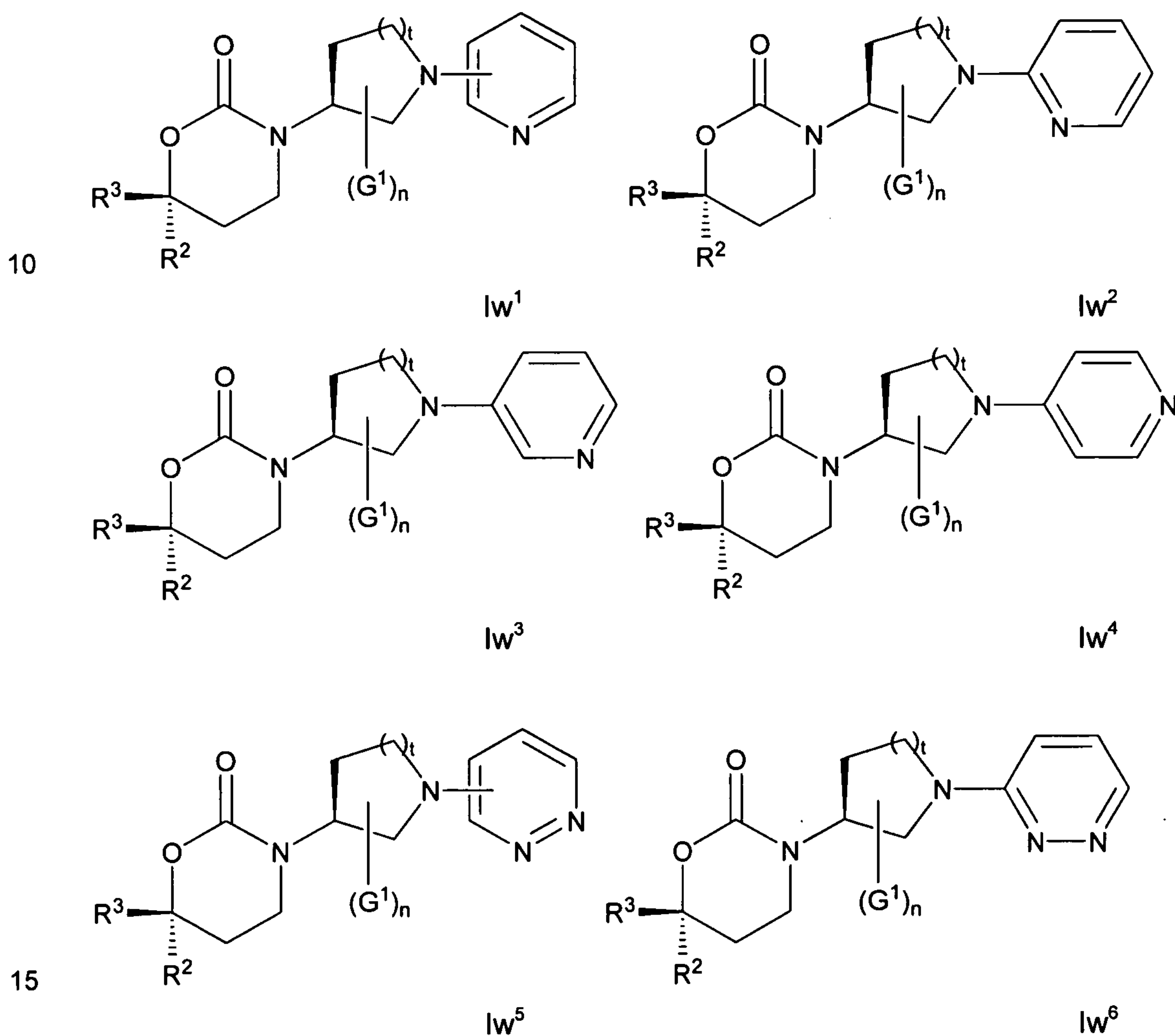
For each of the embodiments described in the paragraph immediately following Formulas Iv¹⁻²⁰, R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Iv¹⁻²⁰, t is preferably 2; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

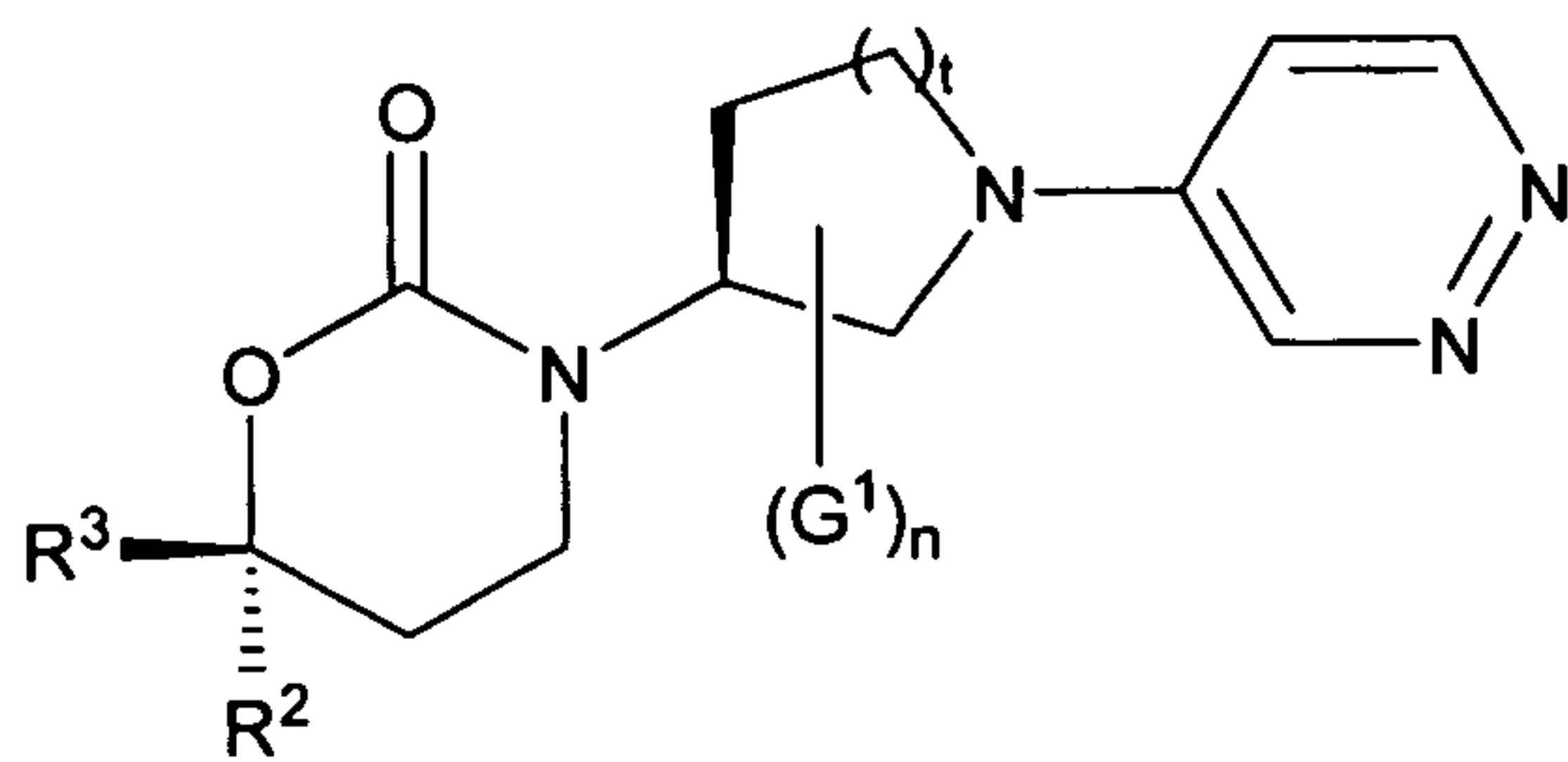
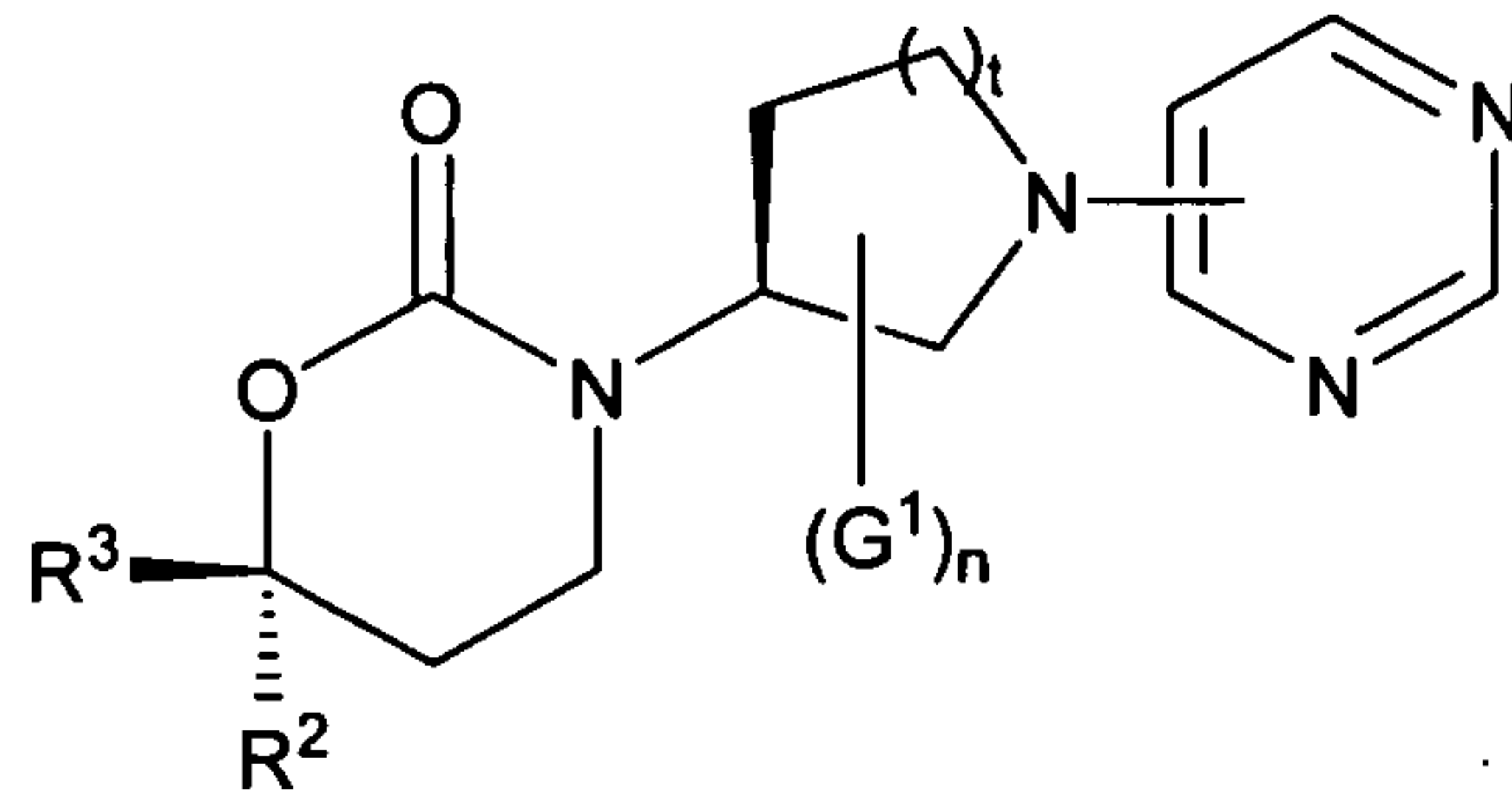
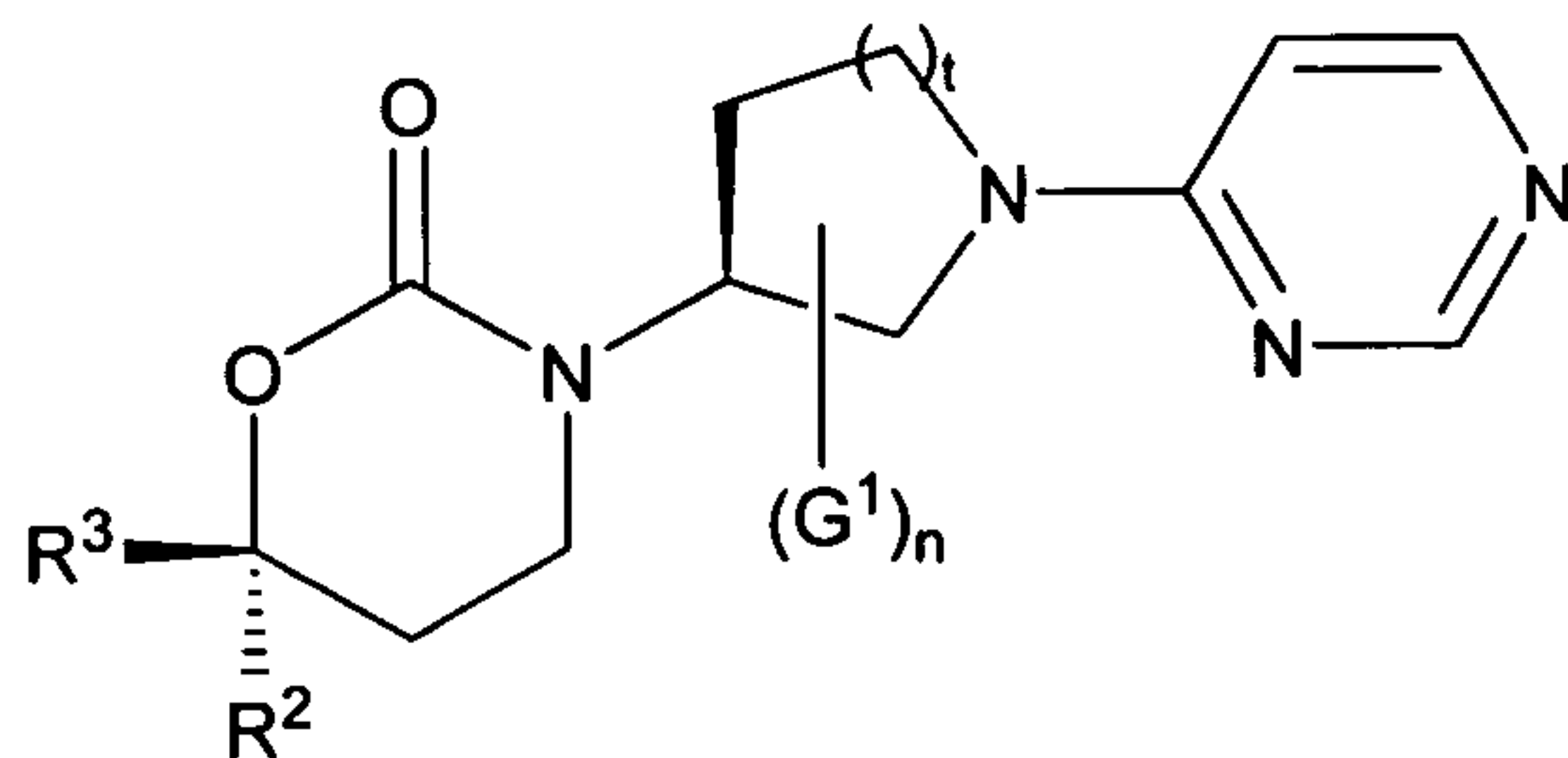
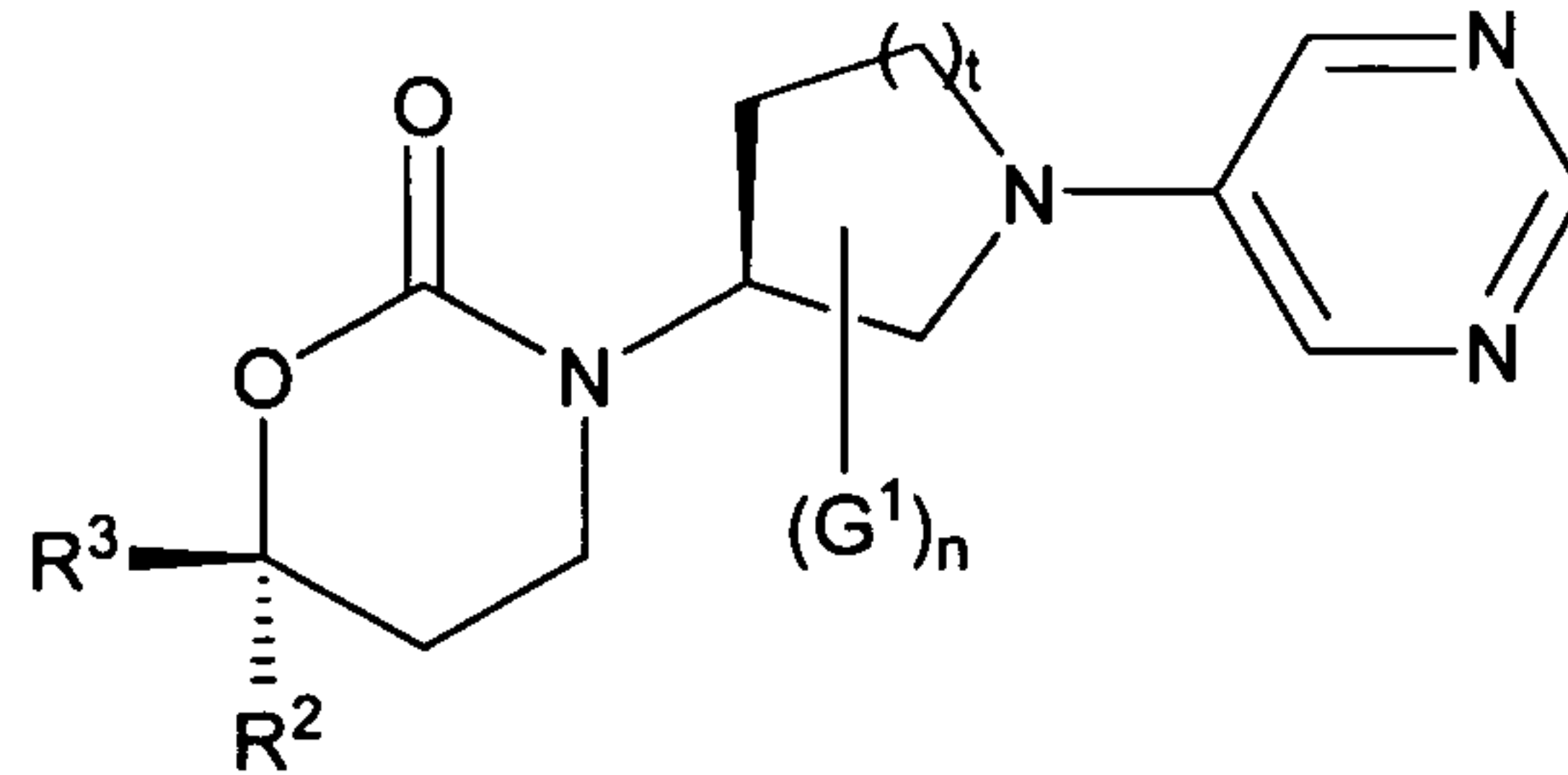
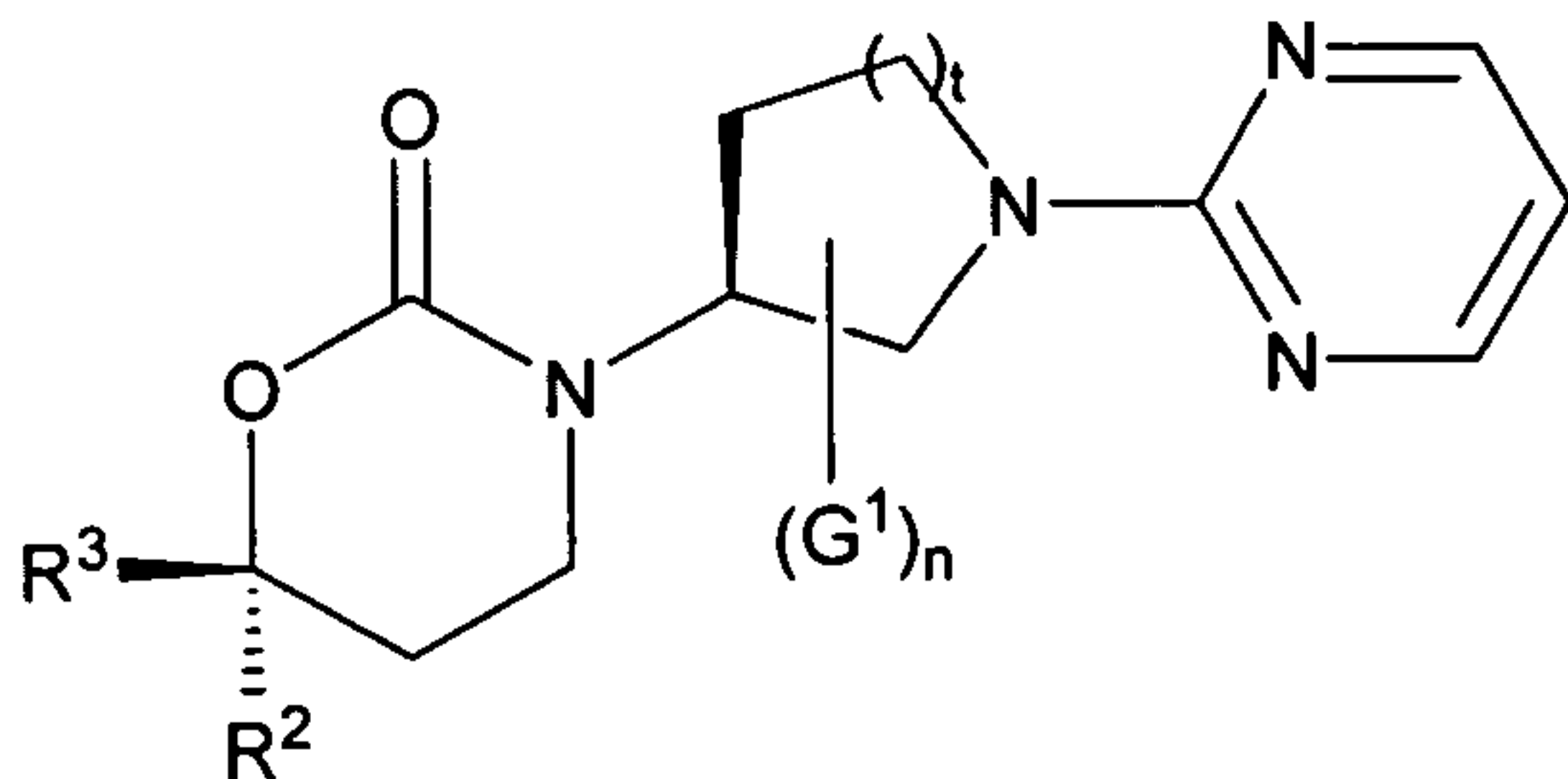
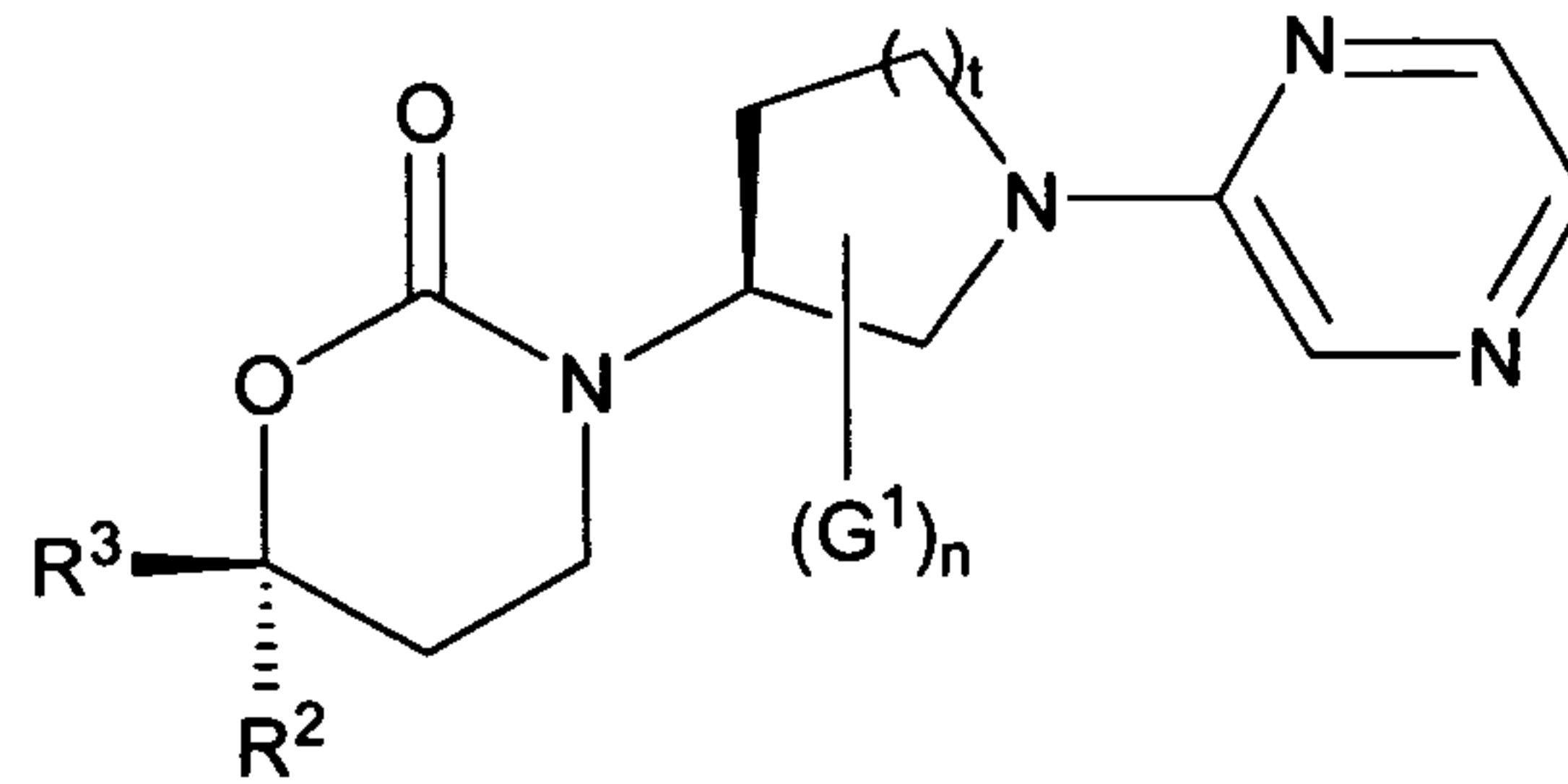
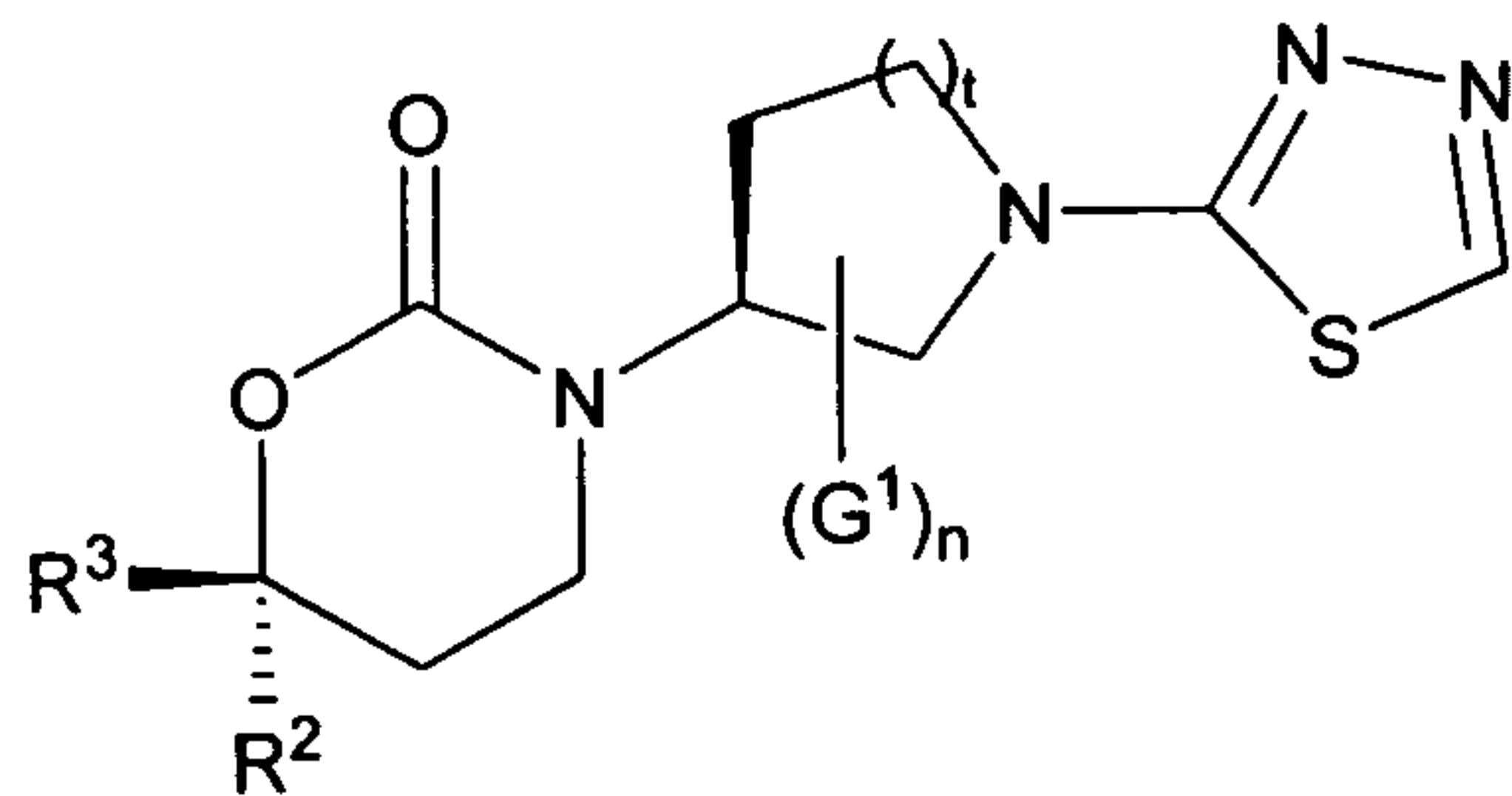
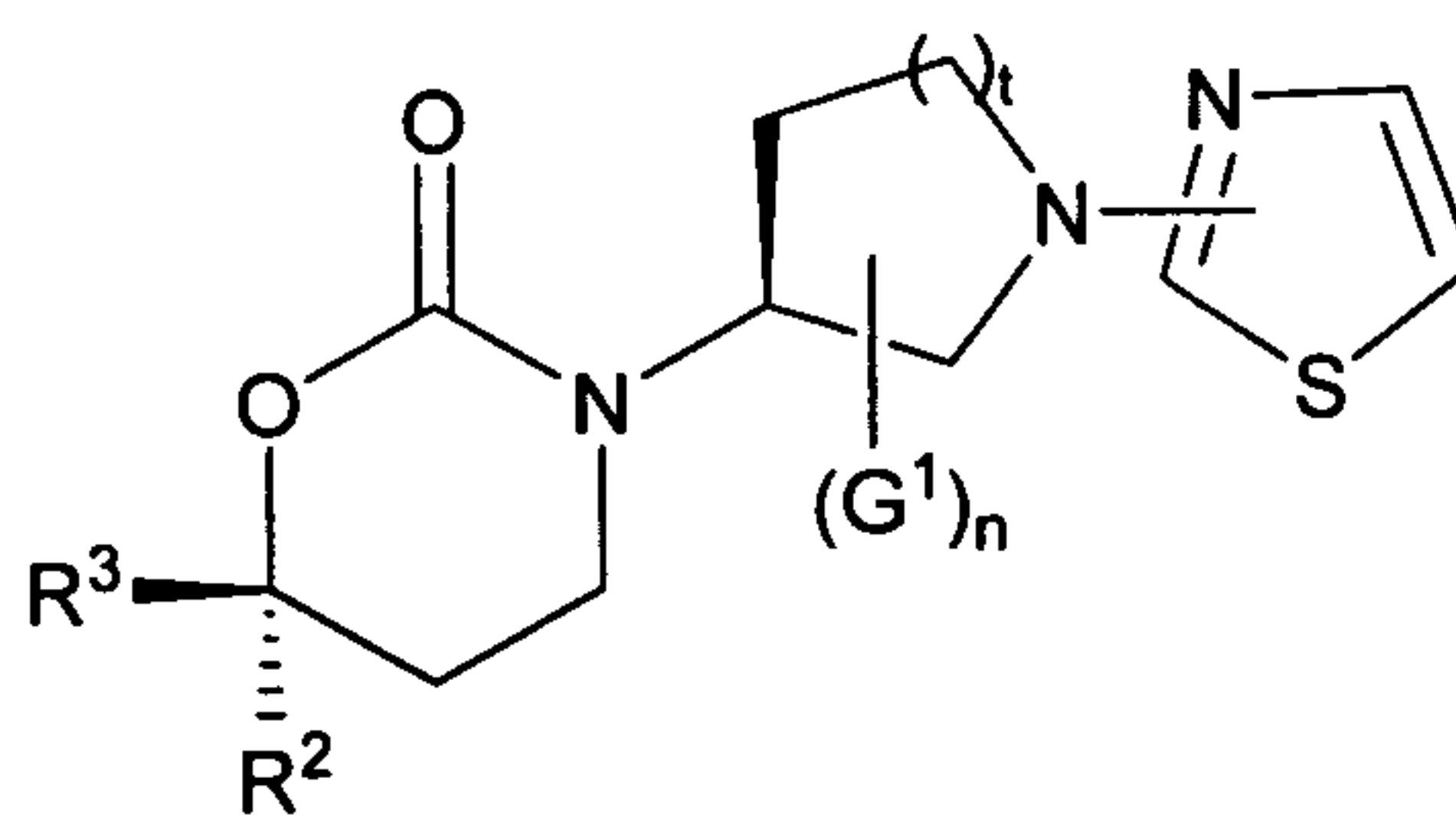
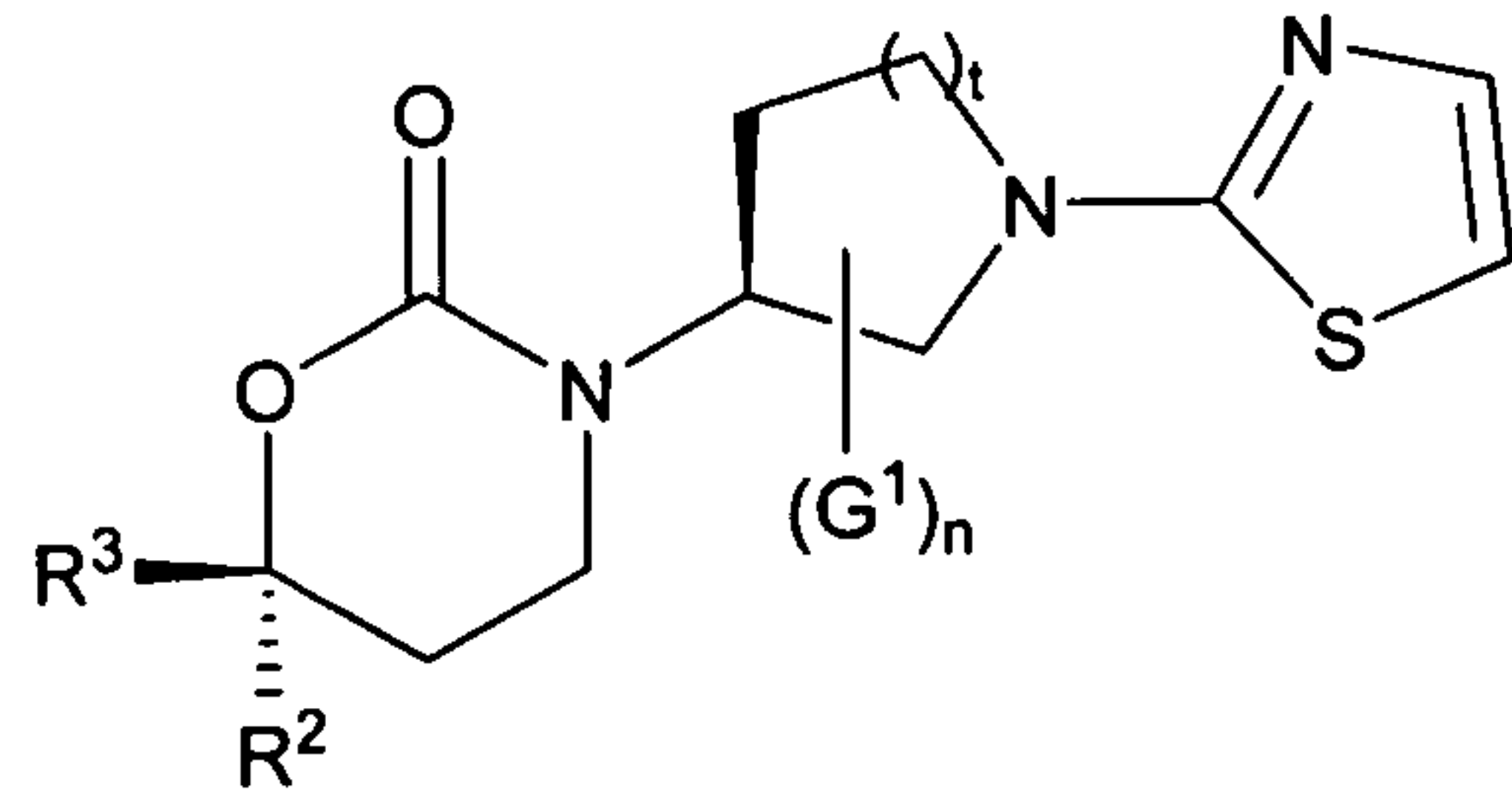
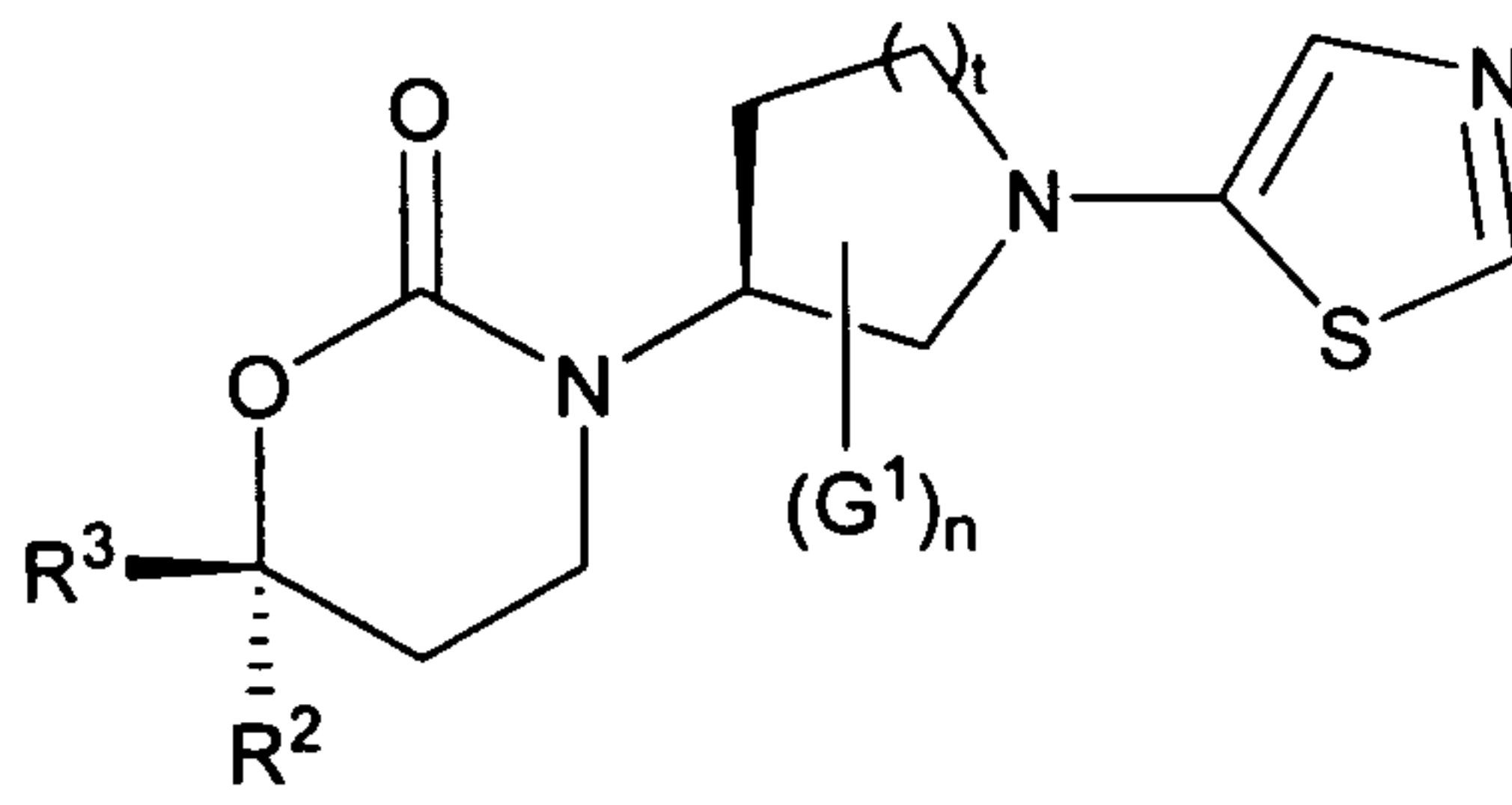
For each of the embodiments described in the paragraph immediately following Formulas Iv¹⁻²⁰, t is preferably 2; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; one or two ring carbon atoms in

the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iv¹⁻²⁰ are optionally substituted with fluoro, chloro, cyano, CONH₂, CONHMe, CONMe₂, CONHc-Pr, methyl, ethyl or CF₃; the substitutable ring nitrogen atom in the pyrazole rings in Formulas Iv¹⁸⁻²⁰ is optionally substituted with (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₂)haloalkyl; the ring nitrogen in the pyridine rings in Formulas Iv¹⁻⁴ is optionally substituted by oxo.

Another embodiment of the invention is a compound of any one of Formulas Iw¹⁻²⁰ or a pharmaceutically acceptable salt thereof:



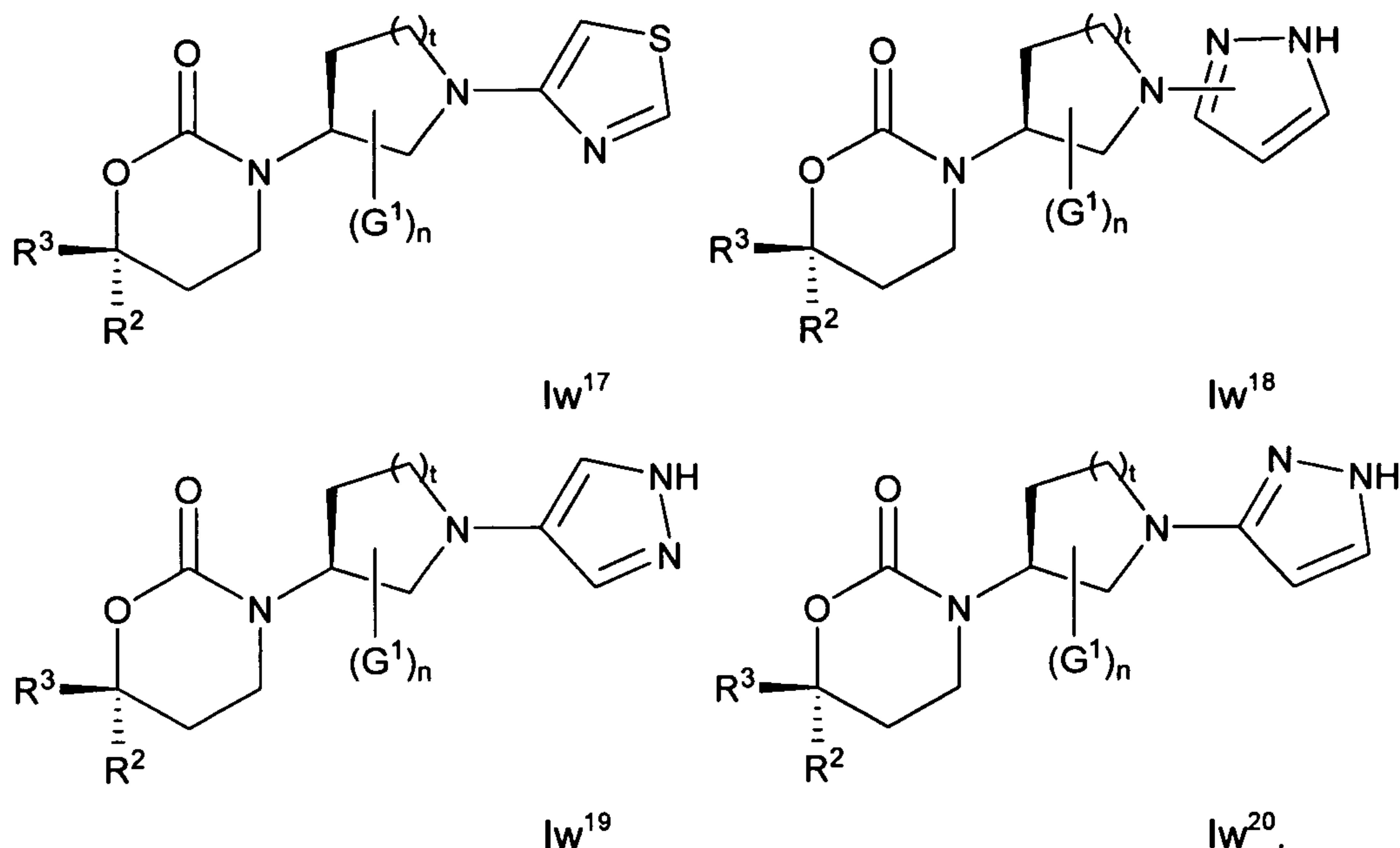
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1w⁷1w⁸1w⁹1w¹⁰1w¹¹1w¹²1w¹³1w¹⁴1w¹⁵1w¹⁶

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- 5 In Formulas Iw¹⁻²⁰, the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iw¹⁻²⁰ are optionally substituted (substitution at ring carbons bonded to hydrogen and ring nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a "substitutable ring nitrogen atom") with up to four substituents as described above for Cy². Suitable substituents for Cy² and suitable values for R² and R³ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments; suitable values for G¹ is as described for Formula If, n is 0, 1 or 2; and t is 1, 2 or 3. Alternatively, suitable values for G¹ are as described for Formula If; substituents for the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iw¹⁻²⁰ are as described for G² in Formula If; n is 0, 1 or 2; t is 1, 2 or 3; and values for R² and R³ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments. Alternatively, suitable values for G¹ include oxo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom in the pyrazole rings in Formulas Iw¹⁸⁻²⁰ include (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₄)haloalkyl; suitable substituents for a ring carbon atom in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iw¹⁻²⁰ include fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl, (C₃-C₄)cycloalkylaminocarbonyl, {(C₁-C₄)alkyl}{(C₃-C₄)cycloalkyl}aminocarbonyl and (C₁-C₄)alkylcarbonylamino; the

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ring nitrogen in the pyridine rings in Formulas Iw¹⁻⁴ is optionally substituted by oxo; n is 0, 1 or 2; t is 1, 2 or 3; and suitable values for R² and R³ are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments.

5 Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Iw¹⁻²⁰, R³ is preferably MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

10 Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Iw¹⁻²⁰, R³ is preferably H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

15 Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Iw¹⁻²⁰, R² is preferably phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is preferably MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

20 Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Iw¹⁻²⁰, R² is preferably phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is preferably H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

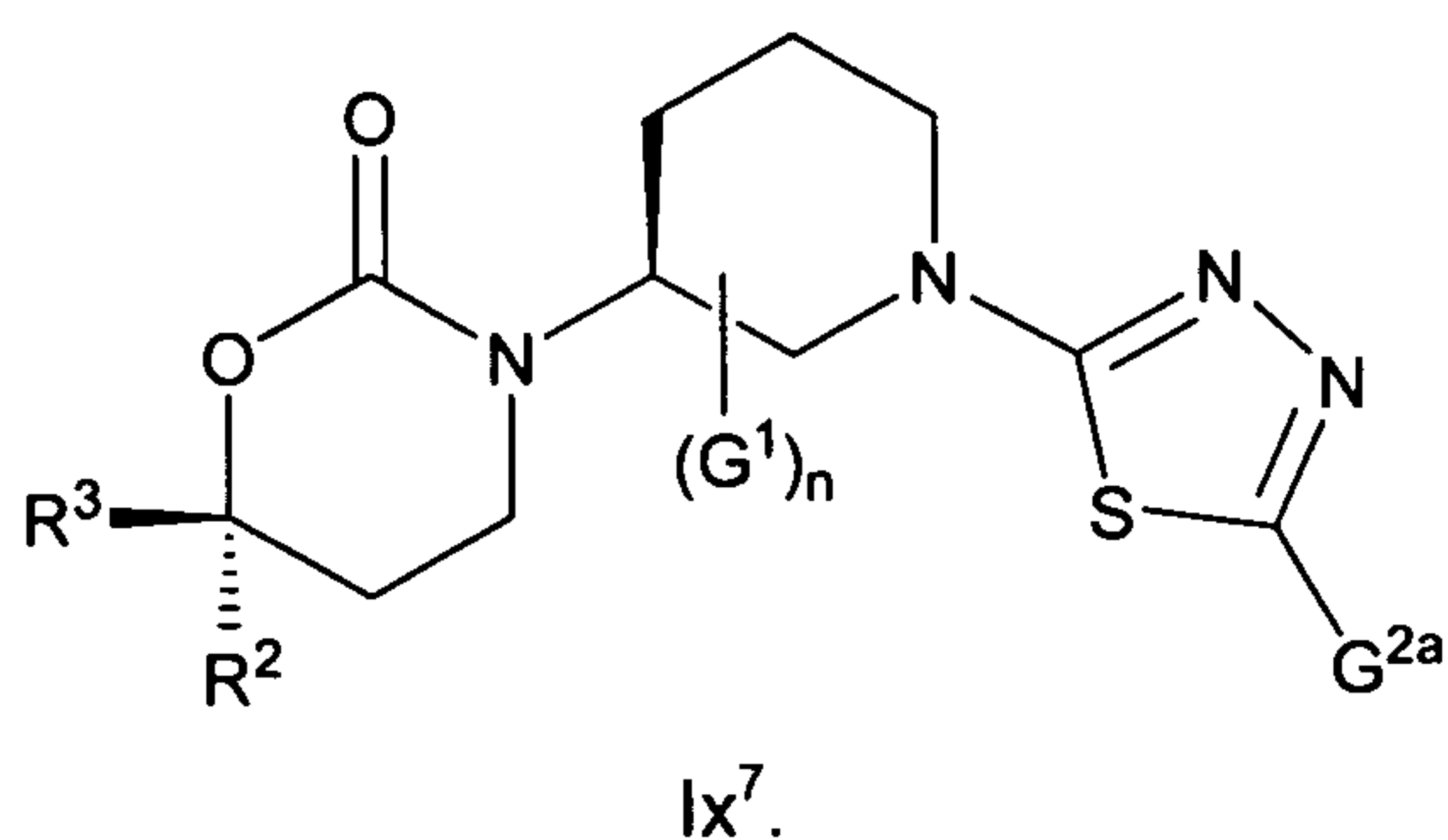
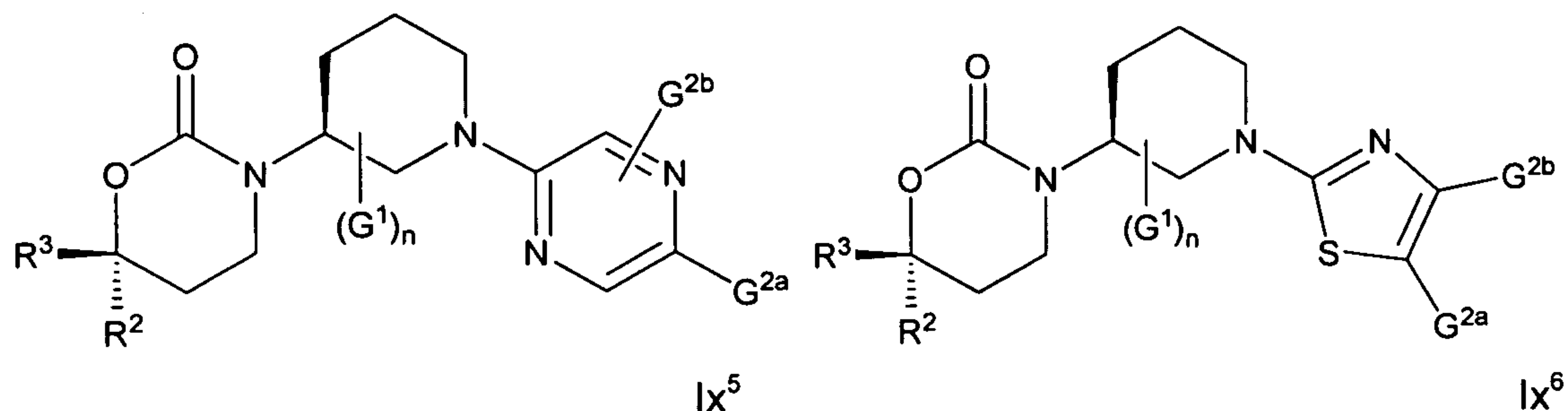
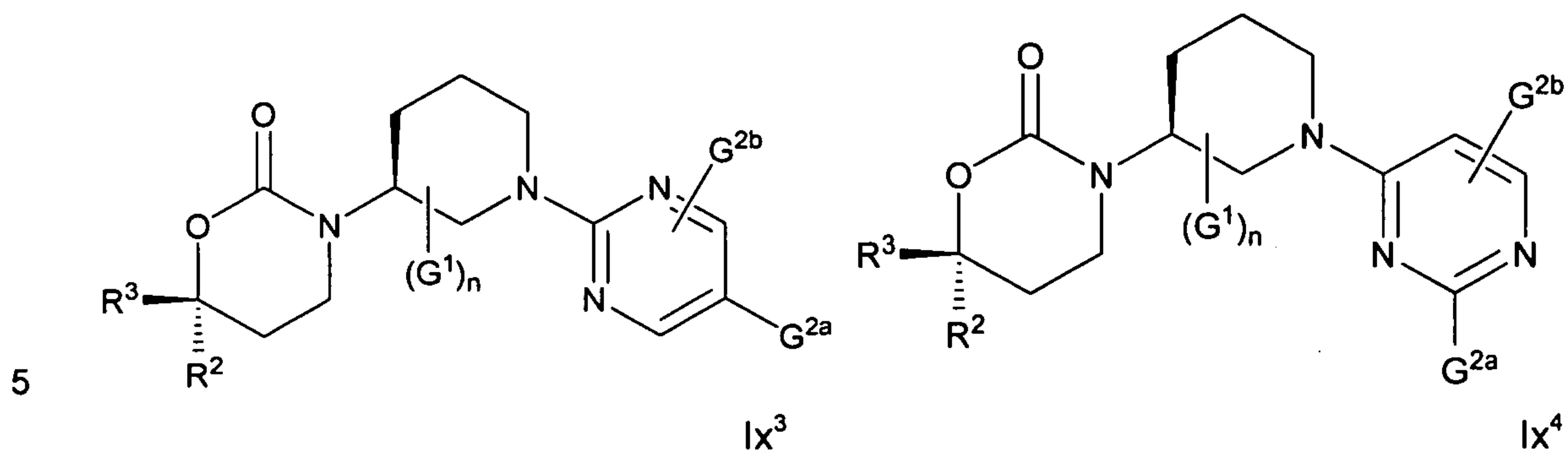
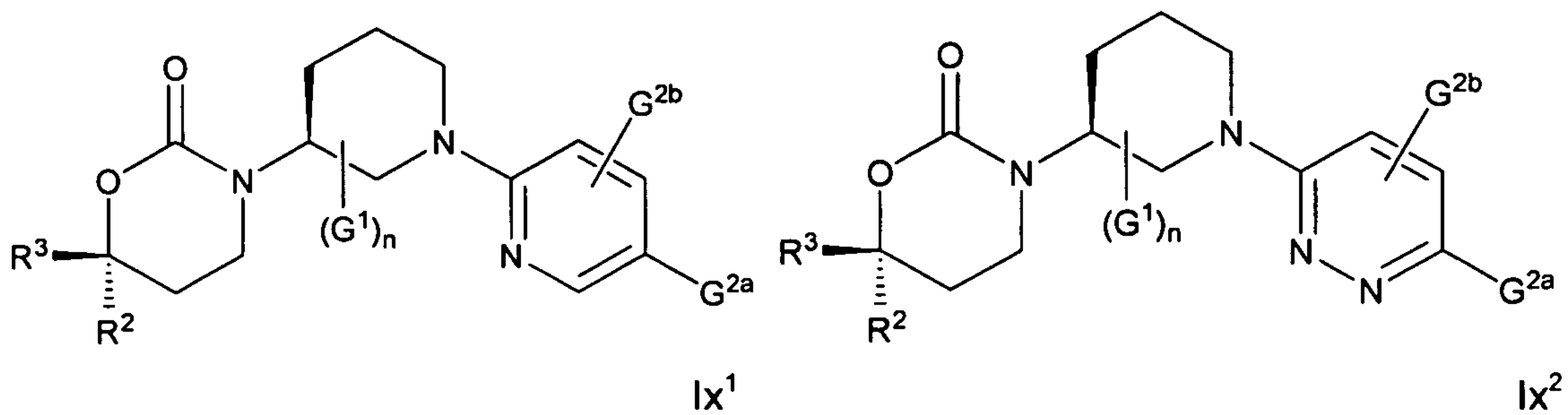
25 Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Iw¹⁻²⁰, t is preferably 2; R² is preferably phenyl or fluorophenyl; and R³ is preferably 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

30 Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Iw¹⁻²⁰ or a pharmaceutically acceptable salt thereof, wherein t is 2; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; one or two ring carbon atoms in the pyridine, pyridazine, pyrimidine, pyrazine, pyrazole, thiazole and thiadiazole rings in Formulas Iw¹⁻²⁰ are optionally substituted with fluoro, chloro, cyano, CONH₂, CONHMe, CONMe₂, CONHc-Pr, methyl, ethyl or CF₃; the substitutable ring nitrogen atom in the pyrazole rings in Formulas Iw¹⁸⁻²⁰ is optionally substituted with (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₂)haloalkyl; the ring nitrogen in the pyridine rings in Formulas Iw¹⁻⁴ is optionally substituted by oxo.

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Another embodiment of the invention is a compound represented by any one of Formulas Ix¹⁻⁶, or a pharmaceutically acceptable salt thereof:



In Formulas Ix¹⁻⁷, G¹ is oxo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; n is 0, 1 or 2; G^{2a} and G^{2b} are independently selected from hydrogen, fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl, (C₃-C₄)cycloalkylaminocarbonyl, {(C₁-C₄)alkyl}{(C₃-C₄)cycloalkyl}aminocarbonyl and (C₁-C₄)alkylcarbonylamino; and suitable values for

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R^2 and R^3 are as defined in any one of the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh or twelfth embodiments.

Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Ix¹⁻⁷, R^3 is preferably MeSO₂NHCH₂CH₂CH₂,
 5 H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Ix¹⁻⁷, R^3 is preferably H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

10 Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Ix¹⁻⁷, R^2 is preferably phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R^3 is preferably MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl,
 15 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

Alternatively, for each of the embodiments described in the paragraph immediately following Formulas Ix¹⁻⁷, R^2 is preferably phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R^3 is preferably H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.
 20

In another alternative for each of the embodiments described in the paragraph immediately following Formulas Ix¹⁻⁷, R^2 is preferably phenyl or fluorophenyl; and R^3 preferably is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

25 Compounds of the invention are also disclosed in INHIBITORS OF 11 β -HYDROXYSTEROID DEHYDOGENASE I, U.S. Provisional Application No. 61/_____, filed July 25, 2008 (Attorney Docket No. 4370.1000-000), the entire teachings of which are incorporated herein by reference.

The present invention further provides methods of inhibiting 11 β -HSD1 by
 30 contacting 11 β -HSD1 with a compound of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il, Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ of the invention.

The present invention further provides methods of inhibiting or reducing the conversion of cortisone to cortisol in a cell using a compound of Formula I, Ia, Ib, Ic,
 35 Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il, Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ of the invention.

The present invention further provides methods of inhibiting or reducing production of cortisol in a cell using a compound of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il, Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ of the invention.

5 The present invention further provides methods of increasing insulin sensitivity in a subject in need thereof using a compound of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il, Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ of the invention.

10 The present invention further provides methods of treating a subject with a disease associated with activity of expression of 11 β -HSD1 using a compound of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il, Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ of the invention.

15 Preferred values for the variables in the above-described structural formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il, Im¹⁻¹², In¹⁻¹², Io¹⁻¹², Ip¹⁻⁷, Iq¹⁻²¹, Ir¹⁻²¹, Is¹⁻²¹, It¹⁻⁷, Iu¹⁻²⁰, Iv¹⁻²⁰, Iw¹⁻²⁰ or Ix¹⁻⁷ are provided below:

A¹ is a bond. Alternatively, A¹ is (C₁-C₃)alkylene. In another specific embodiment, A¹ is methylene. In another specific embodiment, A¹ is CH when R¹ is present.

R¹ is (C₁-C₆)alkyl. Alternatively, R¹ is methyl or ethyl.

20 Cy¹ is optionally substituted aryl or optionally substituted heteroaryl. Alternatively, Cy¹ is optionally substituted phenyl or optionally substituted pyridyl. In another alternative, Cy¹ is optionally substituted phenyl. In yet another specific embodiment, Cy¹ is substituted with fluorine or bromine. In another embodiment A² is a bond, Cy² is H and Cy¹ is optionally substituted monocyclic cycloalkyl. In another
25 embodiment A² is a bond, Cy² is H and Cy¹ is optionally substituted cyclohexyl. In another embodiment A² is a bond, Cy² is H and Cy¹ is phenyl substituted with fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl, hydroxymethyl or 2-hydroxy-2-propyl. In another embodiment Cy¹ is phenyl substituted with trifluoromethoxy or 2,2,2-trifluoroethoxy. Alternatively Cy¹ is optionally substituted
30 heterocyclyl. In another embodiment Cy¹ is optionally substituted pyrrolidinyl, piperidinyl or azepanyl.

A² is a bond and Cy² is hydrogen. Alternatively, A² is a bond and Cy² is cyclopropyl. Alternatively, A² is a bond and Cy² is (C₃-C₇)cycloalkyl. Alternatively, A² is a bond and Cy² is optionally substituted aryl or optionally substituted heteroaryl. In
35 another specific embodiment, A² is a bond and Cy² is optionally substituted phenyl or optionally substituted pyridyl. In yet another specific embodiment, A² is a bond and

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Cy² is optionally substituted phenyl. In yet another specific embodiment, A² is a bond and Cy² is substituted with 1 to 4 groups independently selected from chlorine or fluorine. In yet another specific embodiment, A² is a bond and Cy² is difluorophenyl. In yet another specific embodiment, A² is a bond and Cy² is fluorophenyl. In yet another specific embodiment A² is a bond and Cy² is optionally substituted 2-thienyl, 1-pyrazolyl, 3-pyrazolyl, 1,2,4-thiadiazol-3-yl, thiazolyl or 2-oxo-1,2-dihydro-5-pyridyl. In yet another specific embodiment, A² is a bond and Cy² is phenyl or thienyl substituted with amino(C₁-C₆)alkyl. In another embodiment A² is a bond and Cy² is optionally substituted pyridazinyl, pyrimidinyl, pyrazinyl, 1,2-dihydro-2-oxopyridyl, 2,3-dihydro-3-oxopyridazinyl, 1,2-dihydro-2-oxopyrimidinyl, 3,4-dihydro-4-oxopyrimidinyl or 1,2-dihydro-2-oxopyrazinyl. In yet another embodiment A² is a bond and Cy² is unsubstituted, methyl substituted or ethyl substituted pyridazinyl, pyrimidinyl, pyrazinyl, 1,2-dihydro-2-oxopyridyl, 2,3-dihydro-3-oxopyridazinyl, 1,2-dihydro-2-oxopyrimidinyl, 3,4-dihydro-4-oxopyrimidinyl or 1,2-dihydro-2-oxopyrazinyl. In yet another specific embodiment A² is a bond and Cy² is 6-oxo-1,6-dihydropyridin-3-yl, 1-methyl-6-oxo-1,6-dihydropyridin-3-yl, 1-methyl-2-oxo-1,2-dihydropyridin-4-yl, 1-ethyl-6-oxo-1,6-dihydropyridin-3-yl or 1-methyl-6-oxo-1,6-dihydropyridazin-3-yl. In another embodiment A² is a bond and Cy² is optionally substituted heterocyclyl. In another embodiment A² is a bond and Cy² is heterocyclyl substituted by one oxo group and up to 3 groups independently selected from amino, fluoro, chloro, cyano, CONH₂, CONHMe, CONMe₂, CONHc-Pr, methyl, ethyl, isopropyl, t-butyl, cyclopropyl, methoxy, ethoxy or trifluoromethyl. In yet another specific embodiment A² is a bond and Cy² is 1,5-dimethyl-6-oxo-1,6-dihydropyridin-3-yl, 1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl, 6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl, 1,6-dimethyl-2-oxo-1,2-dihydropyridin-4-yl, 1-ethyl-2-oxo-1,2-dihydropyridin-4-yl, 1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl, 2-oxo-1-(2,2,2-trifluoroethyl)-1,2-dihydropyridin-4-yl, 1-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl, 1-ethyl-6-oxo-1,6-dihydropyridazin-3-yl, 1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl or 6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridazin-3-yl. In another specific embodiment, A² is a bond and Cy² is heteroaryl optionally substituted with by up to 2 groups independently selected from amino, halo, cyano, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl, cyclo(C₃-C₅)alkylaminocarbonyl, (C₁-C₄)alkyl, (C₁-C₄)alkoxy or (C₁-C₂)haloalkyl, (C₁-C₂)haloalkoxy. In yet another embodiment A² is a bond and Cy² is pyridinyl, N-oxopyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl or thiazolyl optionally substituted by up to 2 groups independently selected from amino, halo, cyano, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl, cyclo(C₃-

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C_5)alkylaminocarbonyl, (C_1-C_4) alkyl, (C_1-C_4) alkoxy or (C_1-C_2) haloalkyl, (C_1-C_2) haloalkoxy. In yet another embodiment A^2 is a bond and Cy^2 is pyridinyl, N-oxo-pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl or thiazolyl optionally substituted by up to 2 groups independently selected from amino, fluoro, chloro, cyano, $CONH_2$, $CONHMe$, $CONMe_2$, $CONHc-Pr$, $CONHt-Bu$, methyl, ethyl, methoxy, ethoxy or trifluoromethyl. In yet another embodiment A^2 is a bond and Cy^2 is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-3-yl, 1,3,4-thiadiazol-2-yl, thiazol-2-yl or thiazol-5-yl optionally substituted by up to 2 groups independently selected from amino, fluoro, chloro, cyano, $CONH_2$, $CONHMe$, $CONMe_2$, $CONHc-Pr$, methyl, ethyl, methoxy, ethoxy or trifluoromethyl. In yet another embodiment A^2 is a bond and Cy^2 is pyridinyl or thiazolyl optionally substituted by up to 2 groups independently selected from fluoro, chloro, cyano, $CONHMe$, $CONMe_2$, $CONHc-Pr$, methyl, ethyl, methoxy, ethoxy or trifluoromethyl. In yet another specific embodiment A^2 is a bond and Cy^2 is 5-fluoropyridin-2-yl, 5-(trifluoromethyl)pyridin-2-yl, 5-cyanopyridin-2-yl, 5-carbamoylpyridin-2-yl, 5-(methylcarbamoyl)pyridin-2-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 6-methoxypyridin-3-yl, 5-fluoropyridin-3-yl, 5-chloropyridin-3-yl, 2-methylpyridin-4-yl, 2,6-dimethylpyridin-4-yl, 6-methylpyridazin-3-yl, 2-methylpyrimidin-5-yl, 2-methylpyrimidin-4-yl, 5-methylpyrazin-2-yl, 5-cyanopyrazin-2-yl, 6-cyanopyrazin-2-yl, 5-(dimethylcarbamoyl)thiazol-2-yl, 6-carbamoylpyrazin-2-yl, 6-ethoxy-5-methylpyridin-3-yl, or 5-(cyclopropylcarbamoyl)pyridin-2-yl.

R^3 is hydroxy (C_2-C_4) alkyl. Alternatively, R^3 is dihydroxy (C_3-C_4) alkyl. In another specific embodiment, R^3 is ω - $H_2NCO(C_1-C_3)$ alkyl. In yet another specific embodiment, R^3 is (C_1-C_2) alkoxy (C_1-C_3) alkyl. In yet another specific embodiment, R^3 is $H_2NSO_2O(C_2-C_4)$ alkyl. In yet another specific embodiment, R^3 is $H_2NSO_2NH(C_2-C_4)$ alkyl. In yet another specific embodiment, R^3 is oxo (C_2-C_4) alkyl. In yet another specific embodiment, R^3 is alkenyl. In yet another specific embodiment, R^3 is allyl. In yet another specific embodiment, R^3 is $MeC(=O)NH(C_2-C_4)$ alkyl. In yet another specific embodiment R^3 is 2-hydroxy-2-methylpropyl, 3-hydroxypropyl, 2-hydroxypropyl or 2-hydroxyethyl. In yet another specific embodiment R^3 is 2,3-dihydroxypropyl. In yet another specific embodiment R^3 is $H_2NC(=O)CH_2CH_2-$. In yet another specific embodiment R^3 is 2-(4-morpholino)ethyl. In yet another embodiment R^3 is $MeSO_2NH(C_2-C_4)$ alkyl. In yet another specific embodiment R^3 is $MeSO_2NHCH_2CH_2CH_2$.

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R^3 is $(HO)_2P(=O)(C_1-C_4)alkyl$. R^3 is hydroxy(C_2-C_5)alkyl. In yet another specific embodiment R^3 is 3-hydroxybutyl, 3-hydroxy-3-methylbutyl, 3-hydroxypropyl, 2-hydroxypropyl, 2-hydroxy-2-methylpropyl, or 2-hydroxyethyl. Alternatively, R^3 is dihydroxy(C_3-C_4)alkyl. In yet another specific embodiment R^3 is 2,3-dihydroxypropyl.

5 R^3 is amino(C_2-C_5)alkyl or methylamino(C_2-C_5)alkyl, each optionally substituted with hydroxy. In another specific embodiment, R^3 is ω - $H_2NCO(C_1-C_3)alkyl$. In another specific embodiment, R^3 is $H_2NCONH(C_1-C_3)alkyl$, optionally substituted with hydroxy. In another specific embodiment, R^3 is $H_2NCH_2CONH(C_1-C_3)alkyl$, optionally substituted with hydroxy. In another specific embodiment, R^3 is (C_1 -

10 C_3)alkylHNCONH(C_1-C_3)alkyl. In yet another specific embodiment, R^3 is $H_2NC(=O)C_1-C_4 alkyl$. In yet another specific embodiment, R^3 is $MeC(=O)NHC_1-C_4 alkyl$. In yet another specific embodiment, R^3 is $MeOC(=O)NHC_1-C_4 alkyl$. In yet another specific embodiment, R^3 is $MeNHC(=O)C_1-C_4 alkyl$. In yet another specific embodiment R^3 is $H_2NC(=O)OC_1-C_4 alkyl$. In yet another specific embodiment, R^3 is

15 $MeHNC(=O)OC_1-C_4 alkyl$. In yet another specific embodiment, R^3 is (C_1 - C_2)alkoxy(C_1-C_3)alkyl, optionally substituted with hydroxy. In yet another specific embodiment, R^3 is (C_1 - C_2)alkylthio(C_1-C_3)alkyl, optionally substituted with hydroxy. In yet another specific embodiment, R^3 is $H_2NSO_2O(C_2-C_4)alkyl$. In yet another specific embodiment, R^3 is $H_2NSO_2NH(C_2-C_4)alkyl$. In yet another specific embodiment, R^3

20 is oxo(C_2-C_4)alkyl. In yet another specific embodiment, R^3 is $MeCO(C_1-C_2alkyl)$. In yet another specific embodiment, R^3 is $HOCO(C_1-C_2alkyl)$. In yet another specific embodiment, R^3 is alkenyl. In yet another specific embodiment, R^3 is alkyl. In yet another specific embodiment, R^3 is allyl. In yet another specific embodiment, R^3 is $MeC(=O)NH(C_2-C_4)alkyl$. In yet another specific embodiment, R^3 is

25 $MeOC(=O)NH(C_2-C_4)alkyl$. In yet another specific embodiment, R^3 is cyanoalkyl. In yet another specific embodiment, R^3 is alkylsulfonylaminoalkyl. In yet another specific embodiment, R^3 is alkylsulfonylalkyl. In yet another specific embodiment R^3 is $MeSO_2NH(C_2-C_4)alkyl$, optionally substituted with hydroxy. In yet another specific embodiment, R^3 is aminocarbonylaminoalkyl. In yet another specific embodiment,

30 R^3 is aminocarboxyalkyl. In yet another specific embodiment R^3 is 2-(4-morpholino)ethyl. In yet another specific embodiment R^3 is 2-(1-imidazolyl)ethyl. In yet another specific embodiment R^3 is 2-(1-aminoimidazolyl)ethyl.

In another embodiment R^3 is (C_3-C_4)cycloalkyl(C_1-C_2)alkyl. In another specific embodiment R^3 is (1-hydroxycyclopropyl)methyl. In another specific embodiment R^3

35 is 1-(hydroxymethyl)cyclopropyl)methyl. In another specific embodiment R^3 is (1-carbamoylcyclopropyl)methyl. In another specific embodiment R^3 is 2-(1-

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azetidiny)ethyl, 2-(1-pyrrolidiny)ethyl, 2-(3-fluoro-1pyrrolidiny)ethyl, 2-(2-oxo-1-pyrrolidiny)ethyl, 2-(1,1-dioxo-2-isothiazolidiny)ethyl, 2-(3-oxo-1-piperaziny)ethyl, (5-methyl-1,3,4-thiadiazol-2-yl)methyl, 2-(5-methyl-1,3,4-thiadiazol-2-yl)ethyl, (5-methyl-1,3,4-oxadiazol-2-yl)methyl or 2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl. In another
 5 embodiment R^3 is heterocyclyl(C_1 - C_3)alkyl.

In another specific embodiment R^3 is $H_2NCOCHMeCH_2-$, $H_2NCOC(Me)_2CH_2-$, $NCCHMeCH_2-$, $NCC(Me)_2CH_2-$, $H_2NCH_2C(Me)_2CH_2-$, $MeCONHCH_2C(Me)_2CH_2-$, $MeOCONHCH_2C(Me)_2CH_2-$, $MeSO_2NHCH_2C(Me)_2CH_2-$, $HOCH_2CHMeCH_2-$, $HOCH_2C(Me)_2CH_2-$, $MeSO_2NMeCH_2CH_2-$ or $MeSO_2NMeCH_2CH_2CH_2-$. In another
 10 specific embodiment R^3 is methyl, ethyl, $FCMe_2CH_2-$, $MeC(=O)NHCMe_2CH_2-$, $MeOC(=O)NHCMe_2CH_2-$ or $MeS(=O)_2NHCMe_2CH_2-$.

E is a bond.

R^2 is optionally substituted aryl, optionally substituted heteroaryl or cycloalkyl. In one specific embodiment, R^2 is optionally substituted phenyl or optionally
 15 substituted pyridyl. In another specific embodiment, R^2 is optionally substituted phenyl. In yet another specific embodiment, R^2 is fluorophenyl. R^2 is (C_3 - C_5)alkyl. In one specific embodiment R^2 is isopropyl. In another embodiment R^2 is optionally substituted thienyl. In another specific embodiment R^2 is t-butyl.

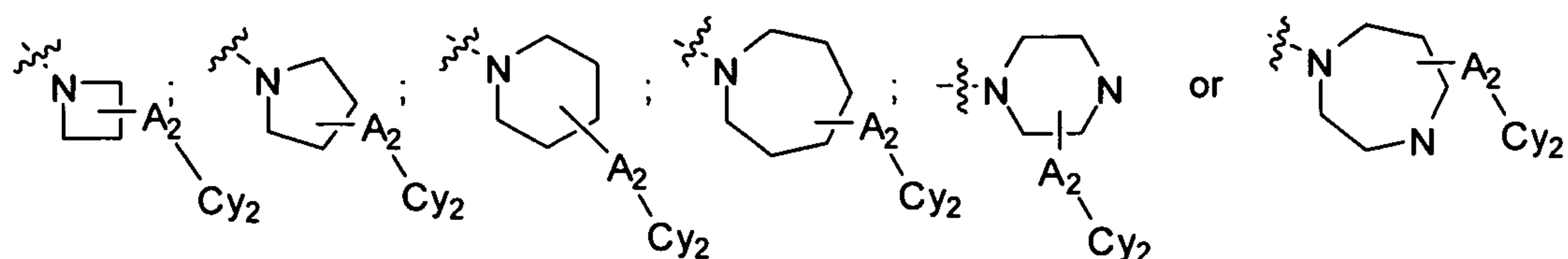
In another embodiment of the invention, the provisos applied to
 20 pharmaceutical compositions comprising compounds of Formula I or Ia-II or Im^{1-12} , In^{1-12} , Io^{1-12} , Ip^{1-7} , Iq^{1-21} , Ir^{1-21} , Is^{1-21} , It^{1-7} , Iu^{1-20} , Iv^{1-20} , Iw^{1-20} or Ix^{1-7} also apply to methods of treatment utilizing any one of the compounds of Formula I or Formulas Ia-II or Im^{1-12} , In^{1-12} , Io^{1-12} , Ip^{1-7} , Iq^{1-21} , Ir^{1-21} , Is^{1-21} , It^{1-7} , Iu^{1-20} , Iv^{1-20} , Iw^{1-20} or Ix^{1-7} .

Another embodiment of the invention is a compound of Formulas I, Ia, Ib, Ic,
 25 Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Il Im^{1-12} , In^{1-12} , Io^{1-12} , Ip^{1-7} , Iq^{1-21} , Ir^{1-21} , Is^{1-21} , It^{1-7} , Iu^{1-20} , Iv^{1-20} , Iw^{1-20} or Ix^{1-7} , or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof, wherein any one of the following provisos apply or any combination thereof:

Proviso 1: If (a) either R^3 or $E-R^2$ is (C_1 - C_4)alkyl or benzyl substituted with halogen or
 30 (C_1 - C_2)alkoxy, and (b) n is not zero, then Y cannot be either oxo or (C_1 - C_3)alkyl at the position β to the nitrogen atom in the ring.

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Proviso 2: If A_1 is a C_2 - C_3 alkylene, then $-Cy^1-A_2-Cy_2$ cannot be



wherein the nitrogen-containing heterocycle represented by Cy^1 is optionally substituted.

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Proviso 3: If (a) A^1 and A^2 are both bonds, (b) R^3 is an alkyl optionally substituted with amino, alkyl, alkoxy, oxo, carboxy, hydroxy, fluorine, or sulfonyl, or an unsubstituted alkynyl (c) $E-R^2$ is (i) a optionally substituted alkyl or an optionally substituted carbocyclic aromatic group wherein the substituent is an amino, alkyl, alkenyl, alkynyl, alkoxy, carboxy, hydroxy, halogen or sulfonyl, or (ii) an unsubstituted cycloalkyl, and (d) Cy^2 is H, then Cy_1 is not (i) an unsubstituted monocyclic cycloalkyl or (ii) a substituted or unsubstituted carbocyclic aromatic group.

10

Proviso 4: If (a) A^1 and A^2 are both bonds, (b) R^3 is an alkyl optionally substituted with amino, alkyl, alkoxy, oxo, carboxy, hydroxy, fluorine, or sulfonyl, or an unsubstituted alkynyl (c) $E-R^2$ is (i) a optionally substituted alkyl or an optionally substituted carbocyclic aromatic group wherein the substituent is an amino, alkyl, alkenyl, alkynyl, alkoxy, carboxy, hydroxy, halogen or sulfonyl, or (ii) an unsubstituted cycloalkyl, and (d) Cy^1 is an optionally substituted carbocyclic aromatic group, then Cy^2 is not an unsubstituted carbocyclic aromatic group.

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Proviso 5: If (a) A^1 is alkyl optionally substituted with amino, alkyl, alkoxy, oxo, carboxy, hydroxy, fluorine, or sulfonyl, (b) R^3 is an alkyl substituted with amino, alkyl, alkoxy, oxo, carboxy, hydroxy, fluorine, or sulfonyl, or an unsubstituted alkynyl (c) $E-R^2$ is (i) a optionally substituted alkyl or an optionally substituted carbocyclic aromatic group wherein the substituent is an amino, alkyl, alkenyl, alkynyl, alkoxy, carboxy, hydroxy, halogen or sulfonyl, or (ii) an unsubstituted cycloalkyl, then Cy^1 is a carbocyclic aromatic group optionally substituted with C_1C_4 alkoxy or halogen.

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Proviso 6: If (a) A^1 is a bond or alkylene, (b) Cy^1 is (C_3-C_7) cycloalkyl, aryl or heteroaryl, and (c) E is a bond, then R^2 is not 3, 4-dialkoxyphenyl optionally substituted with halogen or hydroxy, or 3, 4-dicycloalkoxyphenyl optionally

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substituted with halogen or 3, 4-dialkoxyalkoxyphenyl optionally substituted with halogen.

Proviso 7: If (a) A¹ is a bond, (b) Cy¹ is phenyl, (c) A² is unsubstituted methylene, (d)
5 Cy² is H, and (e) n is 1, then Y is not oxo adjacent to the nitrogen in the oxazinone ring.

Proviso 8: If E is a bond or C₁alkylene, R₂ is aryl, heteroaryl or heterocyclyl, A¹ is (C₁)alkylene, R³ is optionally fluorinated (C₁-C₅)alkyl, (C₂-C₅)alkenyl or (C₂-C₆)alkynyl
10 and Cy¹ is optionally substituted phenyl, then Cy¹ is not substituted at the *ortho* position by optionally substituted aryl, heteroaryl, heterocyclyl or cycloalkyl.

Another embodiment of the present invention is a compound of Formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, or II or a pharmaceutically acceptable salt,
15 enantiomer of diastereomer thereof, wherein all of the above Provisos apply. Yet another embodiment of the present invention is a compound of Formula I or a pharmaceutically acceptable salt, enantiomer of diastereomer thereof, wherein the above Provisos 3-8 apply.

20 Another embodiment of the present invention is a pharmaceutical composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) a compound of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih Ii, Ij, Ik, or II or a pharmaceutically acceptable salt, enantiomer of diastereomer thereof, wherein the above Provisos 1, 2, 6 and 8 apply.

25 Another embodiment of the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent; and ii) a compound of Formulas I, Ia, Ib, Ic, Id, Ie, If, Ig, Ih Ii, Ij, Ik, or II or a pharmaceutically acceptable salt, enantiomer of diastereomer thereof, wherein Provisos 6 and 8 apply.

30 In one embodiment, Proviso 2 applies when the subject is being treated to lower intraocular pressure.

In one embodiment, Proviso 2 applies when the subject is being treated for cardiovascular disorders.

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In one embodiment, Proviso 2 applies when the subject is being treated for dyslipidemia or hypertension.

5 In one embodiment, Proviso 8 applies when the subject is being treated for atherosclerosis, dyslipidemia, or cardiovascular disorders.

In one embodiment, Proviso 8 applies when the subject is being treated for diabetes, atherosclerosis, dyslipidemia, hypertension, obesity or cardiovascular disorders.

10 In another embodiment, Provisos 2 and 8 apply to methods of treatment utilizing any one of the compounds of Formula I or Formulas Ia-II.

DEFINITIONS

15 The term "alkyl" means a straight or branched hydrocarbon radical having 1-10 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl and the like.

20 The term "carbocyclic aromatic group" shall have the same meaning as the term "aryl" is used in U.S. Patent No. 7,186,844, which is incorporated by reference herein in its entirety. For further clarity, the term "carbocyclic aromatic group," as used in U.S. Patent No. 7,186,844, means is an all carbon, monocyclic or polycyclic ring system which obeys Huckel's $4n + 2$ rule (M. B. Smith and J. March, "March's Advanced Organic Chemistry" 5th Edition, p 57, Wiley-Interscience, 2001) and includes, for example, benzene and naphthalene.

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

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

35 The term "heteroaryl" means a 5- and 6-membered heteroaromatic radical which may optionally be fused to a saturated or unsaturated ring containing 0-4 heteroatoms selected from N, O, and S and includes, for example, a heteroaromatic

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radical which is 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3- pyrrolyl, 2-,3-, or 4-pyridyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 3- or 4-pyridazinyl, 1H-indol-6-yl, 1H-indol-5-yl, 1H-benzimidazol-6-yl, 1H-benzimidazol-5-yl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 2-, 3-, 5-, 6-, 7- or 8-quinoxaliny, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinoliny, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinoliny, 2-, 4-, or 5-thiazolyl, 2-, 3-, 4-, or 5-pyrazolyl, 2-, 3-, 4-, or 5-imidazolyl. A heteroaryl is optionally substituted. Exemplary substituents include alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido, or by oxo to form an N-oxide.

10 The term "heterocyclyl" means a 4-, 5-, 6- and 7-membered saturated or partially unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O, and S. Exemplary heterocyclyls include pyrrolidine, pyrrolidin-2-one, 1-methylpyrrolidin-2-one, piperidine, piperidin-2-one, 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-thiaoxazole 1,1-dioxide, tetrahydro-2H-1,2-thiazine 1,1-dioxide, hexahydro-1,2,6-thiadiazine 1,1-dioxide, tetrahydro-1,2,5-thiadiazole 1,1-dioxide isothiazolidine 1,1-dioxide, 6-oxo-1,6-dihydropyridazin-3-yl, 6-oxo-1,6-dihydropyridazin-4-yl, 5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl and 5-oxo-4,5-dihydro-1H-imidazol-2-yl. A heterocyclyl can be optionally substituted with 1-4 substituents. Exemplary substituents include alkyl, haloalkyl, halogen and oxo.

The term "spirocycloalkyl" means a cycloalkyl group which shares one ring carbon with another alkyl or cycloalkyl group.

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

When a disclosed compound or its pharmaceutically acceptable salt is named or depicted by structure, it is to be understood that solvates or hydrates of the compound or its pharmaceutically acceptable salts are also included. "Solvates"

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refer to crystalline forms wherein solvent molecules are incorporated into the crystal lattice during crystallization. Solvate may include water or nonaqueous solvents such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and EtOAc. Solvates, wherein water is the solvent molecule incorporated into the crystal lattice, are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water.

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

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

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

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

The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers

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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.

5 When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. Percent
10 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 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
15 compound free from the corresponding optical isomer, a racemic mixture of the compound and mixtures enriched in one enantiomer relative to its corresponding optical isomer.

 When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has at least two chiral centers, it is to be
20 understood that the name or structure encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diastereomeric pairs in which one diastereomeric pair is enriched relative
25 to the other diastereomeric pair(s).

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

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

 Pharmaceutically acceptable acidic/anionic salts include, the acetate,
35 benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate,

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camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, malonate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, hydrogensulfate, tannate, tartrate, teoclate, tosylate, and triethiodide salts.

10 The following abbreviations have the indicated meanings:

Abbreviation	Meaning
A%	Area percentage
Boc	<i>tert</i> -butoxy carbonyl or <i>t</i> -butoxy carbonyl
(Boc) ₂ O	di- <i>tert</i> -butyl dicarbonate
Cbz	Benzyloxycarbonyl
CbzCl	Benzyl chloroformate
c-Pr	cyclopropyl
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCU	N,N'-dicyclohexylurea
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
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- <i>t</i> -butylsilyl
dr	diastereomer ratio

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EDC.HCl, EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Equiv	equivalents
EtOAc	ethyl acetate
Fmoc	1-[[[(9H-fluoren-9-ylmethoxy)carbonyl]oxy]-
Fmoc-OSu	1-[[[(9H-fluoren-9-ylmethoxy)carbonyl]oxy]-2,5-pyrrolidinedione
h, hr	hour(s)
HOBt	1-hydroxybenzotriazole
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
KHMDS	potassium hexamethyldisilazane
LAH or LiAlH ₄	lithium aluminum hydride
LC-MS	liquid chromatography-mass spectroscopy
LHMDS	lithium hexamethyldisilazane
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
MsCl	methanesulfonyl chloride
Min	minute
MS	mass spectrum
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaN ₃	sodium azide
NaOH	sodium hydroxide
Na ₂ SO ₄	sodium sulfate
NMM	N-methylmorpholine
NMP	N-methylpyrrolidinone

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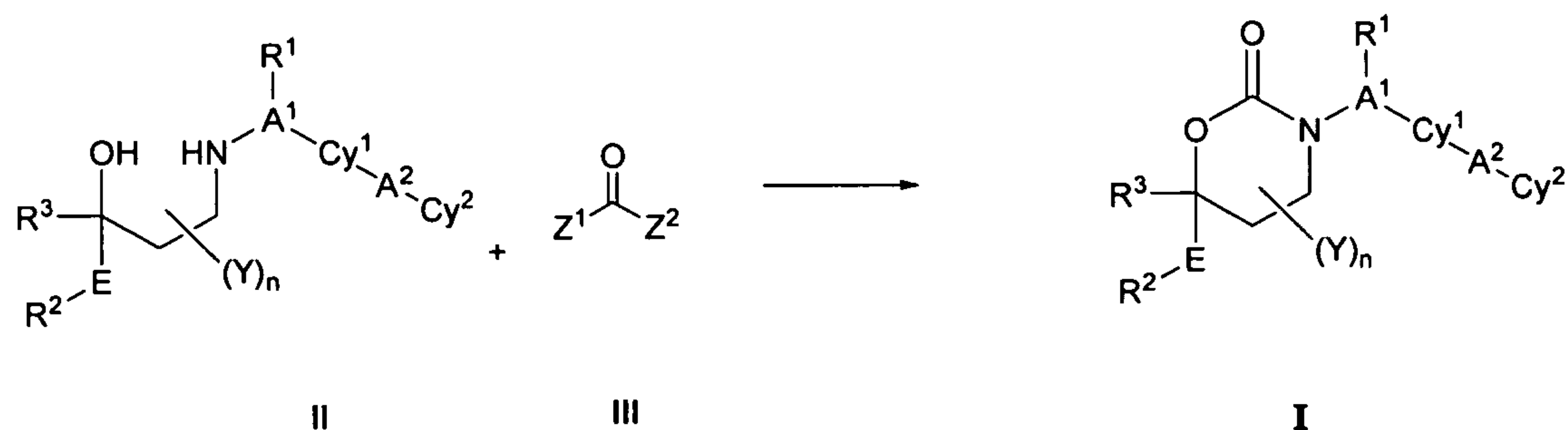
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
PE	petroleum ether
Quant	quantitative yield
rt	room temperature
Satd	saturated
SOCl ₂	thionyl chloride
SFC	supercritical fluid chromatography
SPA	scintillation proximity assay
SPE	solid phase extraction
TBAF	tetrabutylammonium fluoride
TBS	t-butyldimethylsilyl
TBDPS	t-butyldiphenylsilyl
TBSCI	t-butyldimethylsilyl chloride
TBDPSCI	t-butyldiphenylsilyl chloride
TEA	triethylamine or Et ₃ N
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Teoc	1-[2-(trimethylsilyl)ethoxycarbonyloxy]-
Teoc-OSu	1-[2-(trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione
T _{ext}	External temperature
T _{int}	Internal temperature
TFA	trifluoroacetic acid
Tlc, TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCI	chlorotrimethylsilane or trimethylsilyl chloride
t _R	retention time
TsOH	p-toluenesulfonic acid

GENERAL DESCRIPTION OF SYNTHETIC METHODS

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Compounds of Formula I can be prepared by several processes. In the discussion below, A^1 , A^2 , Cy^1 , Cy^2 , E , R^1 , R^2 , R^3 , Y and n have the meanings indicated above unless otherwise noted. In cases where the synthetic intermediates and final products of Formulas I described below contain potentially reactive functional groups, for example amino, hydroxyl, thiol and carboxylic acid groups, that may interfere with the desired reaction, it may be advantageous to employ protected forms of the intermediate. Methods for the selection, introduction and subsequent removal of protecting groups are well known to those skilled in the art. (T.W. Greene and P. G. M. Wuts "Protective Groups in Organic Synthesis" John Wiley & Sons, Inc., New York 1999). Such protecting group manipulations are assumed in the discussion below and not described explicitly. Generally, reagents in the reaction schemes are used in equimolar amounts; however, in certain cases it may be desirable to use an excess of one reagent to drive a reaction to completion. This is especially the case when the excess reagent can be readily removed by evaporation or extraction. Bases employed to neutralize HCl in reaction mixtures are generally used in slight to substantial excess (1.05 – 5 equivalents).

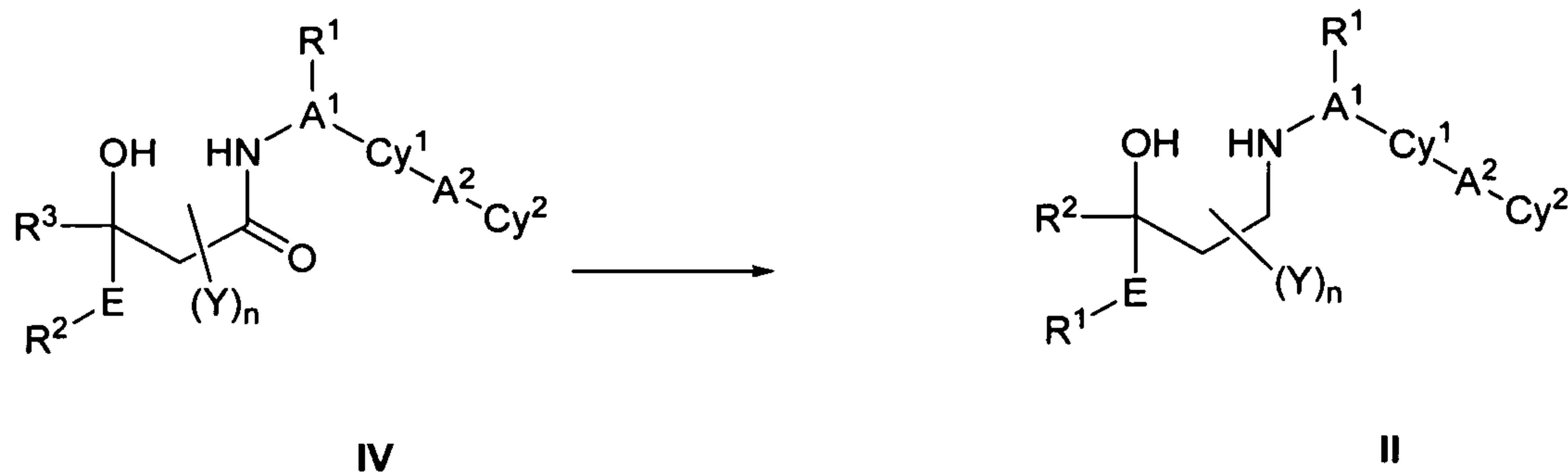
In a first process a compound of Formula I, wherein can be prepared by reaction of an aminoalcohol intermediate of Formula II with a reagent of Formula III, wherein Z^1 and Z^2 are leaving groups such as chloride, 1-imidazolyl or aryloxy in an inert solvent such as THF, CH_2Cl_2 , toluene or MeCN, usually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



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 $OC(=O)Cl$, III is triphosgene and as little as one third of molar equivalent can be used.

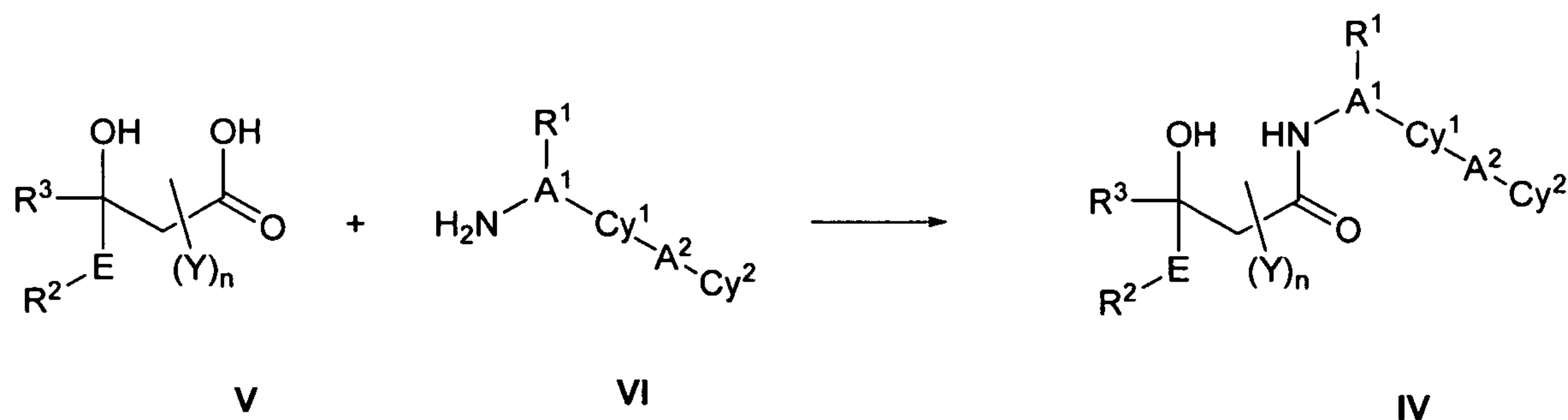
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Aminoalcohol intermediates of Formula II can be prepared by reduction of amides of Formula IV using a hydride reagent such as BH_3 .THF solution, BH_3 .Me₂S or LiAlH_4 in an inert solvent ethereal such as THF or DME at 20 °C to 100 °C for between 1 h and 48 h:



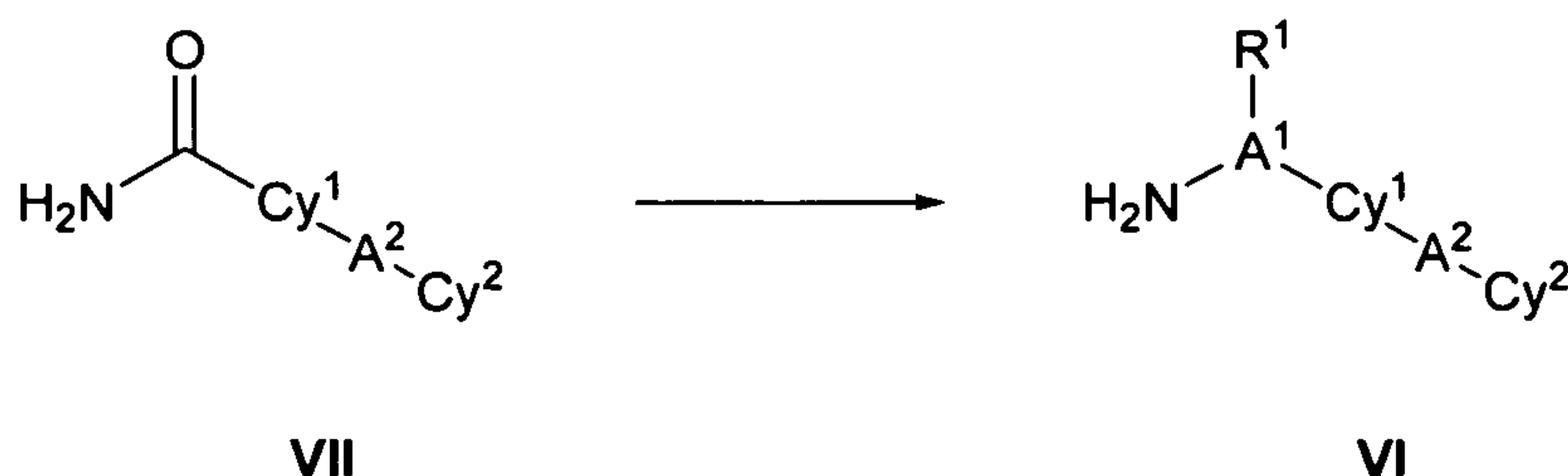
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Intermediates of Formula IV can be prepared by coupling of a β-hydroxyacid of Formula V with an amine of Formula VI using standard peptide coupling reagents such as EDC in the presence of HOBt and N,N-diisopropylethylamine in an inert solvent such as CH₂Cl₂ at 0 – 30 °C for between 1 h and 24 h:



10

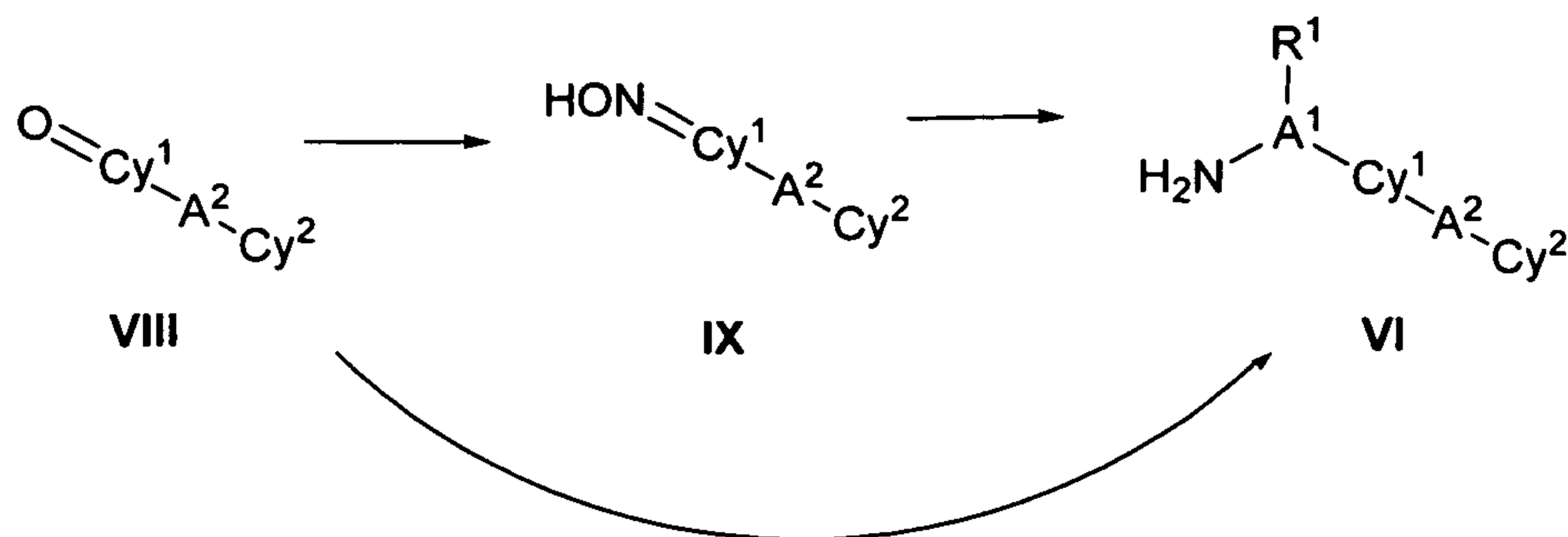
Amine intermediates of Formula VI, wherein A¹ = CH₂ and R¹ is absent, can be prepared by reduction of amides of Formula VII using a hydride reagent such as BH_3 .THF solution, BH_3 .Me₂S or LiAlH_4 in an inert solvent ethereal such as THF or DME at 20 °C to 100 °C for between 1 h and 48 h:



15

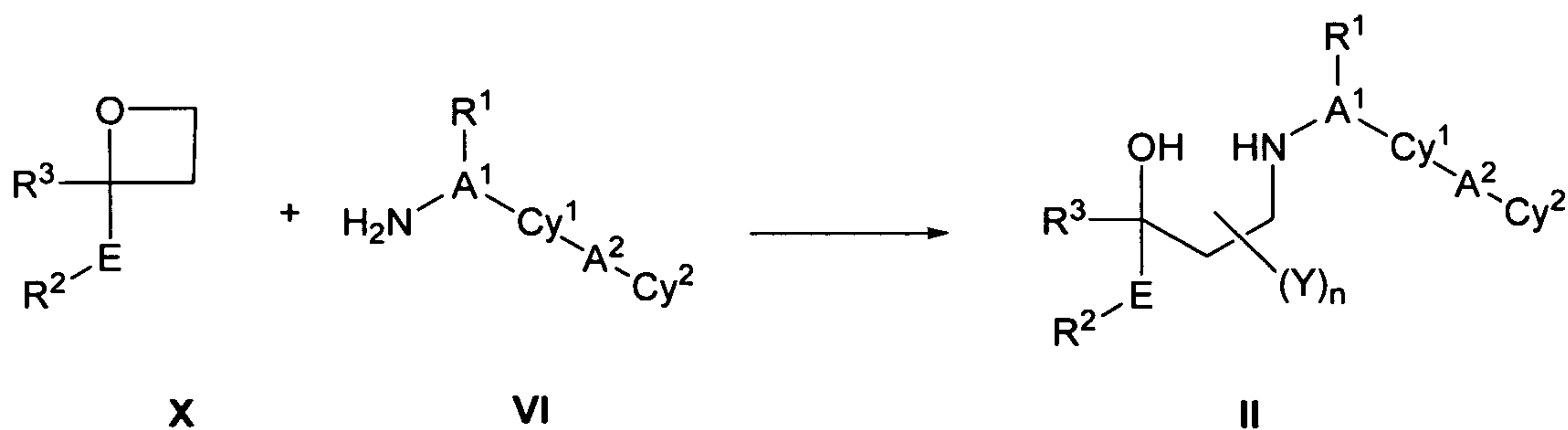
Amine intermediates of Formula VI, wherein A¹ is a bond, R¹ is absent and Cy¹ is not an aromatic or heteroaromatic ring, can be prepared from ketones of formula VIII via oximes of Formula IX or by reductive amination of a ketone of Formula VIII with ammonia:

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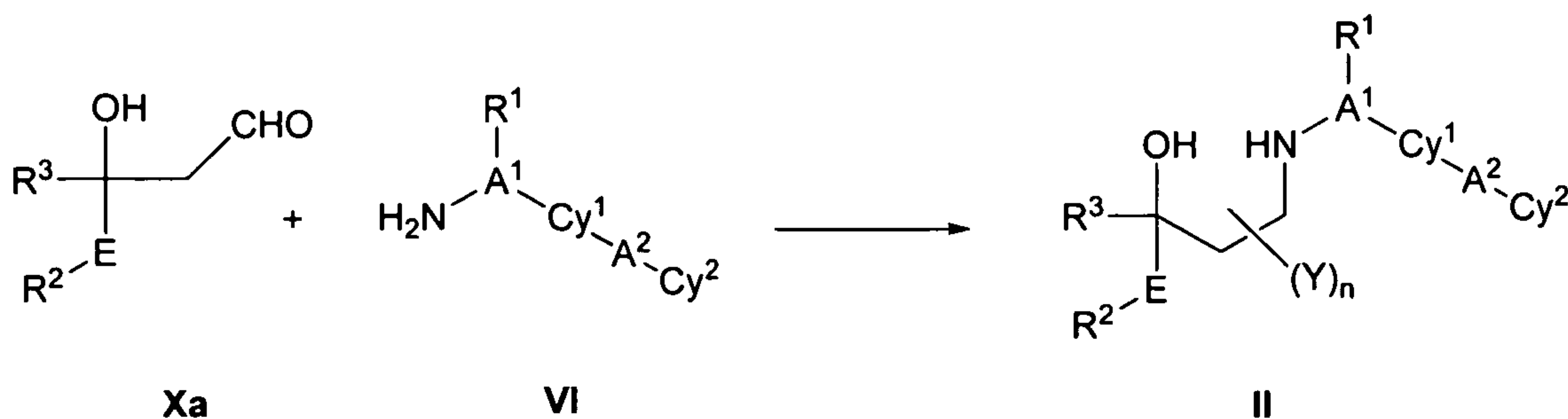


Methods for the conversion of ketones to oximes are described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" pp 1194-1195, 5th Edition, Wiley, New York, NY, 2001. Methods for the reduction of oximes to primary amines are described in Smith, M. B. and March, J. "March's Advanced Organic 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.

Intermediates of Formula II, wherein $n = 0$, can be prepared by reaction of oxetanes of Formula X with amines of Formula VI as described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" p 505, 5th Edition, Wiley, New York, NY, 2001:

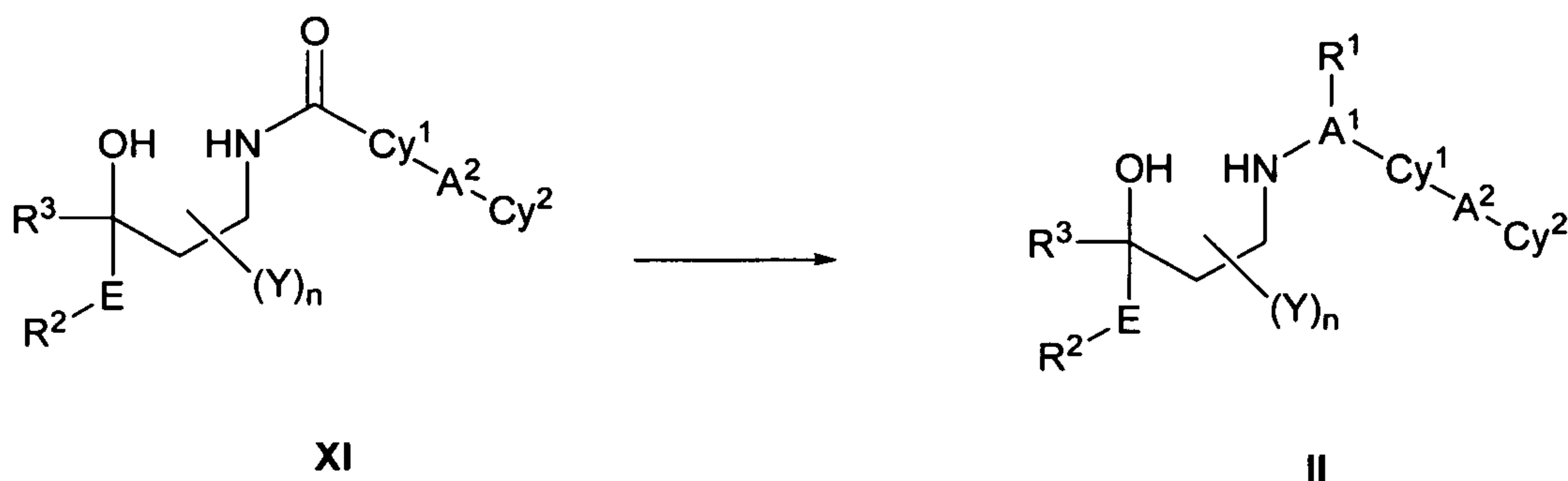


Intermediates of Formula II can also be prepared by reductive amination of β -hydroxyaldehydes of Formula Xa with amines of Formula VI. Methods for the reductive amination of aldehydes are described in Baxter, E. W. and Reitz, A. B. "Organic Reactions" Volume 59, Ed. Overman, L. E., Wiley Interscience, 2002.

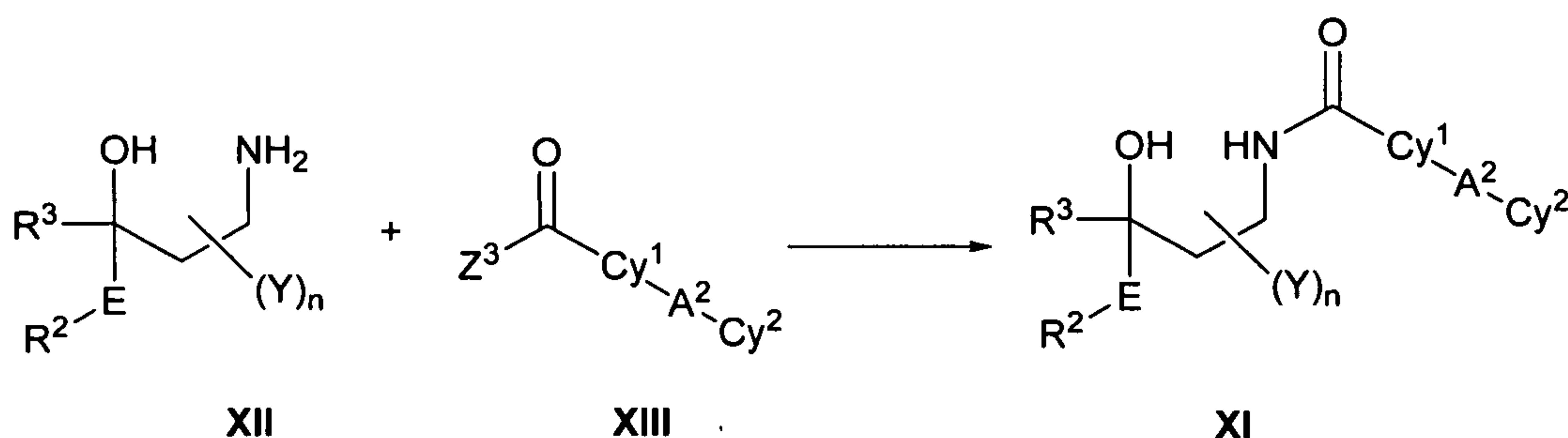


Aldehydes of Formula Xa can be prepared from homoallylic alcohols of Formula XXI by treatment with OsO₄ and NaIO₄.

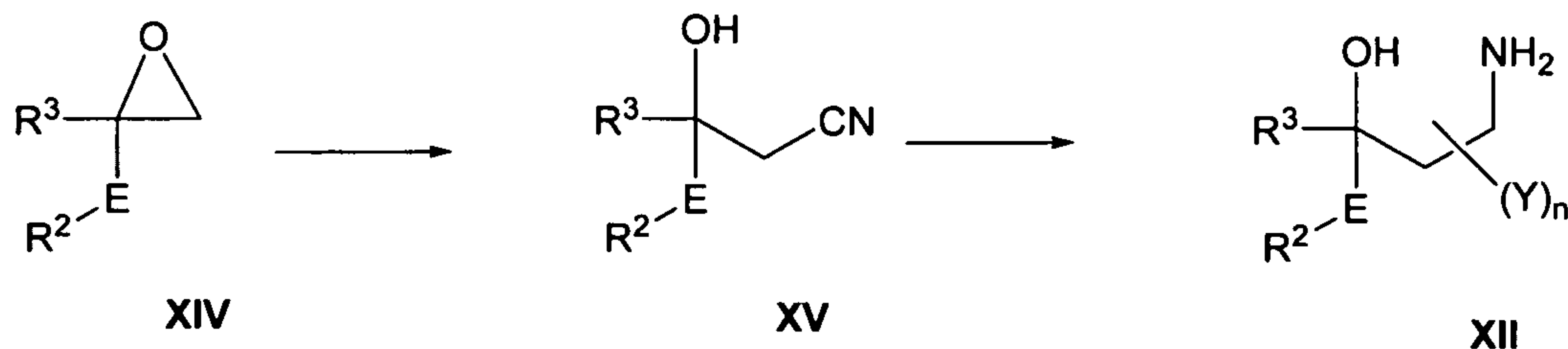
Intermediates of Formula II, wherein A¹ = CH₂ and R¹ is absent, can be prepared by reduction of amide intermediates of formula XI using a hydride reagent
 5 such as BH₃.THF solution, BH₃.Me₂S or LiAlH₄ in an inert solvent ethereal such as THF or DME at 20 °C to 100 °C for between 1 h and 48 h:



Amide intermediates of Formula XI can be prepared by reaction of an amino-alcohol intermediate of Formula XII with activated carboxylic acid of Formula XIII
 10 wherein Z³ = chloride or an activated ester, such as an N-hydroxysuccinimide ester:

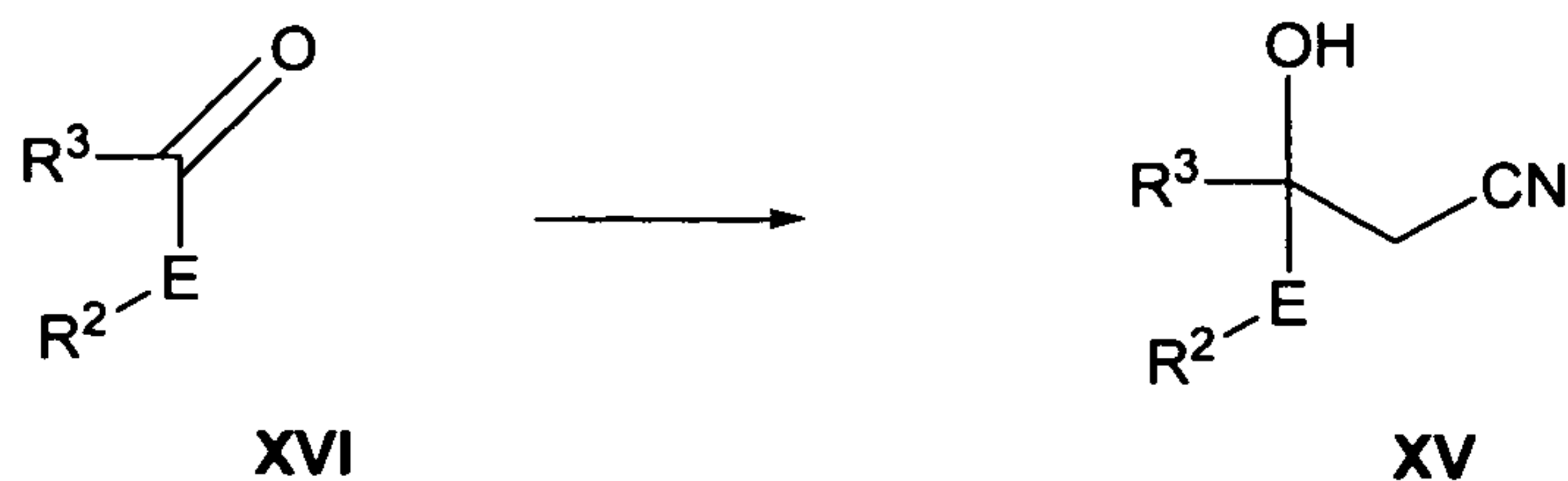


Amino-alcohol intermediates of Formula XII, wherein n = 0, can be prepared by reaction of an epoxide of Formula XIV with cyanide ion followed by reduction of the resulting hydroxynitrile of Formula XV with hydrogen gas in the presence of a
 15 catalyst or with a hydride source such as LiAlH₄:

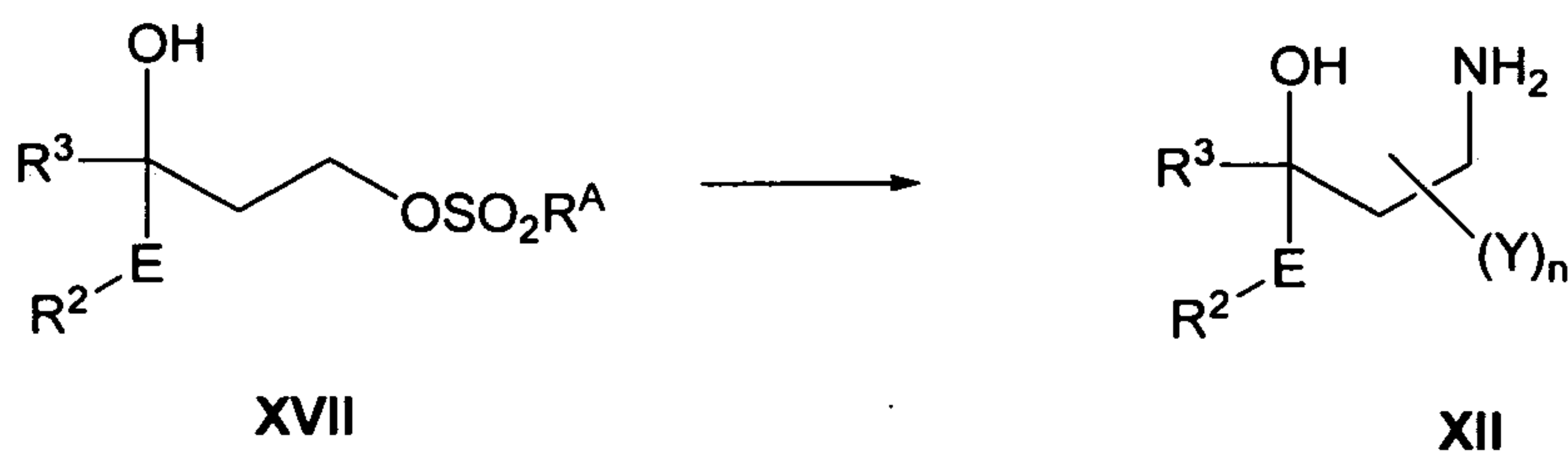


Epoxide compounds of formula XIV can, in turn, be prepared in a number of ways including, as described in Aube, J. "Epoxidation and Related Processes" Chapter 3.2
 20 in Volume 1 of "Comprehensive Organic Synthesis" Edited by B. M. Trost, I. Fleming and Stuart L. Schreiber, Pergamon Press, New York,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

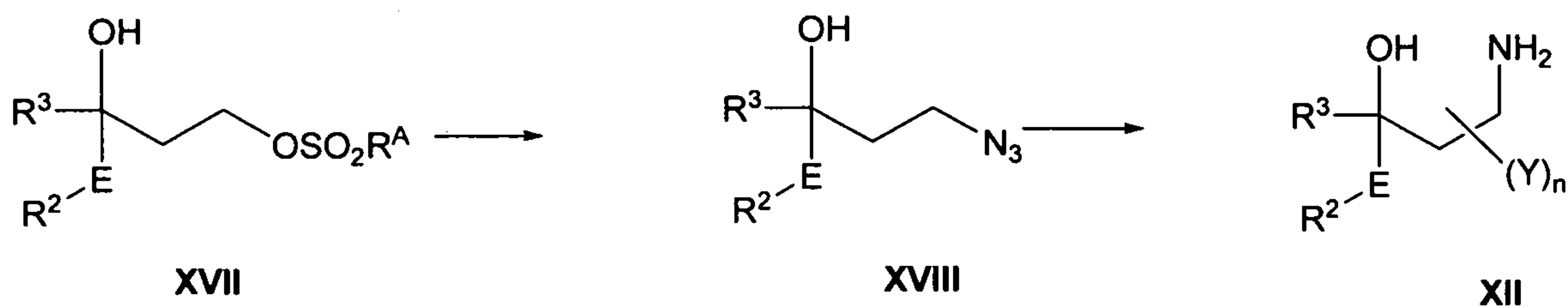
Hydroxynitrile intermediates of Formula XV can be prepared by treatment of ketones of Formula XVI with acetonitrile anion, formed by treatment of acetonitrile with n-BuLi or LDA, in an inert, anhydrous solvent such as THF at low temperature:



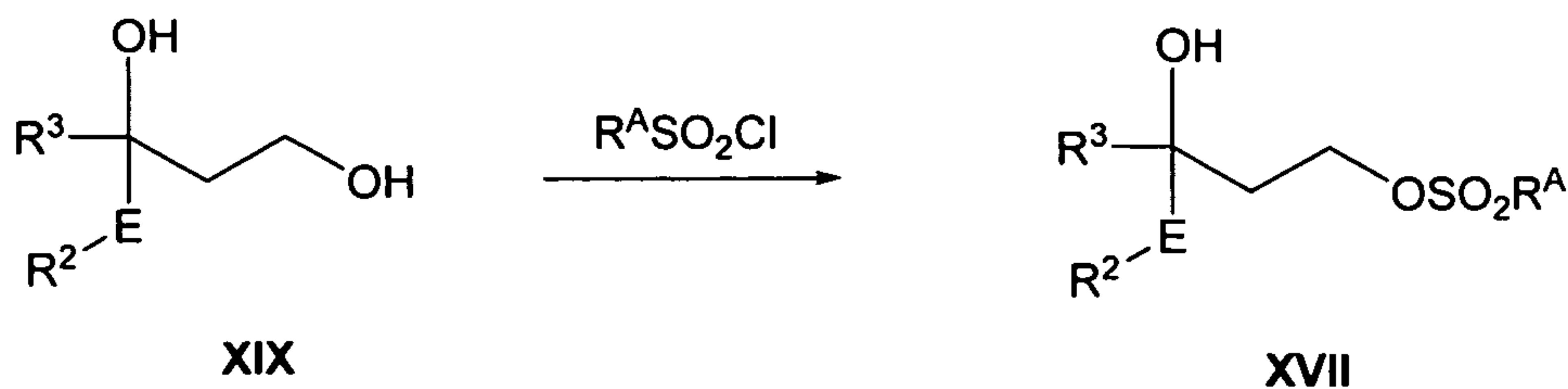
- 5 Amino-alcohol intermediates of Formula XII, wherein n is 0, can be prepared by treatment of sulfonate intermediates of Formula XVII, wherein R^A is for example methyl, trifluoromethyl or p-methylphenyl, with ammonia:



- 10 Amino-alcohol intermediates of Formula XII can be prepared by treatment of sulfonate intermediates of Formula XVII with sodium azide to give an azide intermediate of Formula XVIII, followed by catalytic hydrogenation or by Staudinger reduction with PPh₃ in wet THF:

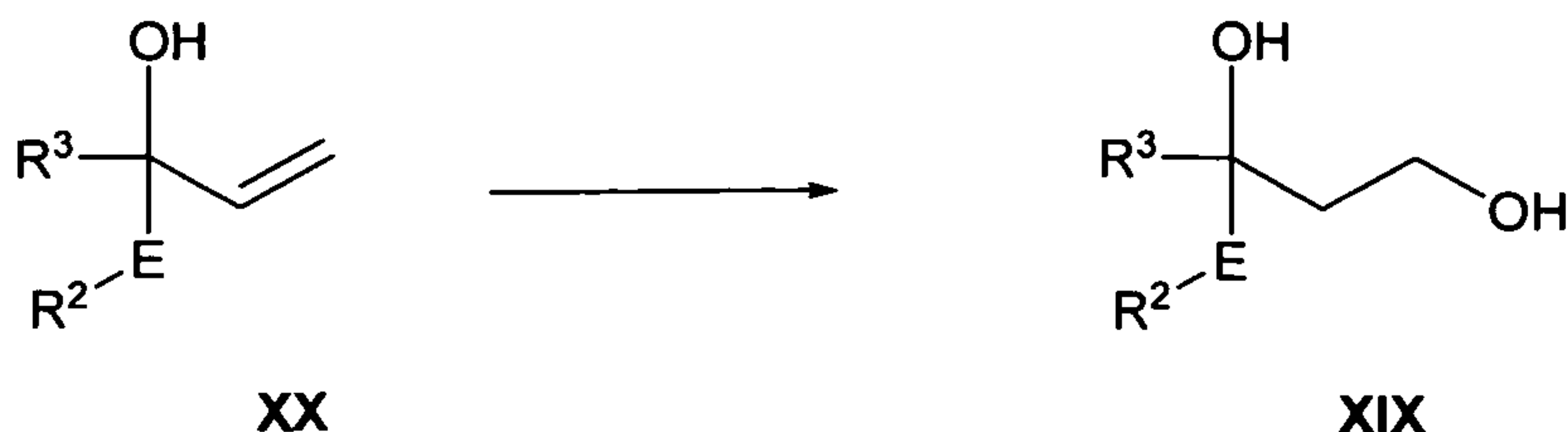


- 15 Sulfonate intermediates of Formula XVII can be prepared from diol intermediates of Formula XIX with a sulfonyl chloride R^ASO₂Cl:

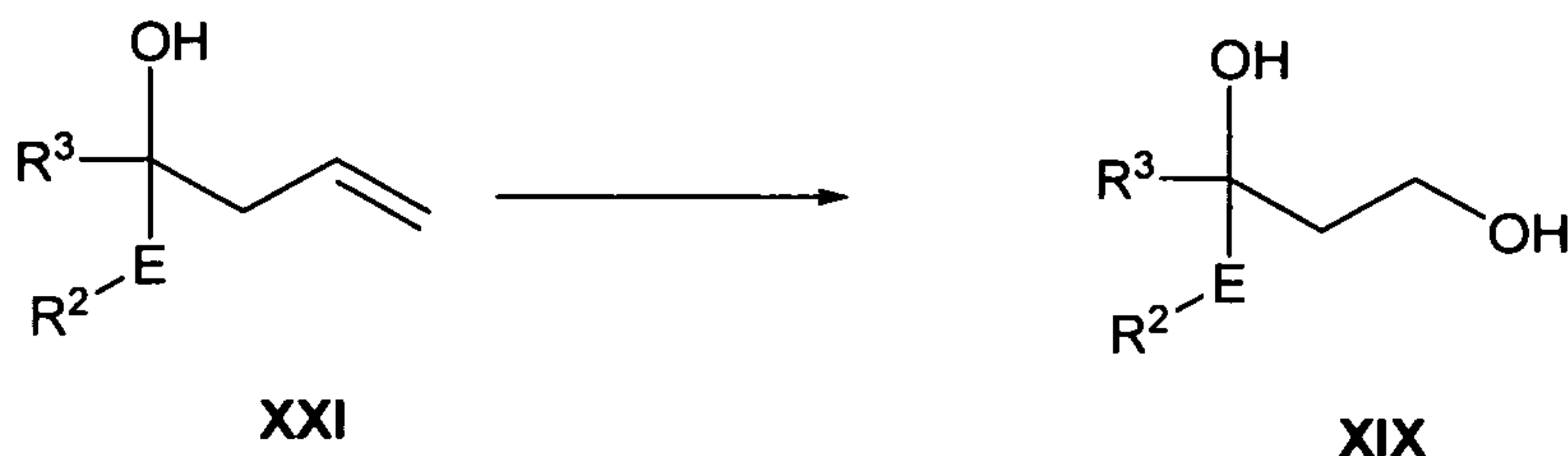


Diol intermediates of Formula XIX can be prepared by hydroboration of allyl alcohols of Formula XX:

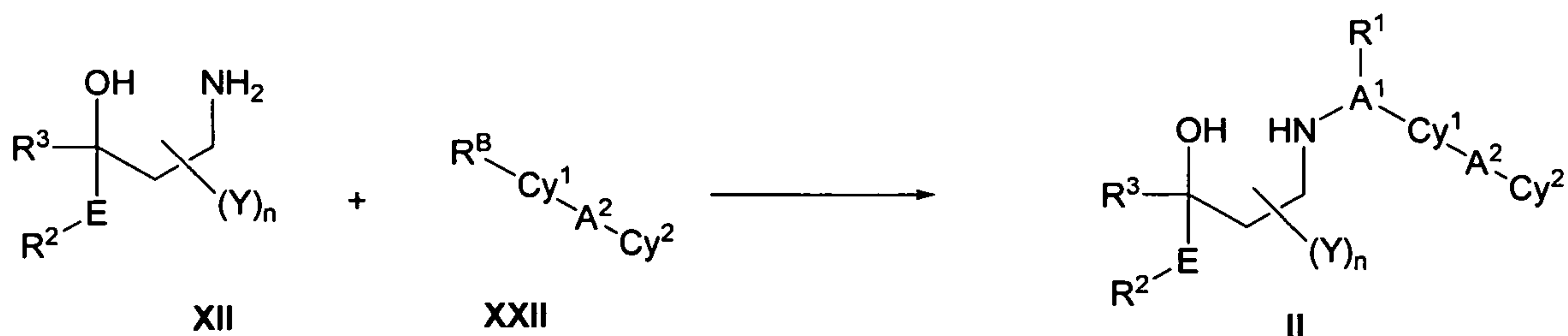
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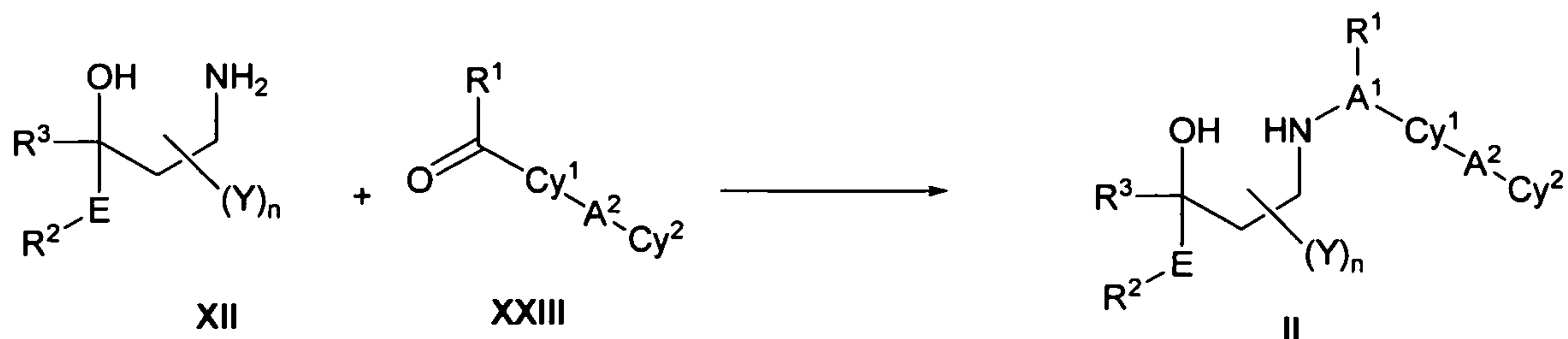
Diol intermediates of Formula XIX can be prepared by ozonolysis and reduction of homoallyl alcohols of Formula XXI:



- 5 Aminoalcohol intermediates of Formula II, wherein A^1 is a bond, R^1 is absent, and Cy^1 is a heteroaryl group or an aryl group bearing at least one strongly electron withdrawing group such as CF_3 , can be prepared by reaction of an aminoalcohol intermediate of Formula XII with a compound of Formula XXII, wherein Cy^1 is a heteroaryl group or an aryl group bearing at least one strongly electron withdrawing group such as CF_3 and R^B is a leaving group such a fluoro, chloro, bromo or iodo:
- 10



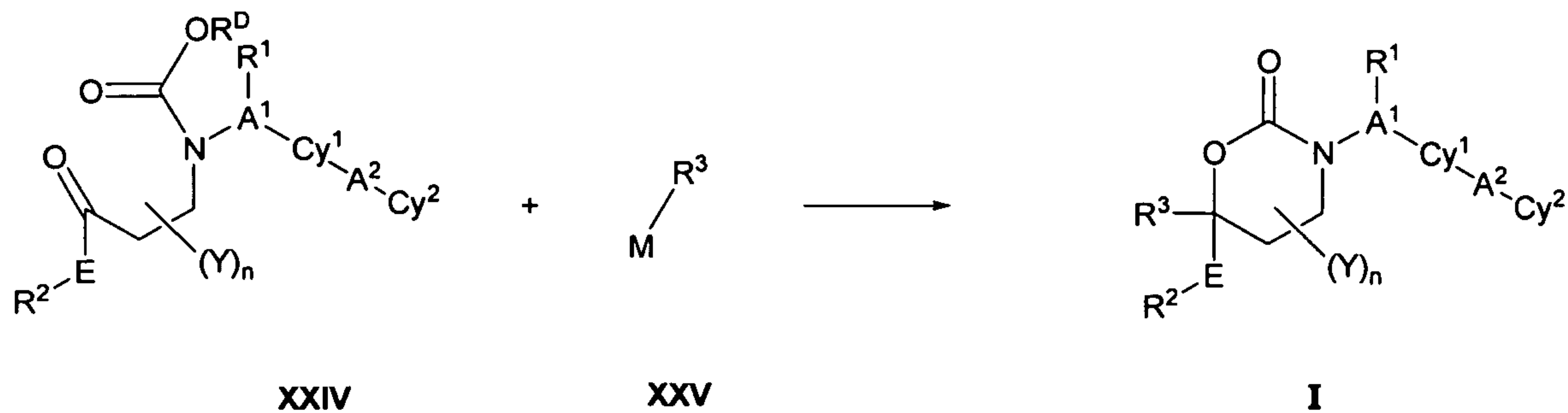
- Aminoalcohol intermediates of Formula II, wherein A^1 is (C_1) alkylene can be prepared by reaction of an aminoalcohol of Formula XII with an aldehyde or methyl ketone of Formula XXIII in the presence of a reducing agent such as $NaCNBH_3$ or $Na(OAc)_3BH$:
- 15



Methods for the reductive amination of aldehydes and ketones are described in Baxter, E. W. and Reitz, A. B. "Organic Reactions" Volume 59, Ed. Overman, L. E., Wiley Interscience, 2002.

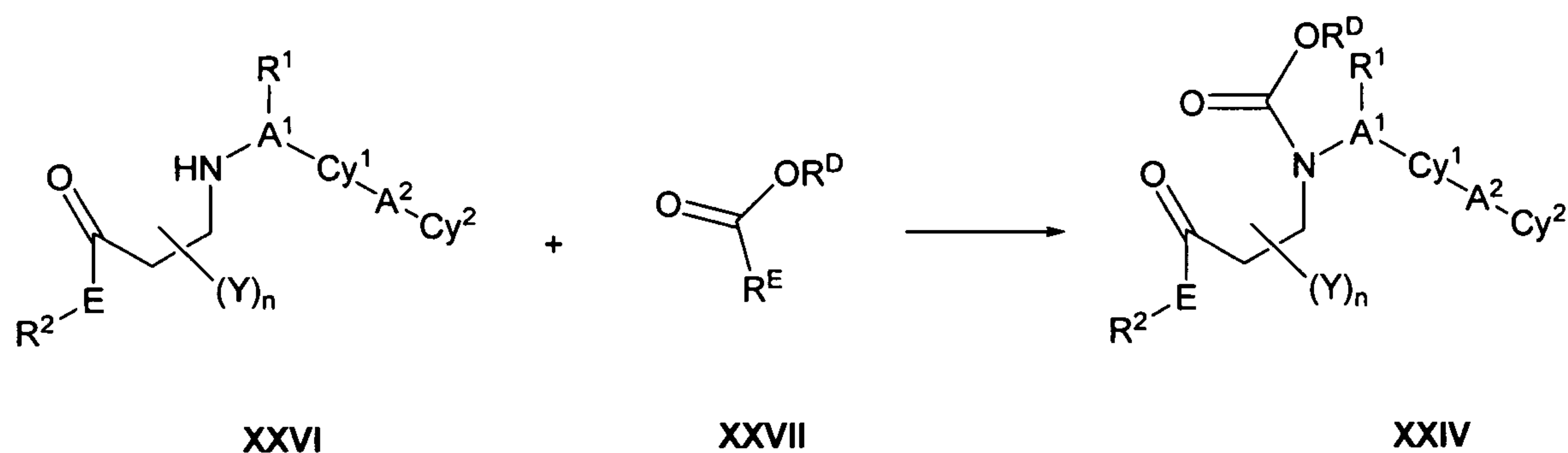
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In a second process a compound of Formula I can be prepared by reaction of a ketocarbamate of Formula XXIV, wherein R^D is alkyl or arylalkyl group such as methyl, t-butyl or benzyl, with an organometallic reagent of Formula XXV wherein M includes, but is not limited to, MgCl, MgBr, MgI or Li:

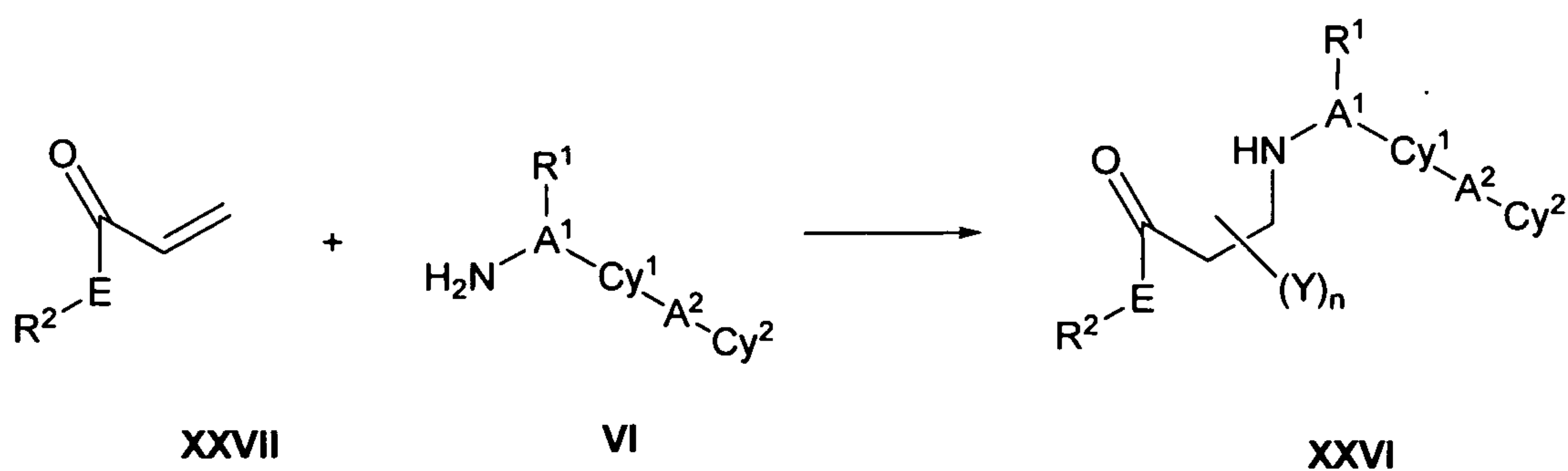


In specific examples, organometallic reagent XXV is allylmagnesium bromide, allylzinc(II) bromide, (2-methylallyl)magnesium chloride or (2-methoxy-2-oxoethyl)zinc(II) bromide. In certain cases when M is MgCl, MgBr or MgI, it is advantageous to add $CeCl_3$ to the reaction mixture.

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

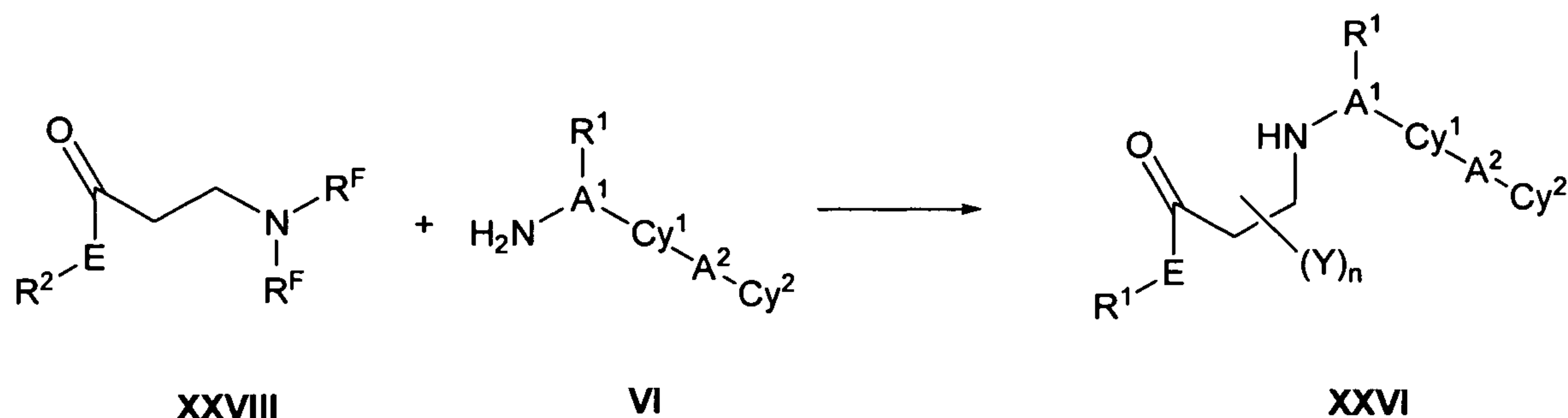


Aminoketones of Formula XXVI, wherein $n = 0$, can be prepared by reaction of α,β -unsaturated ketones of Formula XXVII with amines of Formula VI:



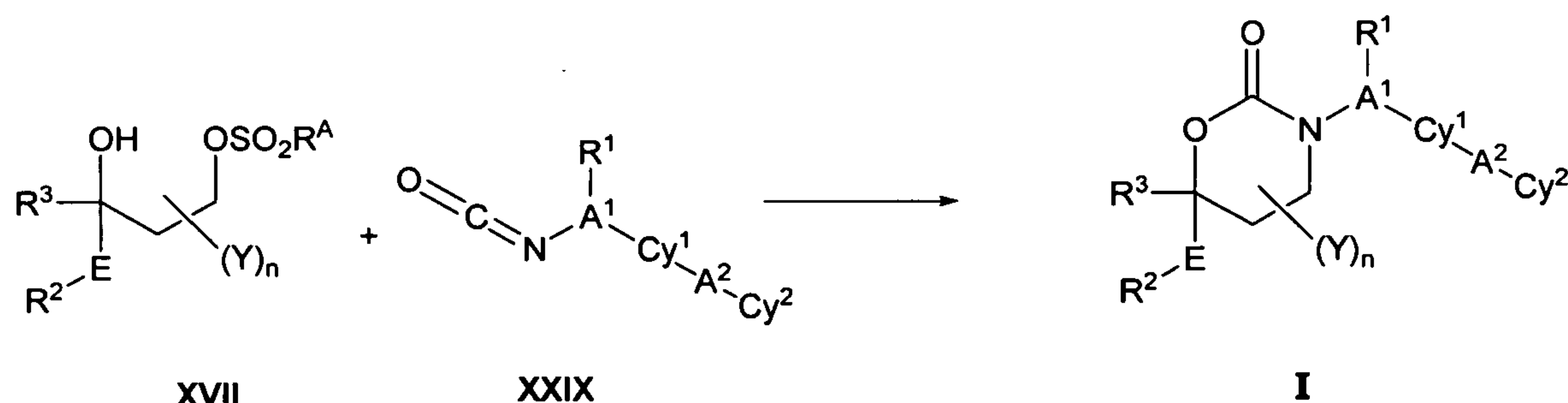
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Aminoketones of Formula XXVI, wherein $n = 0$, can be prepared by reaction of β -dialkylaminoketones of Formula XXVIII, wherein R^F is lower alkyl especially methyl, with amines of Formula VI:



- 5 β -Dialkylaminoketones of Formula XXVIII are in turn derived from α , β -unsaturated ketones of Formula XXVII with dialkylamines of Formula $R^F N H R^F$.

In a third process a compound of Formula I, can be prepared by reaction of a compound of Formula XVII with an isocyanate of Formula XXIX in the presence of a base:



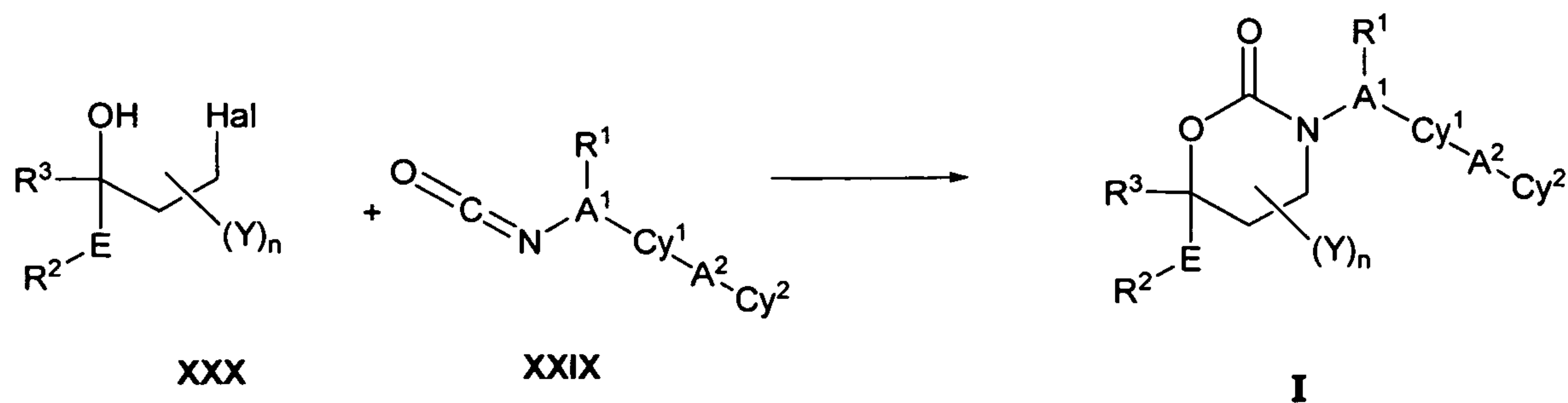
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- Isocyanates of Formula XXIX can be prepared from amines of Formula VI by treatment with phosgene, diphosgene or triphosgene. This third process is described in greater detail in U.S. Provisional Application Serial No. 61/_____, filed July 25, 2008 entitled SYNTHESIS OF INHIBITORS OF 11 β -HYDROXYSTEROID DEHYDROGENASE TYPE 1 (Attorney Docket No. 4370.1001-000), the entire teachings of which are incorporated herein by reference.

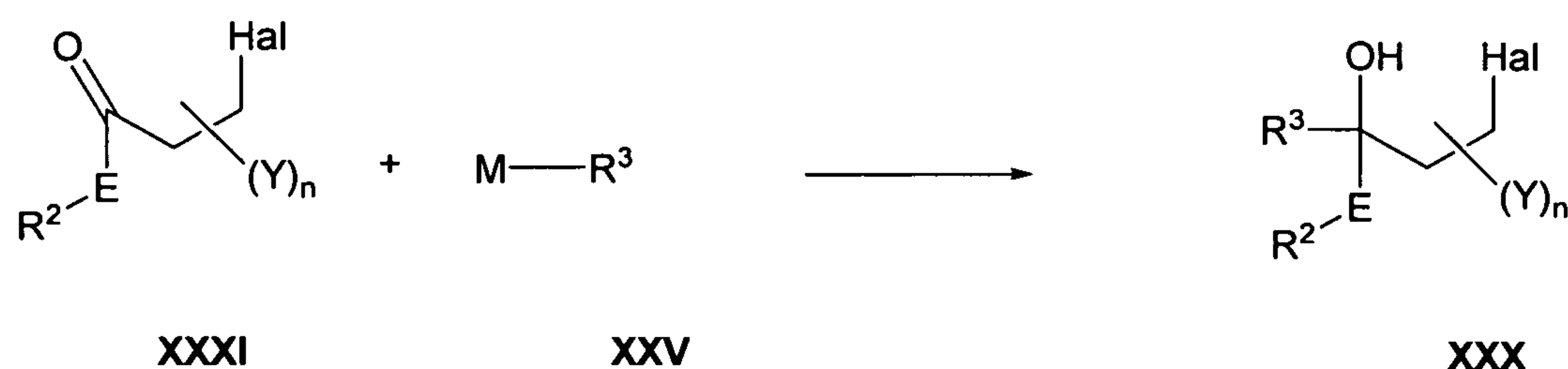
- In a fourth process a compound of Formula I can be prepared by reaction of a halo compound of Formula, wherein Hal is chlorine or bromine, with an isocyanate of Formula XXIX in the presence of a base:

20

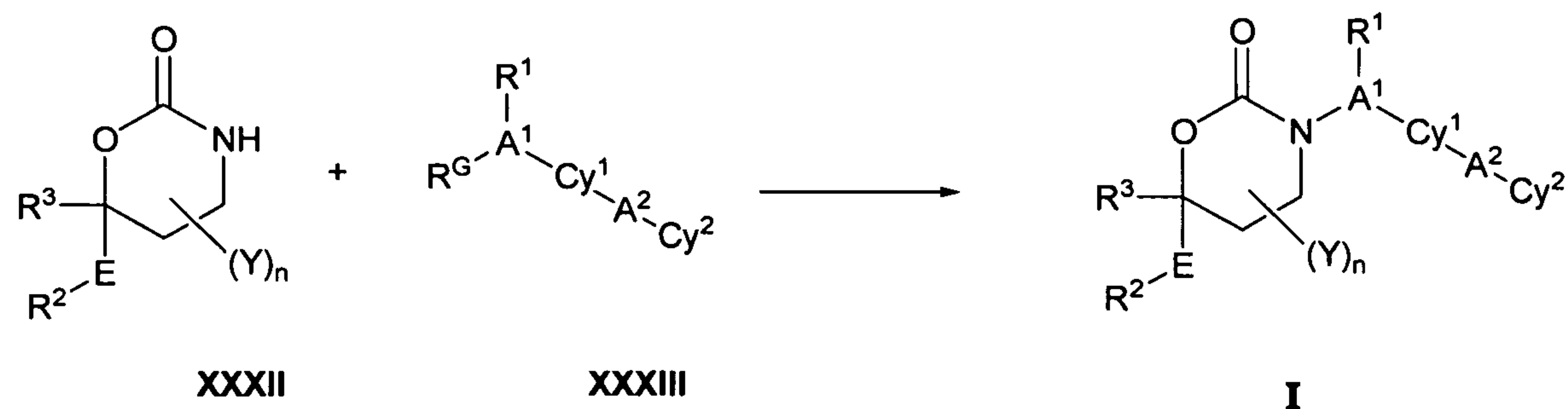
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Halo compounds of Formula XXX can be prepared by reaction of β -haloketones of Formula XXXI with organometallic reagents of Formula XXV wherein M is a metal containing radical including MgCl, MgBr, MgI or Li. The reaction is optionally carried out in the presence of anhydrous cerium trichloride:

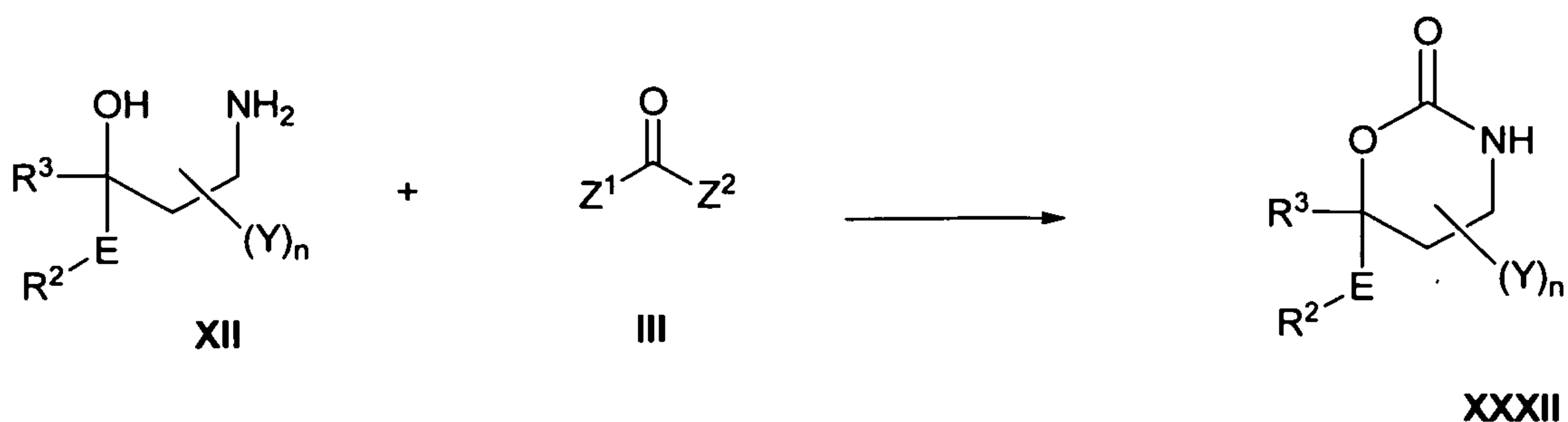


In a fifth process a compound of Formula I, wherein A¹ is CH₂ or CH₂CH₂ and R¹ is absent, can be prepared by reaction of a compound of Formula XXXII, with a compound of Formula XXXIII, wherein A¹ is CH₂ or CH₂CH₂ and R^G is a leaving group such as Br, I, OSO₂Me, OSO₂CF₃ or OSO₂Ph, in the presence of a base such as NaH or K₂CO₃:

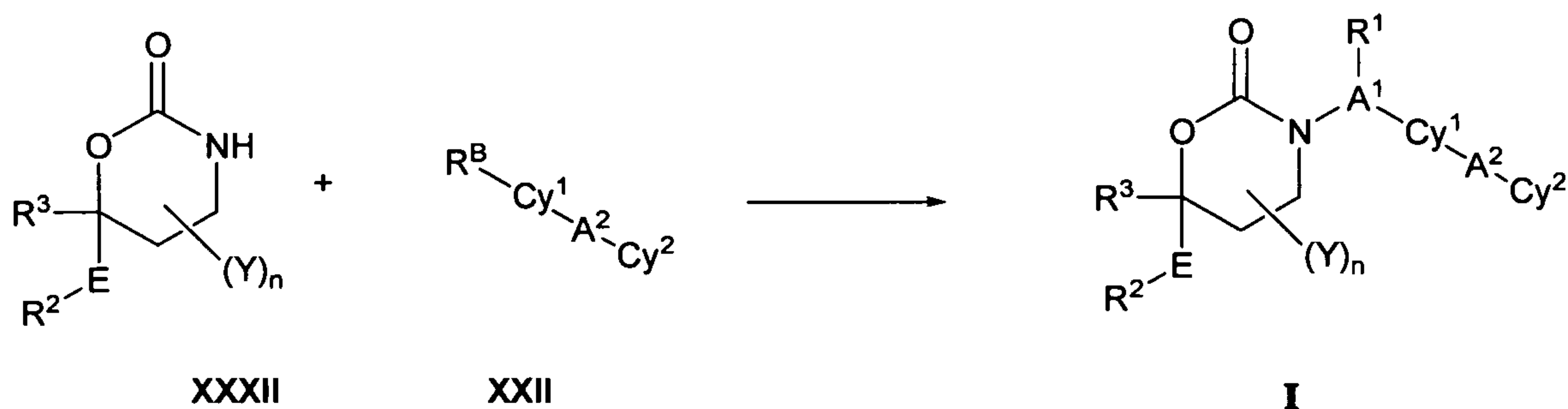


Compounds of Formula XXXII can be prepared by treatment of compounds of Formula XII with various reagents of Formula III, wherein Z¹ and Z² are leaving groups such as chloride, 1-imidazolyl or aryloxy in an inert solvent such as THF, CH₂Cl₂, toluene or MeCN, usually in the presence of an organic or inorganic base such as triethylamine or NaHCO₃ respectively, at -10 °C to 120 °C:

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In a sixth process a compound of Formula I, wherein A is a bond can be prepared by reaction of a compound of Formula XXXII, with a compound of Formula XXII, wherein R^B is a leaving group such as chloro, bromo, iodo or OSO₂CF₃, in the presence of a base such as K₂CO₃ and a copper or palladium catalyst in an inert solvent such as dioxane, DMF or NMP at elevated temperature:



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

(1) a compound of Formula I wherein Cy¹ is substituted with bromine or iodine, A² is a bond and Cy² 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 A² is a bond and Cy² is optionally substituted aryl or heteroaryl.

(2) a compound of Formula I wherein R¹ or R³ is ω-hydroxy(C₂-C₆)alkyl can be oxidized to a compound of Formula I wherein R¹ or R³ is ω-carboxy(C₁-C₅)alkyl using Jones reagent.

(3) a compound of Formula I wherein R¹ or R³ is ω-carboxy(C₁-C₆)alkyl can be coupled with ammonia or a (C₁-C₆)alkylamine using a standard peptide coupling reagent such as EDC to afford a compound of Formula I wherein R¹ or R³ is ω-H₂NC(=O)(C₁-C₆)alkyl or ω-[(C₁-C₆)alkylNHC(=O)](C₁-C₆)alkyl.

(4) a compound of Formula I wherein R¹ or R³ is ω-hydroxy(C₁-C₆)alkyl can be converted to its methanesulfonate or trifluoromethanesulfonate, treated with

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sodium azide and reduced to give a compound of Formula I, wherein R¹ or R³ is ω-amino(C₁-C₆)alkyl.

(5) a compound of Formula I wherein R¹ or R³ is amino(C₁-C₆)alkyl can be reacted with acetic anhydride or acetyl chloride to give a compound of Formula I
5 wherein R¹ or R³ is {acetylamino}(C₁-C₆)alkyl.

(6) a compound of Formula I wherein R¹ or R³ is amino(C₁-C₆)alkyl can be reacted with methanesulfonyl chloride to give a compound of Formula I wherein R¹ or R³ is {methanesulfonylamino}(C₁-C₆)alkyl.

(7) a compound of Formula I, wherein R¹ is (C₂-C₆)alkenyl is hydroborated to
10 afford a compound of Formula I wherein R¹ is hydroxy(C₂-C₆)alkyl.

(8) a compound of Formula I, wherein R³ is (C₂-C₆)alkenyl, is hydroborated to afford a compound of Formula I wherein R³ is hydroxy(C₂-C₆)alkyl.

(9) 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
15 Formula I wherein R¹ is vicinal dihydroxy(C₂-C₆)alkyl,.

(10) 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,.

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

(12) 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.

(13) a compound of Formula I wherein R¹ or R³ is amino(C₁-C₆)alkyl can be
25 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.

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

(15) 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.

(16) a compound of Formula I wherein R¹ or R³ is amino(C₁-C₆)alkyl can be
35 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.

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(17) a compound of Formula I wherein R^1 or R^3 is hydroxy(C_1 - C_6)alkyl can be reacted with chlorosulfonyl isocyanate to give a compound of Formula I wherein R^1 or R^3 is aminosulfonyloxy(C_1 - C_6)alkyl.

5 (18) 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 - C_6)alkyl aminocarboxy(C_1 - C_6)alkyl or di(C_1 - C_6)alkyl aminocarboxy(C_1 - C_6)alkyl.

10 (19) 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 $(HO)_2P(=O)O(C_1-C_6)alkyl$.

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

(21) a compound of Formula I wherein Cy^1 is aryl or heteroaryl substituted with bromine or iodine, A^2 is a bond and Cy^2 is hydrogen can be reacted with bis(pinacolato)diboron in the presence of a palladium catalyst to give a boronate ester which can be further reacted with (a) an aryl, heteroaryl or heterocyclyl halide again in the presence of a palladium catalyst to give a compound of Formula I wherein A^2 is a bond and Cy^2 is aryl, heteroaryl or heterocyclyl.

(22) a compound of Formula I, wherein R^3 is allyl or homoallyl can be reacted with oxygen in the presence of $PdCl_2$ and $CuCl$ to afford a compound of Formula I, wherein R^3 is 2-oxopropyl or 3-oxobutyl respectively.

(23) a compound of Formula I, wherein R^3 is 2-oxopropyl or 3-oxobutyl can be reacted with $MeMgX$, wherein X is Cl , Br or I , to give a compound of Formula I, wherein R^3 is 2-hydroxy-2-methylpropyl or 3-hydroxy-3-methylpropyl respectively.

30 (24) a compound of Formula I, wherein R^3 is $-CH_2CO_2Me$ can be treated with $MeMgX$, wherein X is Cl , Br or I , to give a compound of Formula I, wherein R^3 is 2-hydroxy-2-methylpropyl.

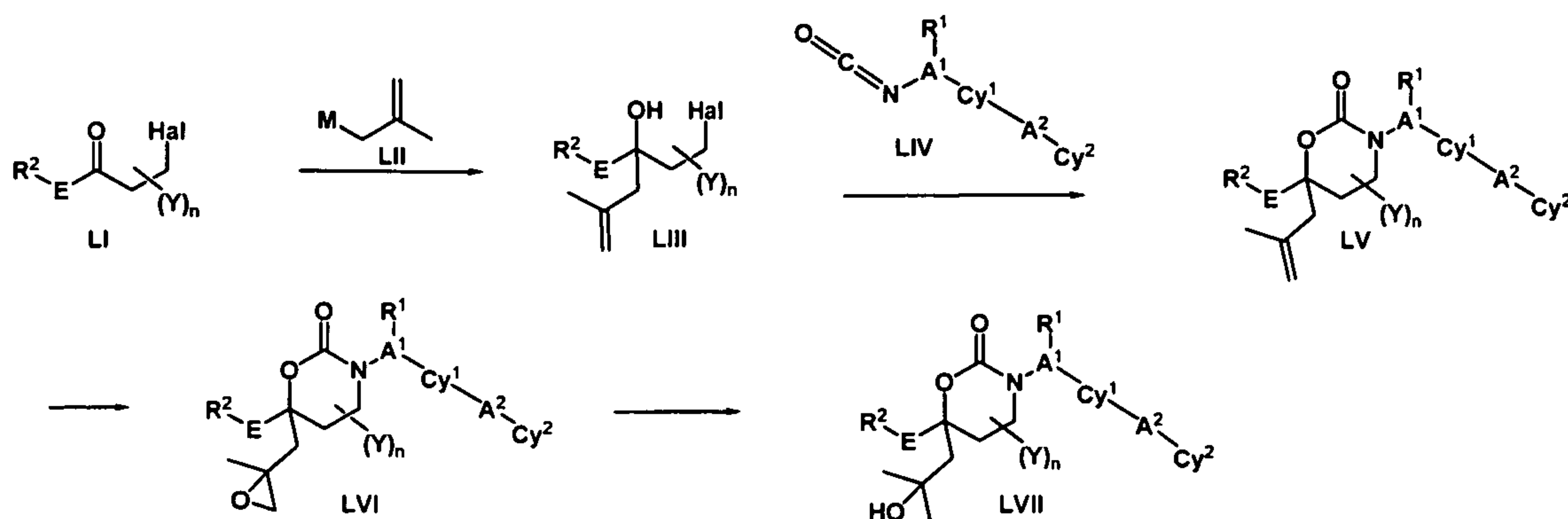
(25) a compound of Formula I, wherein R^3 is allyl or $-CH_2C(Me)=CH_2$ can be hydrocyanated with $TsCN$ in the presence of triphenylsilane and various cobalt catalysts to afford compounds of Formula I, wherein R^3 is $-CH_2CH(CN)Me$ or $-CH_2CMe_2CN$ respectively.

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(26) a compound of Formula I, wherein R^3 is $\text{CH}_2\text{C}(\text{Me})_2\text{CN}$, can be treated with acetamide in the presence of PdCl_2 to give a compound of Formula I, wherein R^3 is $\text{CH}_2\text{CMe}_2\text{CONH}_2$.

(27) a compound of Formula I, wherein R^3 is $-\text{CH}_2\text{C}(\text{Me})=\text{CH}_2$ can be treated with m-CPBA followed by lithium triethylborohydride to afford a compound of Formula I, wherein R^3 is 2-hydroxy-2-methylpropyl.

In an eighth process, compounds of the invention as prepared as follows:



10 Halo compounds of Formula LIII can be formed by the treatment of β -haloketones of Formula LI with organometallic reagents of Formula LII, wherein M denotes MgCl , and the reaction is performed in the presence of anhydrous cerium trichloride in an inert anhydrous solvent, such as tetrahydrofuran, at about -25 to 0°C for about 0.5 h.

15 Cyclic carbamates of Formula LV can be prepared from the reaction between β -haloalcohols of Formula LIII where Hal is a chloride and Isocyanates of Formula LIV in the presence of a base, such as but not limited to DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), in a refluxing inert solvent, such as but not limited to tetrahydrofuran.

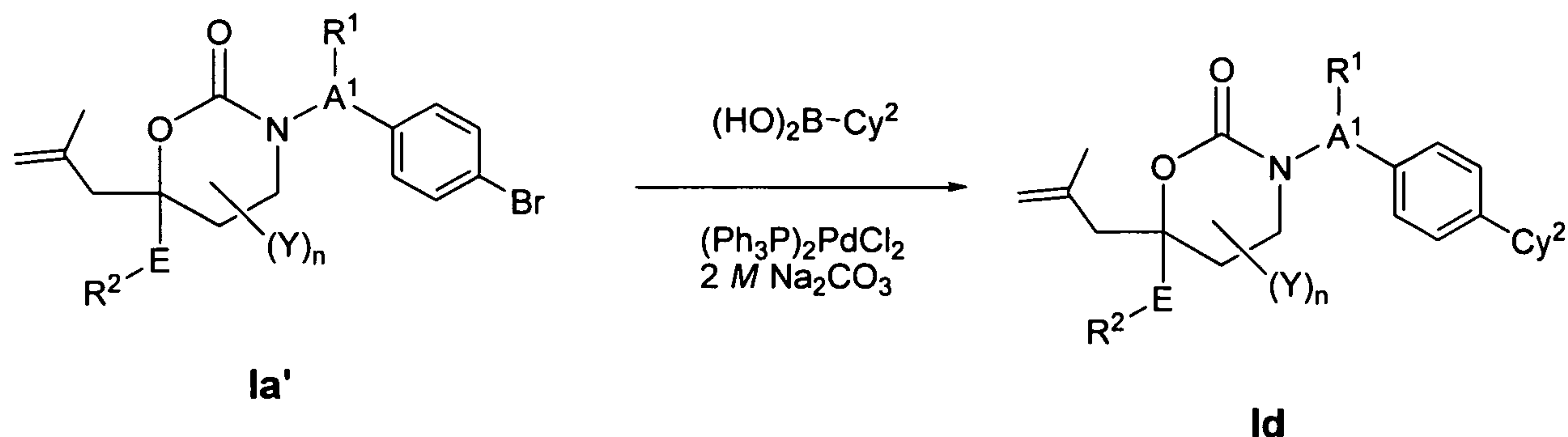
20 Tertiary alcohols of Formula LVII can be derived from trisubstituted alkenes of Formula LV by first epoxidizing the alkene with an epoxidation reagent, such as m-CPBA (3-chloroperbenzoic acid), in an inert solvent, such as dichloromethane to produce the corresponding epoxides of Formula LVI. The resulting epoxide is then reductively ring opened to provide the corresponding tertiary alcohol LVII via
25 treatment with a strong hydride reagent, such as triethylborohydride, in an anhydrous inert solvent, such as tetrahydrofuran.

This eighth process is described in greater detail in U.S. Provisional Application Serial No. 61/_____, filed July 25, 2008 entitled SYNTHESIS OF INHIBITORS OF 11β -HYDROXYSTEROID DEHYDROGENASE TYPE 1 (Attorney

Docket No. 4370.1001-000), the entire teachings of which are incorporated herein by reference.

In another variation, Id is prepared from Ia' by using a "Suzuki" coupling reaction with $\text{Cy}^2\text{-B(OH)}_2$ and $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ as described in, for example, Example

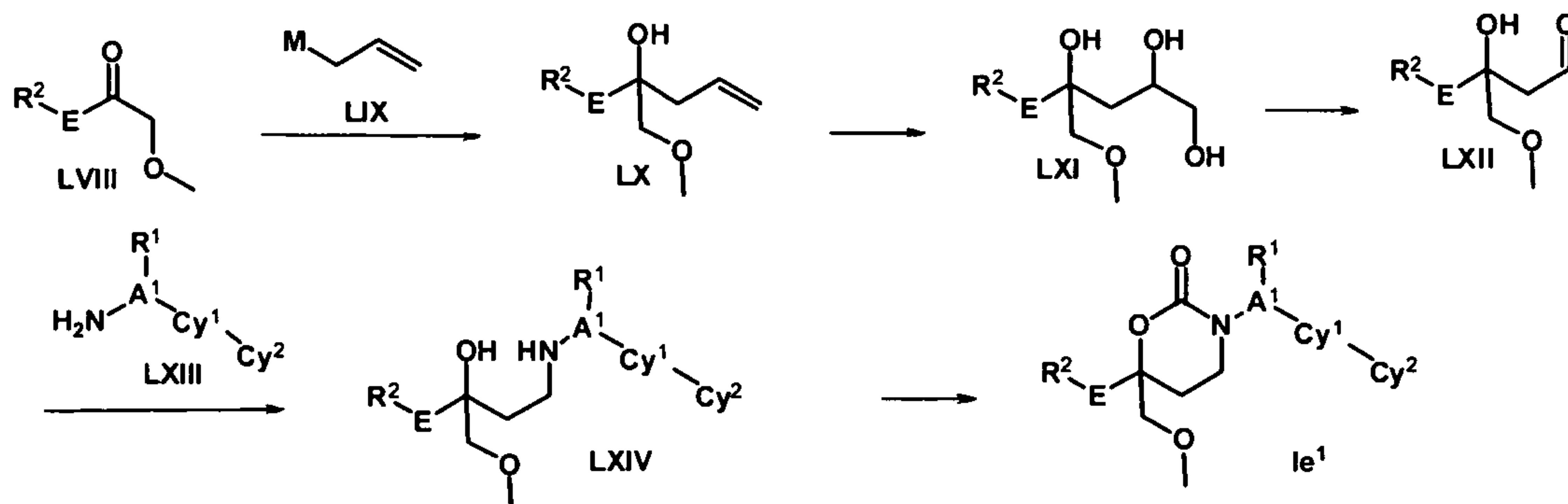
5 111:



The 2-methyl-2-hydroxypropyl group is introduced via epoxidation and hydride ring opening as described above.

10

In a ninth process, compounds of Formula Ie' can be prepared according to the following scheme:



15

A methoxymethyl ketone of Formula LVIII is reacted with an organometallic allyl reagent of Formula LIX wherein M includes, but is not limited to, MgCl, MgBr, MgI or Li to yield an allyl compound of Formula LX. In specific examples, organometallic reagent LIX is allylmagnesium chloride, allylmagnesium bromide or allylzinc(II) bromide. In certain cases when M is MgCl, MgBr or MgI, it is advantageous to add CeCl_3 to the reaction mixture.

20

Allyl compound of Formula LX is converted to the aldehyde of Formula LXII by ozonolysis or by OsO_4 catalysed dihydroxylation followed by cleavage of the glycol of Formula LXI by periodates like sodium periodate. Aminocarbinol of Formula LXIV can be prepared by reductive amination with an amine of Formula LXIII using sodium

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cyanoborohydride or sodium triacetoxyborohydride as reducing agent. Cyclisation of the aminocarbinal of Formula LXIV to the compounds of Formula Ie¹ can be achieved by reacting with activated carbonic acid derivatives such as phosgene, diphosgene, triphosgene or 1,1'-carbonyl-diimidazol.

5

PURIFICATION METHODS

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

10

LC-MS METHODS

Method 1 [LC-MS (3 min)]

Column: Chromolith SpeedRod, RP-18e, 50 x 4.6 mm; Mobile phase: A:

15 0.01%TFA/water, B: 0.01%TFA/CH₃CN; Flow rate: 1 mL/min; Gradient:

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

Method 2 (10-80)

Column	YMC-PACK ODS-AQ , 50×2.0mm 5µm		
Mobile Phase	A: water (4 L) + TFA (1.5 mL))		
	B: acetonitrile (4 L) + TFA (0.75 mL))		
	TIME(min)	A%	B%
	0	90	10
	2.2	20	80
	2.5	20	80
Flow Rate	1mL/min		
Wavelength	UV 220 nm		

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Oven Temp	50 °C
MS ionization	ESI

Method 3 (30-90)

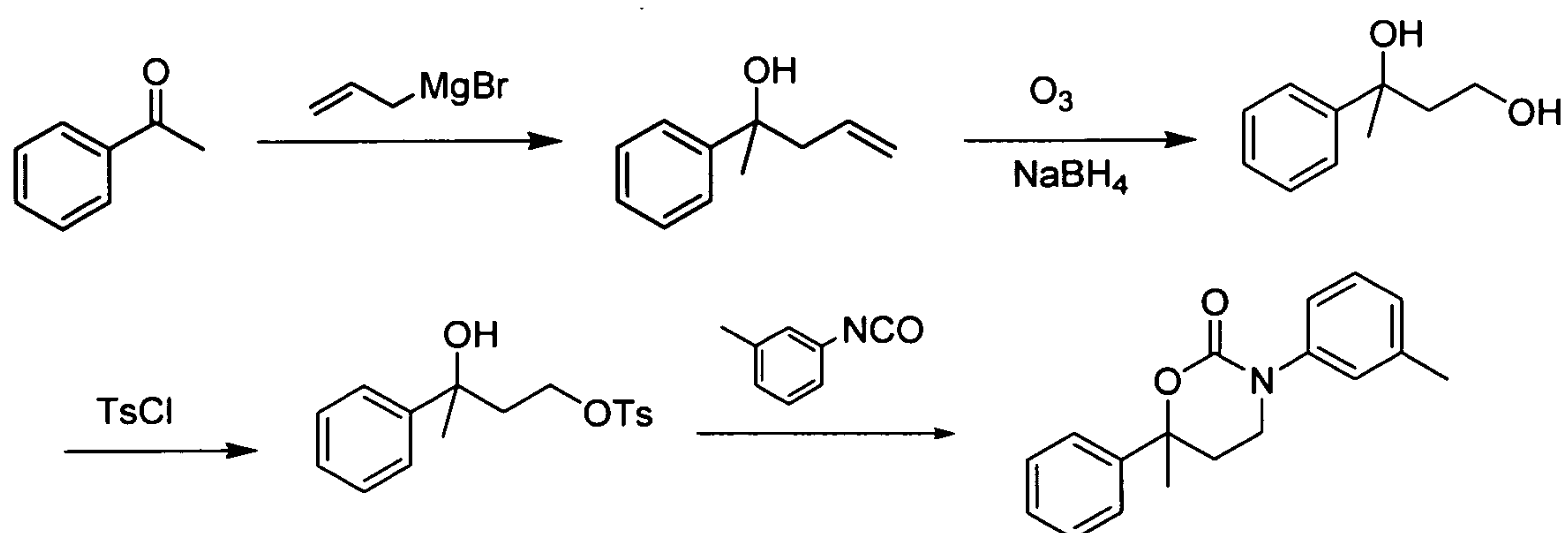
Column	YMC-PACK ODS-AQ , 50×2.0mm 5μm		
Mobile Phase	A: water (4 L) + TFA (1.5 mL))		
	B: acetonitrile (4 L) + TFA (0.75 mL))		
	TIME(min)	A%	B%
	0	70	30
	2.2	10	90
	2.5	10	90
Flow Rate	1 mL/min		
Wavelength	UV220		
Oven Temp	50 °C		
MS ionization	ESI		

Method 4 [50-100]

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EXAMPLE 1

6-methyl-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one



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Step 1. 2-Phenylpent-4-en-2-ol

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To a solution of acetophenone (30 g, 0.25 mol) in dry THF (250 mL) at -78 °C was added dropwise 1M allylmagnesium bromide (1.25 L, 1.25 mol). After addition was complete, the mixture was allowed to stir at rt for 3 h. The reaction was quenched with satd aq NH₄Cl solution (30 mL). The mixture was extracted with EtOAc (200 mL). The organic layer was washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated to give 2-phenylpent-4-en-2-ol (40.2 g), which was used for the next step without purification.

Step 2. 3-Phenylbutane-1,3-diol

A solution of 2-phenylpent-4-en-2-ol (74 g, 0.457 mol) in dry CH₂Cl₂ (1 L) was treated with ozone at -78 °C until the mixture turned blue. The system was then flushed with oxygen to remove excess ozone. NaBH₄ (42.8 g, 1.143 mol) was added to the mixture in portions at -20 °C. The mixture was stirred overnight at rt. The mixture was quenched with water and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x). The organic layers were combined, washed with brine, dried over anhydrous Na₂SO₄ and concentrated to give 3-phenylbutane-1,3-diol (67.8 g), which was used for the next step without purification.

Step 3. 3-Hydroxy-3-phenylbutyl 4-methylbenzenesulfonate

To a solution of 3-phenylbutane-1,3-diol (68 g, 0.41 mol) in dry CH₂Cl₂ (500 mL) was added dropwise a solution of TsCl (78 g, 0.41 mol) and triethylamine (71 mL, 0.45 mol) in dry CH₂Cl₂ (500 mL) at 0 °C. The mixture was stirred overnight. The mixture was poured into water and separated. The aqueous layer was extracted with CH₂Cl₂ (200 mL) twice. The organic layer was combined, washed with brine, dried over anhydrous Na₂SO₄ and concentrated to give the crude product. The crude product was purified by column chromatography to give 3-hydroxy-3-phenylbutyl 4-methylbenzenesulfonate (62 g, 42%). ¹H NMR (400MHz, CDCl₃): δ=1.55 (s, 3H), 1.93 (w, 1H), 2.19~2.24 (q, 2H), 2.45 (s, 3H), 3.87~4.01(m, 1H), 4.09~4.16 (m, 1H), 7.19~7.34 (m, 7H), 7.68~7.76 (d, 2H).

Step 4. 6-methyl-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one

To a solution of 3-hydroxy-3-phenylbutyl 4-methylbenzenesulfonate (1 g, 3.12 mmol) and DBU (1.4 g, 9.26 mmol) in CH₂Cl₂ (15 mL) was added a solution of 3-methylphenyl isocyanate (623 mg, 4.68 mmol) in CH₂Cl₂ (5 mL) at 0 °C over 0.5 h. The mixture was stirred at rt overnight. The mixture was concentrated to give the crude product, which was purified by column chromatography and then by preparative HPLC to afford 6-methyl-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one. LC-MS Method 2, t_R = 2.706 min, m/z = 282. ¹H NMR (CDCl₃) 1.75 (s, 3H), 2.30 (s, 3H),

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2.35-2.50 (m, 2H), 3.30 (m, 1H), 3.50 (m, 1H), 6.95 (m, 2H), 7.05 (m, 1H), 7.20-7.30 (m, 1H), 7.35 (m, 1H), 7.42-7.50 (m, 4H).

Step 5. Enantiomers of 6-methyl-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one

Chiral preparative SFC using a ChiralPak-AD, 400 × 25 mm I.D, 20 μm (Daicel Chemical Industries, Ltd) column maintained at 35 C eluted with 70:30 supercritical CO₂/0.1% diethylamine in MeOH at a flow rate of 70 mL min⁻¹ and a nozzle pressure of 100 bar afforded two isomers.

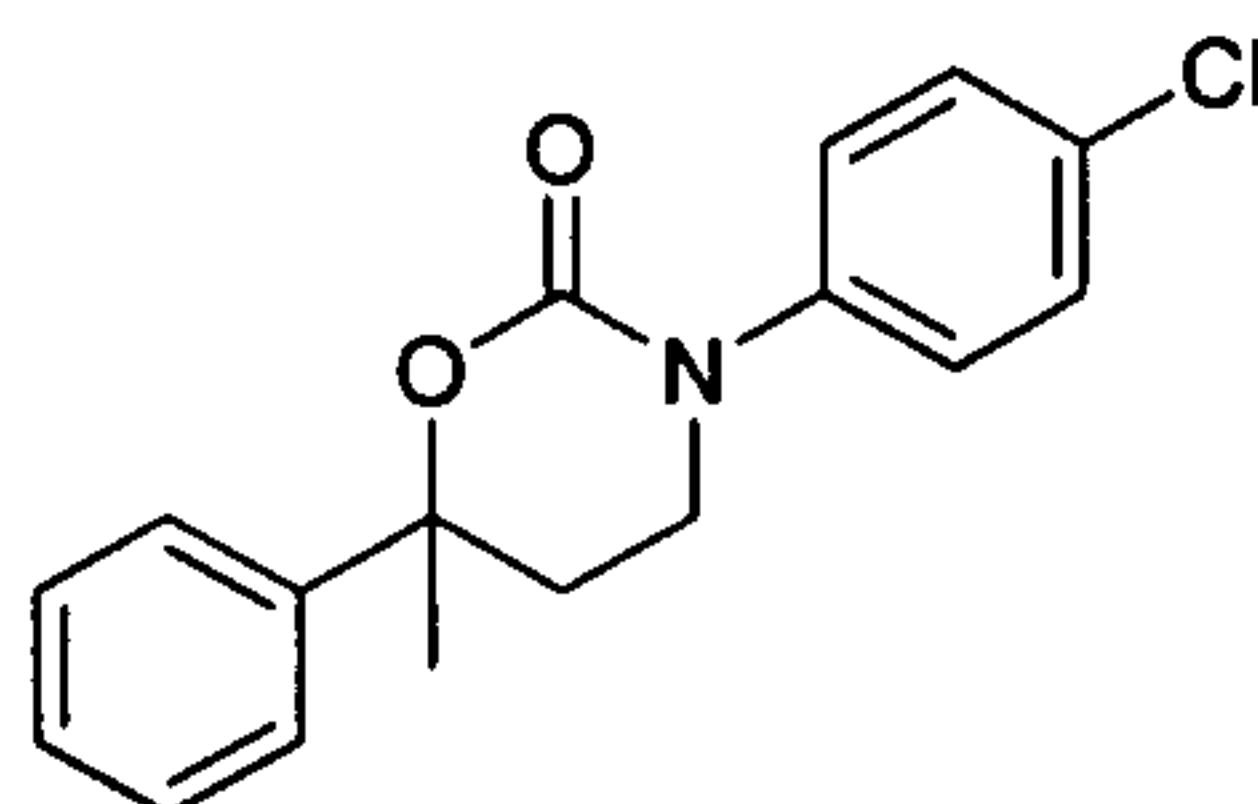
Isomer 1 (90 mg) gave the following spectral data: ¹H NMR (400MHz, CDCl₃): δ=1.62 (m, 1H), 1.76 (s, 3H), 2.31 (s, 3H), 2.48 (m, 2H), 3.28 (m, 1H), 3.50 (m, 1H), 6.95 (m, 1H), 7.04 (m, 1H), 7.23 (t, 1H), 7.35 (m, 1H), 7.44 (m, 4H);

Isomer 2 (100 mg) gave the following spectral data: (400MHz, CDCl₃): δ=1.62 (m, 1H), 1.76 (s, 3H), 2.31 (s, 3H), 2.48 (m, 2H), 3.28 (m, 1H), 3.50 (m, 1H), 6.95 (m, 1H), 7.04 (m, 1H), 7.23 (t, 1H), 7.35 (m, 1H), 7.44 (m, 4H).

15

EXAMPLE 2

3-(4-chlorophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

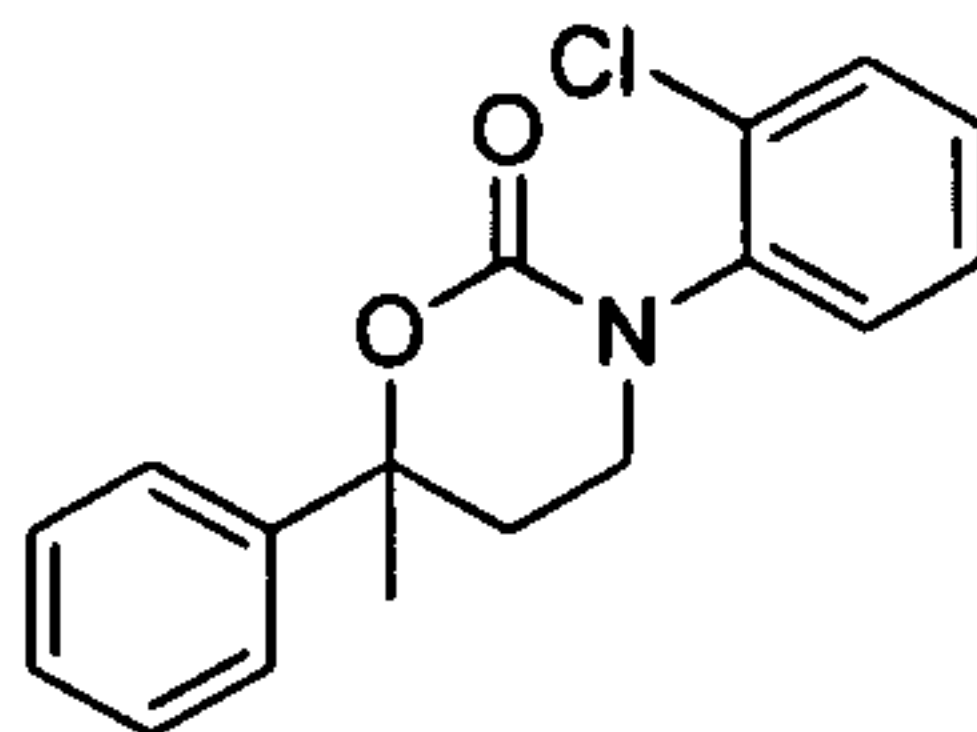


The title compound was prepared following procedures analogous to those described in Example 1 Steps 1 – 4 using 4-chlorophenyl isocyanate in Step 4. LC-MS Method 2, t_R = 2.798 min, m/z = 324. ¹H NMR (CD₃OD) 1.75 (s, 3H), 2.45 (m, 1H), 2.65 (m, 1H), 3.27 (m, 1H), 3.60 (m, 1H), 7.15 (d, 2H), 7.35 (dd, 3H), 7.47 (m, 4H).

25

EXAMPLE 3

3-(2-chlorophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



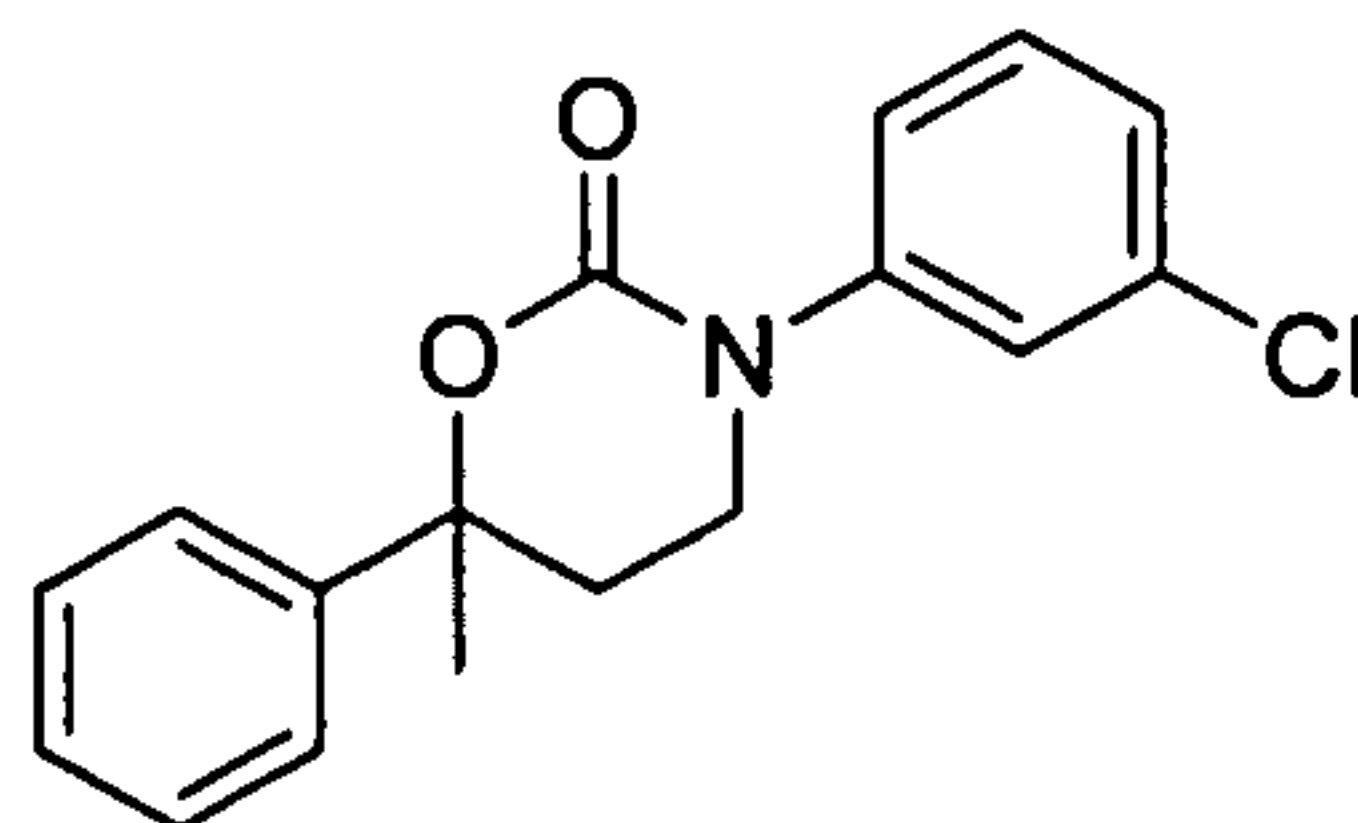
The title compound was prepared following procedures analogous to those described in Example 1 Steps 1 – 4 using 2-chlorophenyl isocyanate in Step 4. LC-MS Method 3, t_R = 1.14 min, m/z = 625.1. ¹H NMR (CD₃OD) 1.80 (d, 3H), 2.50 (m,

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1H), 2.62 (m, 1H), 3.20-3.30 (m, 1H), 3.42 (m, 1H), 3.50-3.60 (m, 2H), 7.03 (d, 1H), 7.30-7.50 (m, 5H), 7.50-7.60 (m, 4H).

EXAMPLE 4

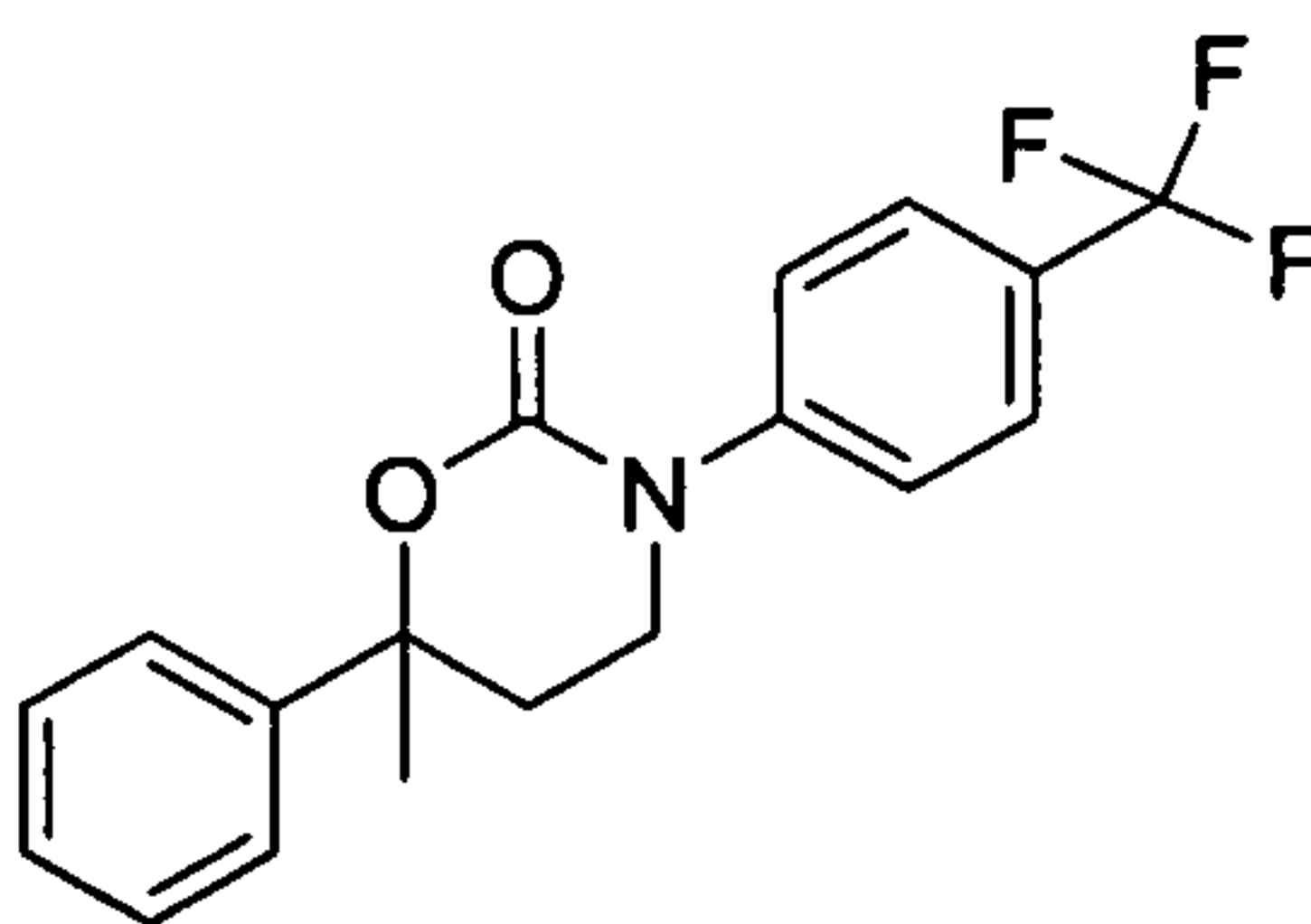
5 3-(3-chlorophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those described in Example 1 Steps 1 – 4 using 3-chlorophenyl isocyanate in Step 4. LC-MS Method 2, t_R = 2.291 min, m/z = 301. ^1H NMR (CD_3OD) 1.75 (s, 3H), 2.50 (m, 1H), 2.70 (m, 1H), 3.30 (m, 1H), 3.68 (m, 1H), 7.12 (d, 1H), 7.30-7.45 (m, 4H), 7.50 (d, 4H).

EXAMPLE 5

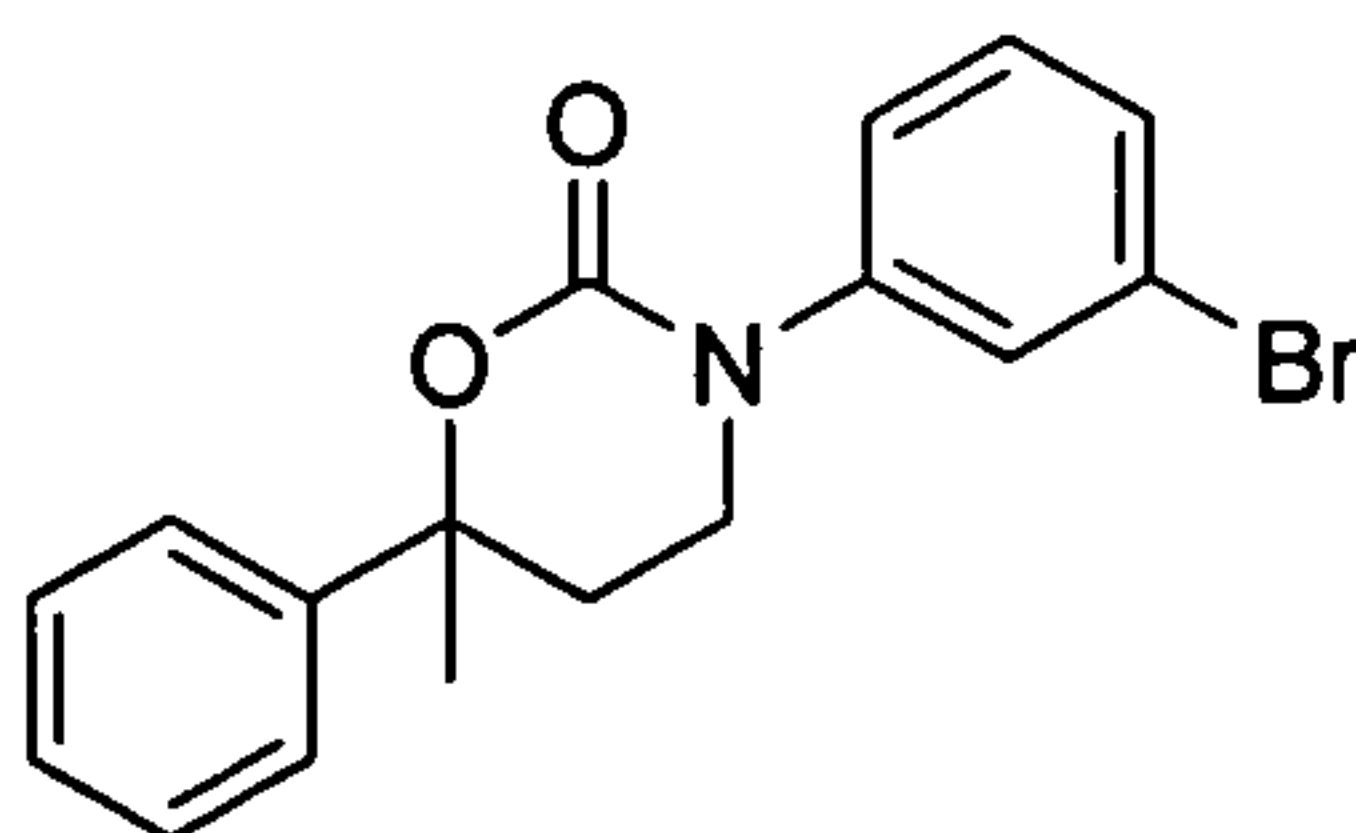
6-methyl-6-phenyl-3-(4-(trifluoromethyl)phenyl)-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those described in Example 1 Steps 1 – 4 using 4-(trifluoromethyl)phenyl isocyanate in Step 4. LC-MS Method 2, t_R = 2.903 min, m/z = 336. ^1H NMR (CD_3OD) 1.75 (s, 3H), 2.50 (m, 1H), 2.70 (m, 1H), 3.40 (m, 1H), 3.70 (m, 1H), 7.32-7.42 (m, 3H), 7.45-7.50 (m, 4H), 7.70 (d, 2H).

EXAMPLE 6

3-(3-bromophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

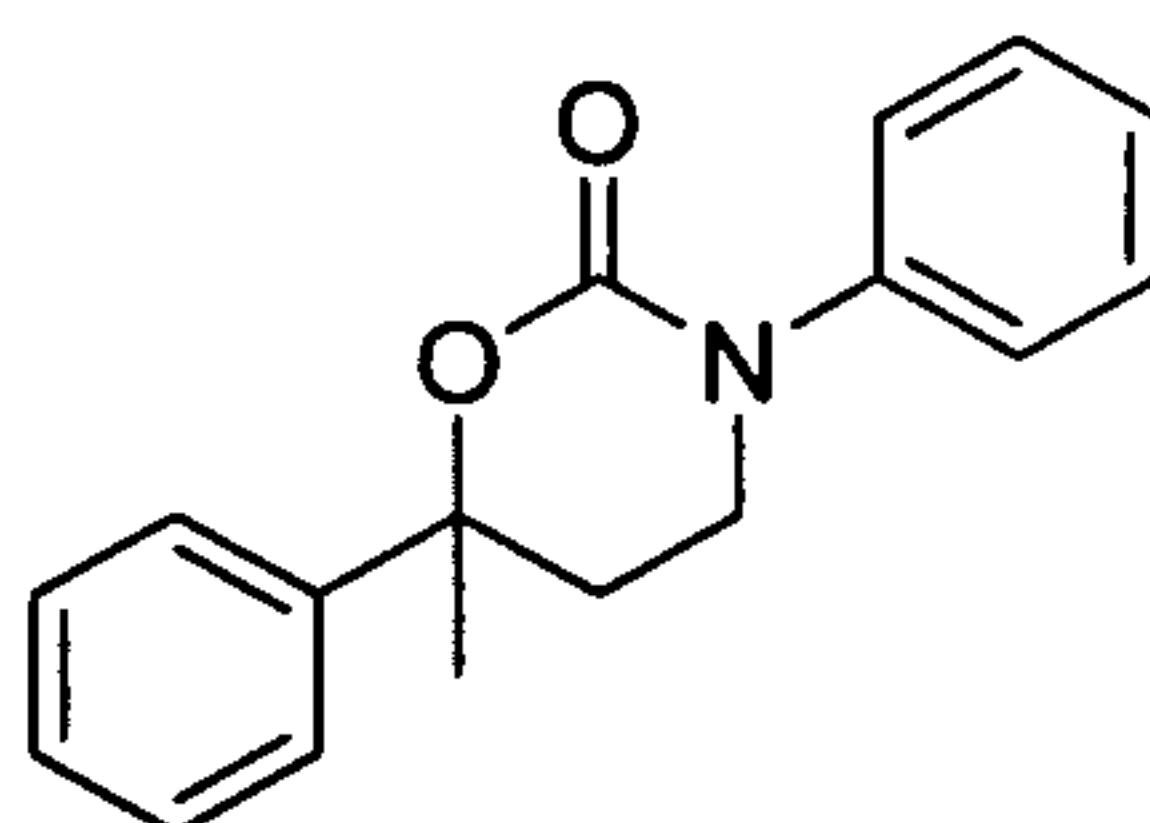


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The title compound was prepared following procedures analogous to those described in Example 1 Steps 1 – 4 using 3-bromophenyl isocyanate in Step 4. LC-MS Method 3, t_R = 1.232 min, m/z = 367.9. ^1H NMR (CDCl_3) 1.70 (s, 2H), 2.30-2.40 (m, 1H), 3.45 (m, 1H), 7.07 (d, 1H), 7.12 (t, 1H), 7.22-7.30 (m, 3H), 7.35-7.40 (m, 4H).

EXAMPLE 7

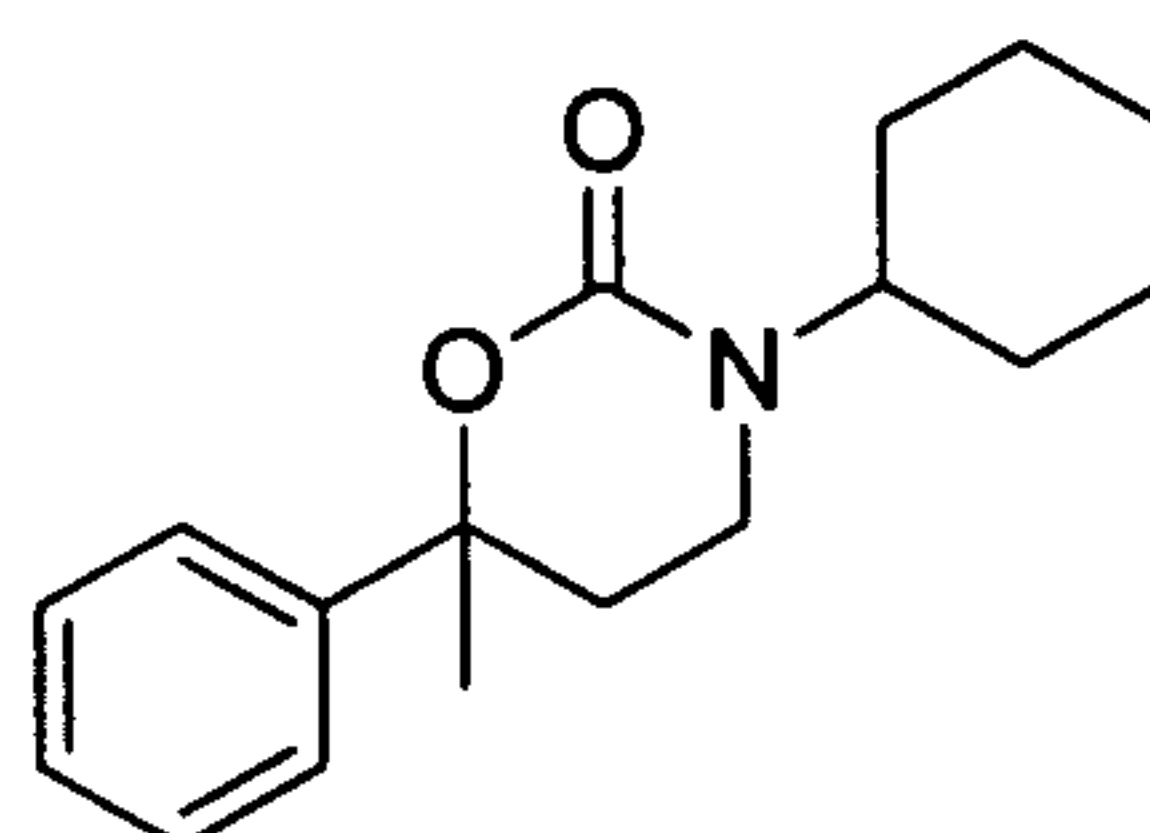
6-methyl-3,6-diphenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those described in Example 1 Steps 1 – 4 using phenyl isocyanate in Step 4. LC-MS Method 2, t_R = 1.99 min, m/z = 268. ^1H NMR (CD_3OD) 1.75 (s, 3H), 2.45 (m, 1H), 2.65 (m, 1H), 3.25 (m, 1H), 3.60 (m, 1H), 7.12 (d, 2H), 7.25 (t, 1H), 7.35 (m, 3H), 7.45-7.53 (m, 4H).

EXAMPLE 8

3-cyclohexyl-6-methyl-6-phenyl-1,3-oxazinan-2-one

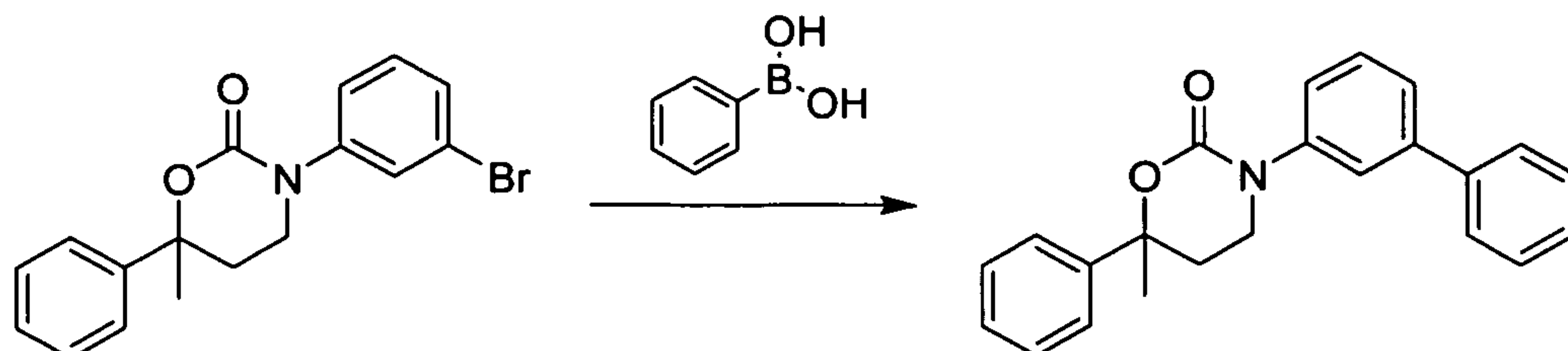


The title compound was prepared following procedures analogous to those described in Example 1 Steps 1 – 4 using cyclohexyl isocyanate in Step 4. LC-MS Method 3, t_R = 1.529 min, m/z = 274.1. ^1H NMR (CDCl_3) 0.97-1.15 (m, 3H), 1.20-1.37 (m, 2H), 1.55 (d, 1H), 1.65 (m, 2H), 1.80-1.90 (m, 2H), 2.05 (s, 1H), 2.75 (m, 2H), 3.40 (b, 1H), 4.10 (t, 2H), 5.08 (s, 1H), 7.18 (m, 1H), 7.25 (m, 2H), 7.34 (dd, 2H).

EXAMPLE 9

3-(biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

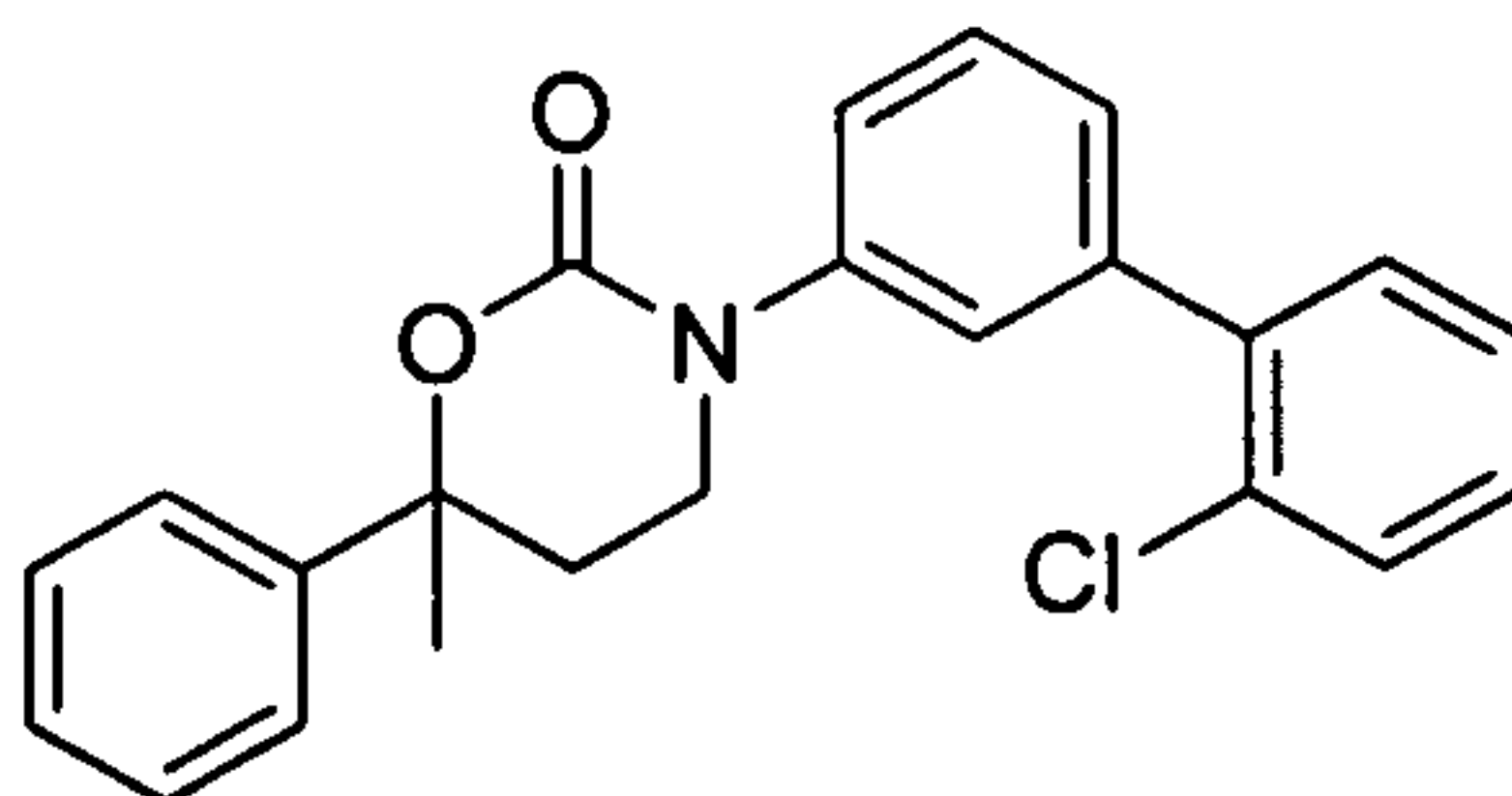
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To a solution of 3-(3-bromophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (50 mg, 0.14 mmol) and phenylboronic acid (35 mg, 0.29 mmol) in THF (2 mL) was added a solution of NaHCO₃ (31 mg, 0.29 mmol) in H₂O (2 mL) followed by Pd(PPh₃)Cl₂ (9 mg, 0.01 mmol). The mixture was refluxed overnight. The mixture was concentrated to give the crude product, which was purified by column chromatography, followed by preparative HPLC to afford 3-(biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (10 mg, 20%). ¹H NMR: (400MHz, CDCl₃): δ 1.71 (s, 3H), 2.40 (m, 1H), 2.48 (m, 1H), 3.31 (m, 1H), 3.54 (m, 1H), 7.08 (m, 1H), 7.30 (m, 3H), 7.7.32-7.42 (m, 8H), 7.46 (m, 2H). LC-MS Method 3, t_R = 1.362 min, m/z = 344. ¹H NMR (CDCl₃) 1.75 (s, 3H), 2.32-2.43 (m, 1H), 2.50 (m, 1H), 3.20 (m, 1H), 3.52 (m, 1H), 7.10 (d, 1H), 7.25-7.45 (m, 11H), 7.50 (d, 2H).

EXAMPLE 10

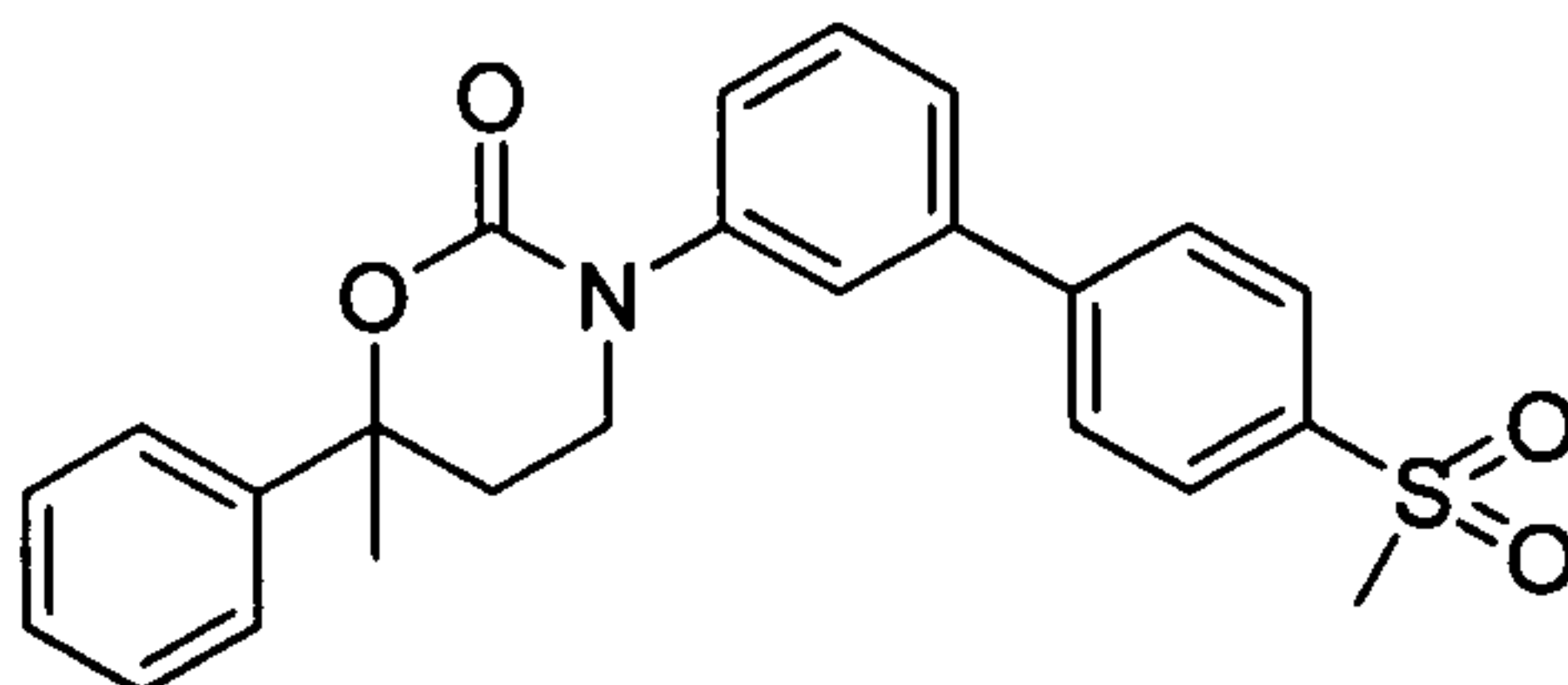
3-(2'-chlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those in Example 9 using 2-chlorophenylboronic acid. LC-MS Method 3, t_R = 1.479 min, m/z = 378.1. ¹H NMR (CDCl₃) 1.63 (s, 3H), 2.38 (m, 1H), 2.67 (m, 1H), 3.18-3.26 (m, 1H), 3.59 (m, 1H), 7.09 (m, 2H), 7.24 (m, 5H), 7.38 (m, 6H).

EXAMPLE 11

3-(4'-Methanesulfonyl-biphenyl-3-yl)-6-methyl-6-phenyl-[1,3]oxazinan-2-one



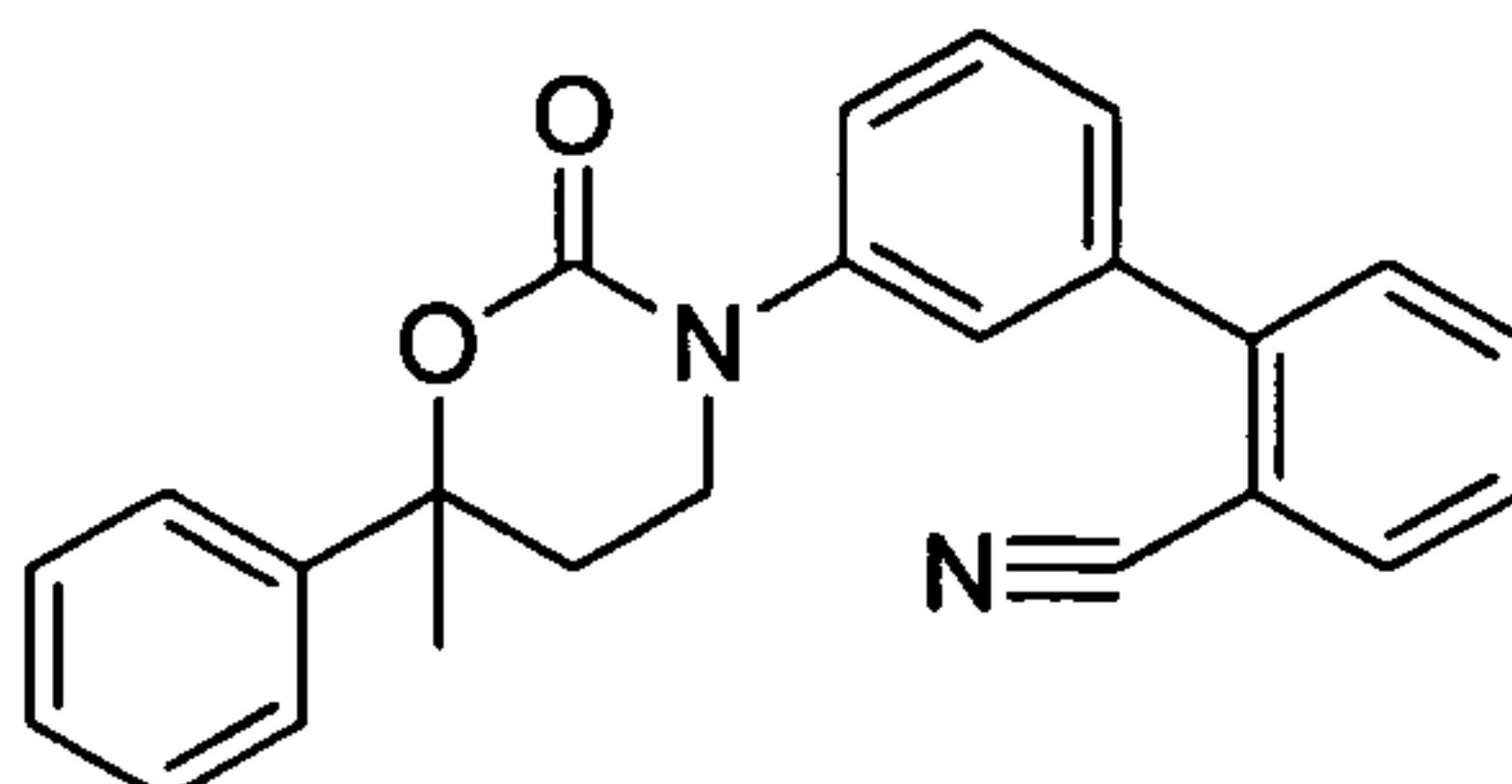
The title compound was prepared following procedures analogous to those in Example 9 using 4-(methanesulfonyl)phenylboronic acid. LC-MS Method 3, t_R = 2.042

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min, m/z = 422.1. ^1H NMR (CD_3OD) 1.69 (s, 3H), 2.40-2.50 (m, 1H), 2.50-2.60 (m, 1H), 3.20 (s, 1H), 3.51-3.60 (m, 1H), 4.5 (m, 1H), 7.05-7.11 (m, 2H), 7.20-7.30 (m, 5H), 7.30-7.45 (m, 6H).

EXAMPLE 12

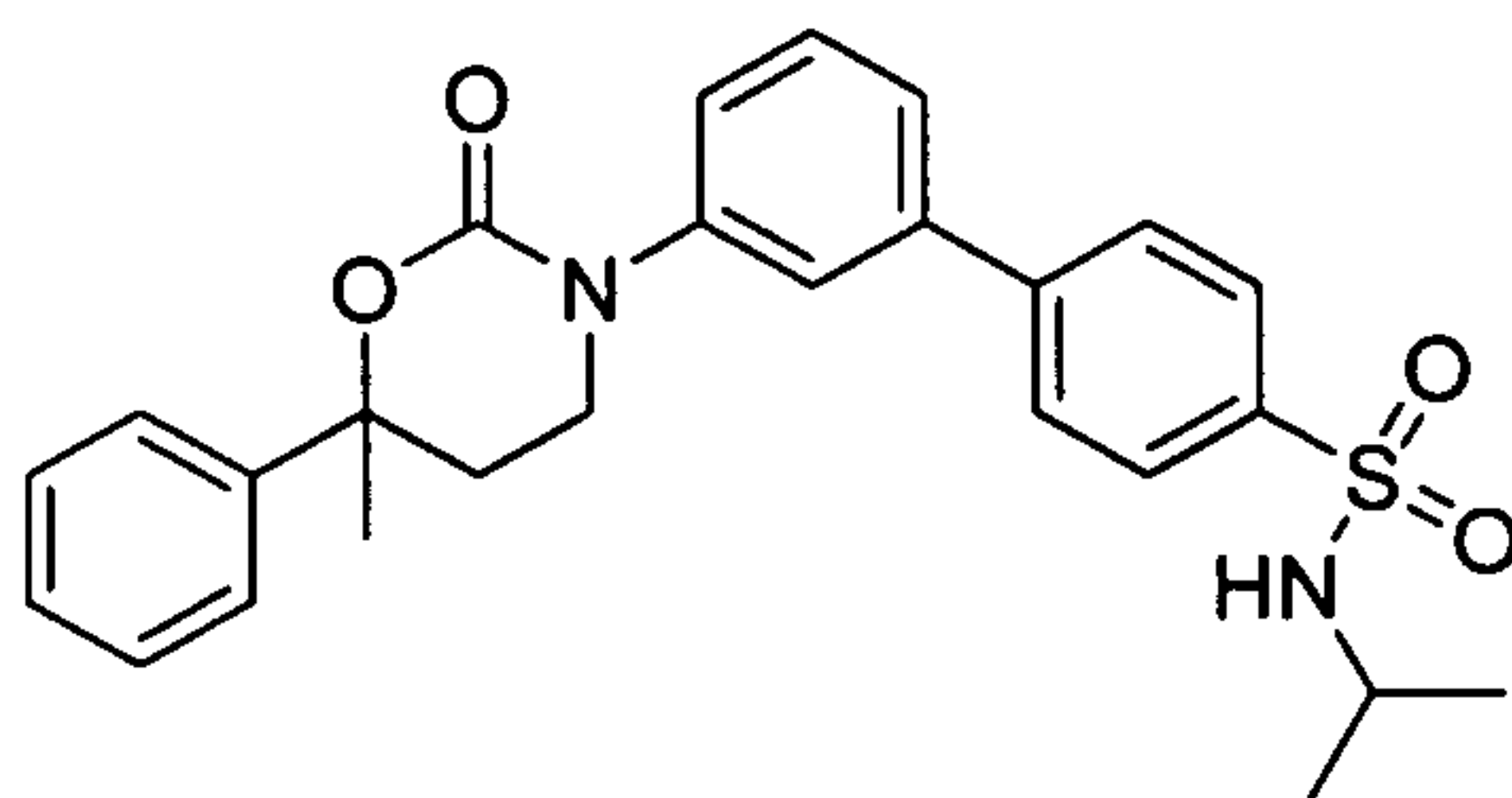
5 3'-(6-Methyl-2-oxo-6-phenyl-[1,3]oxazinan-3-yl)-biphenyl-2-carbonitrile



The title compound was prepared following procedures analogous to those in Example 9 using 2-cyanophenylboronic acid. LC-MS Method 3, t_R = 1.376 min, m/z = 369.1. ^1H NMR (CD_3OD) 1.73(s, 3H), 2.38-2.60 (m, 1H), 2.62-2.78 (m, 1H), 3.38-3.52(m, 1H), 3.65-3.78 (m, 1H), 7.22-7.28(m, 1H), 7.32-7.39(m, 2H), 7.40-7.52(m, 6H), 7.53-7.62(m, 2H), 7.68-7.85 (m, 2H).

EXAMPLE 13

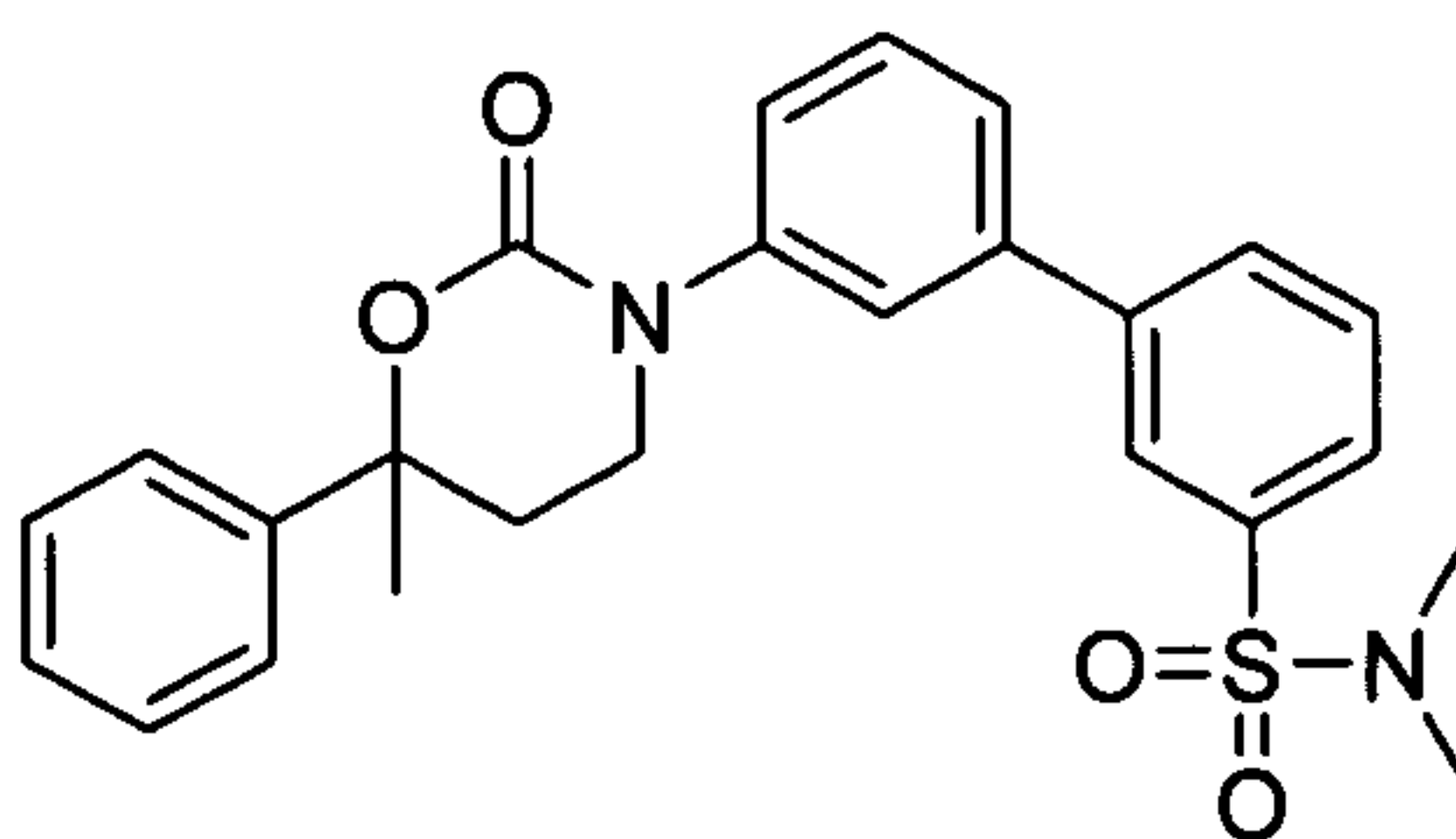
N-isopropyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-sulfonamide



15 The title compound was prepared following procedures analogous to those in Example 9 using 4-(isopropylaminosulfonyl)phenylboronic acid. LC-MS Method 3, t_R = 1.566 min, m/z = 465.1. ^1H NMR (CDCl_3) 1.11-1.15(m, 6H), 1.79 (s, 3H), 2.40-2.50 (m, 1H), 2.50-2.60 (m, 1H), 3.40 (s, 4H), 3.45-3.62 (m, 2H), 7.15-7.20(m, 1H), 7.32-7.55 (m, 8H), 7.60-7.68 (m, 2H), 7.92-7.96(m, 2H).

EXAMPLE 14

N,N-dimethyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-sulfonamide

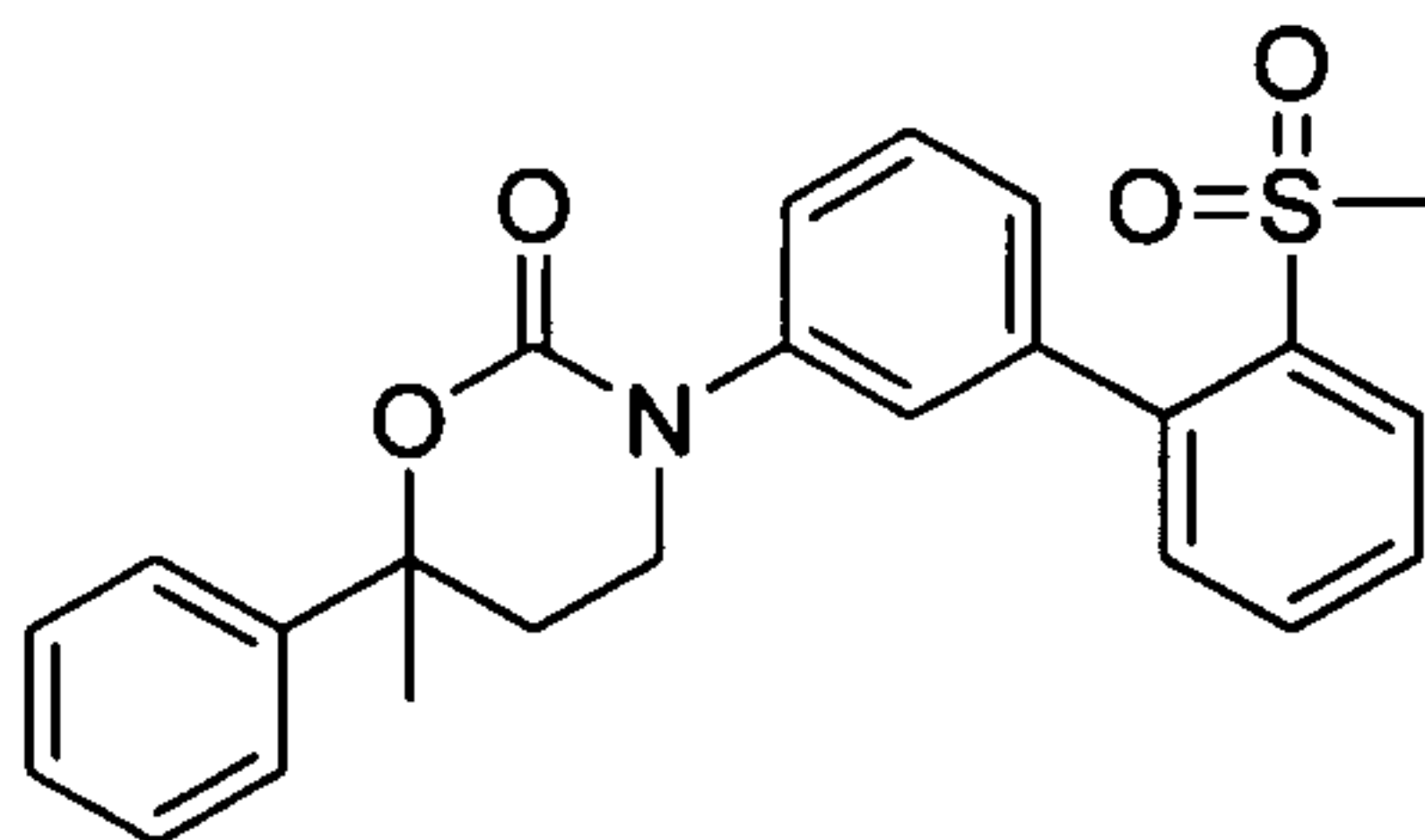


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The title compound was prepared following procedures analogous to those in Example 9 using 3-(dimethylaminosulfonyl)phenylboronic acid. LC-MS Method 3, t_R = 1.459 min, m/z = 451.1. ^1H NMR (CDCl_3) 1.71(s, 3H), 2.40-2.50 (m, 1H), 2.50-2.58 (m, 1H), 3.25-3.35 (m, 1H), 3.51-3.65 (m, 1H), 7.10-7.12 (m, 1H), 7.25-7.40 (m, 8H), 7.50-7.60(m, 1H), 7.65-7.70(m, 2H), 7.80-7.85 (m, 1H).

EXAMPLE 15

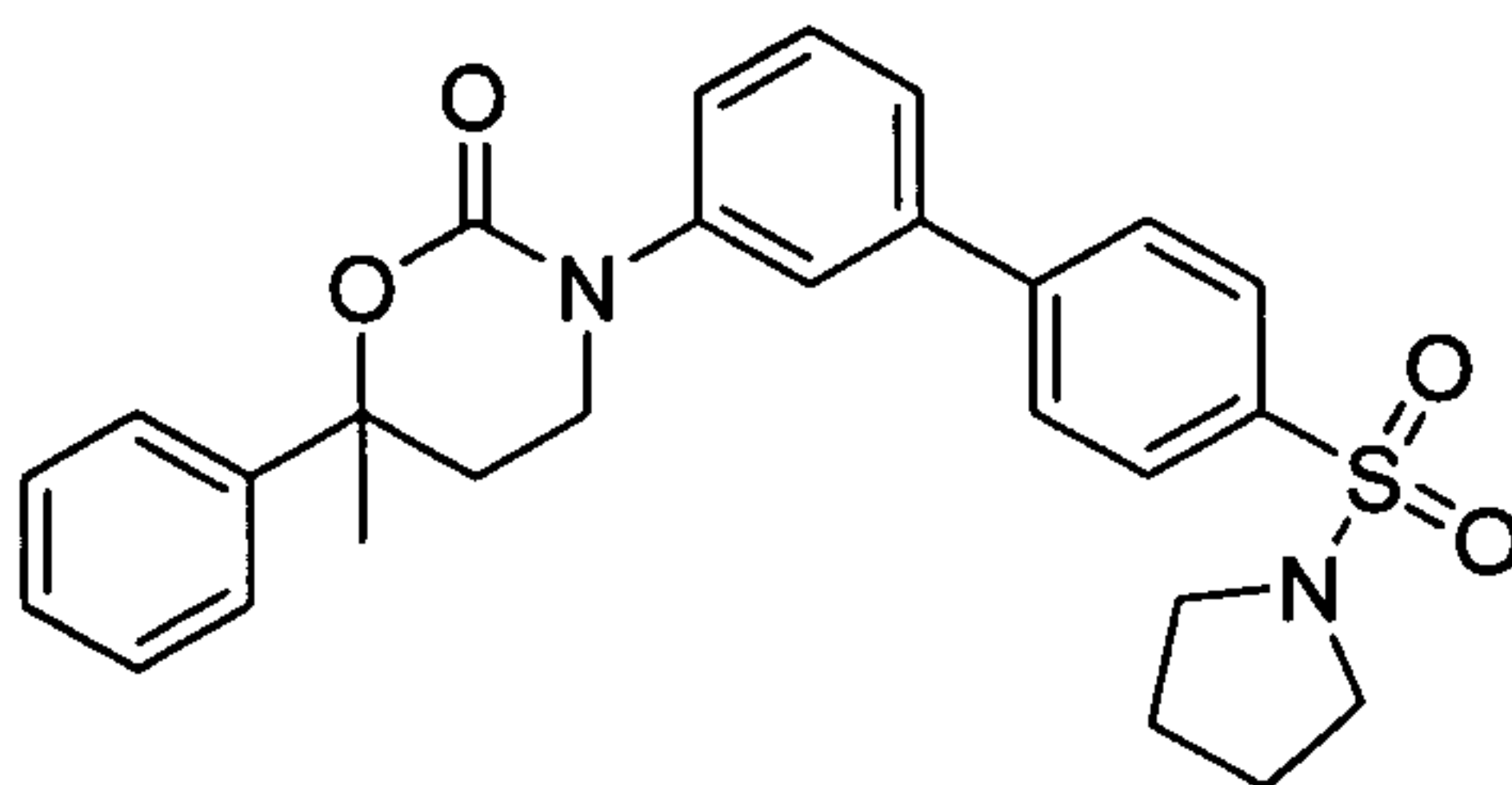
6-methyl-3-(2'-(methylsulfonyl)biphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those in Example 9 using 2-(methylsulfonyl)phenylboronic acid. LC-MS Method 3, t_R = 1.464 min, m/z = 422. ^1H NMR (CDCl_3) 1.77 (s, 3H), 2.40-2.50 (m, 1H), 2.50-2.60 (m, 1H), 2.60-2.68(m, 3H), 3.38-3.48 (m, 1H), 3.62-3.70 (m, 1H), 4.90-5.02 (s, 2H), 7.30-7.45 (m, 5H), 7.45-7.50 (m, 5H), 7.52-7.70(m, 2H), 8.20-8.25(m, 1H).

EXAMPLE 16

6-methyl-6-phenyl-3-(4'-(pyrrolidin-1-ylsulfonyl)biphenyl-3-yl)-1,3-oxazinan-2-one

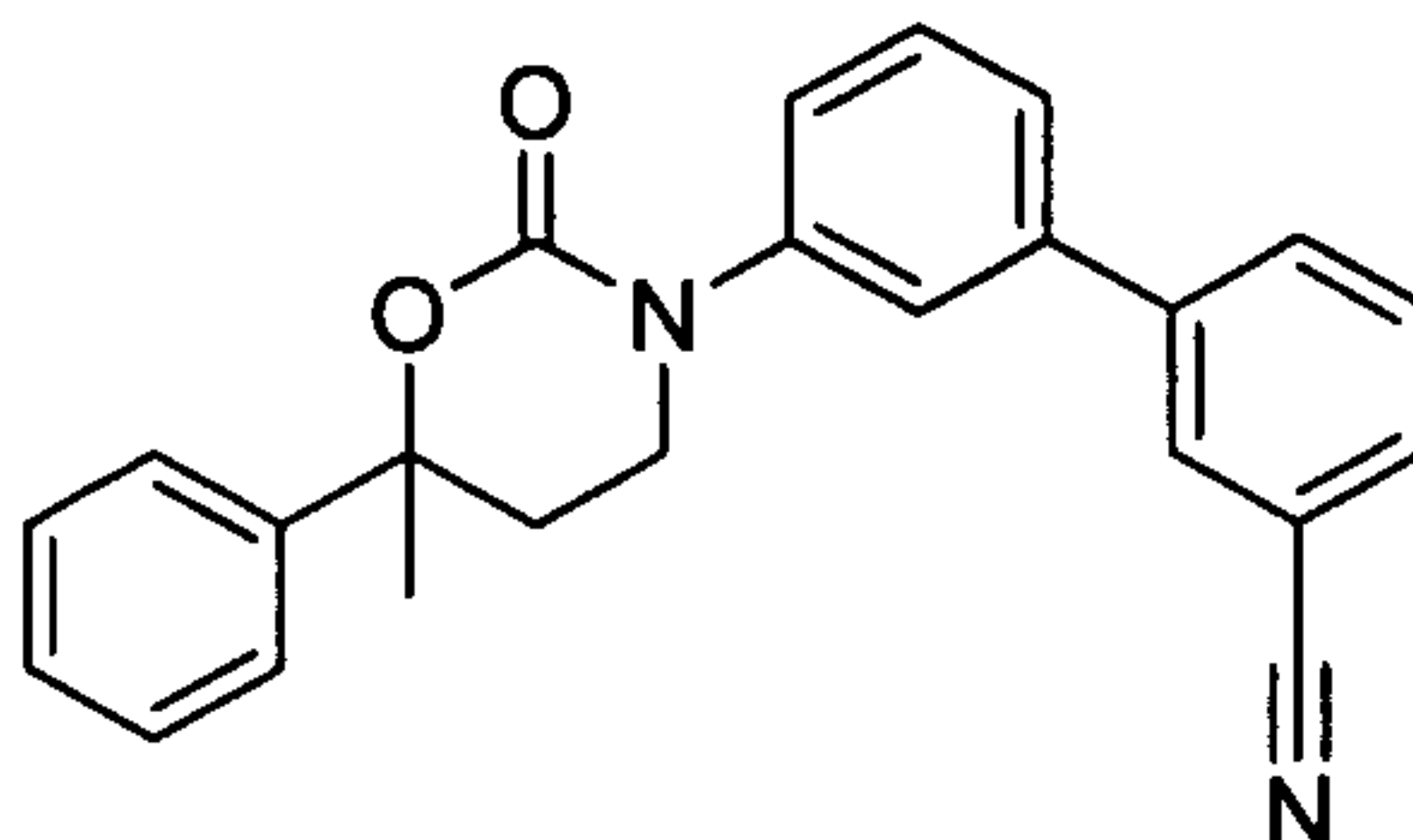


The title compound was prepared following procedures analogous to those in Example 9 using 4-(pyrrolidin-1-ylsulfonyl)phenylboronic acid. LC-MS Method 3, t_R = 1.504 min, m/z = 477.2. ^1H NMR (CDCl_3) 1.72-1.75 (m, 7H), 2.35-2.42 (m, 1H), 2.45-2.52 (m, 1H), 3.20-3.28 (m, 6H), 3.30-3.35 (m, 1H), 3.50-3.58 (m, 1H), 7.10-7.15 (m, 1H), 7.26-7.40 (m, 4H), 7.52-7.60(m, 2H), 7.60-7.70(m, 2H), 7.80-7.90(m, 3H).

EXAMPLE 17

3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-carbonitrile

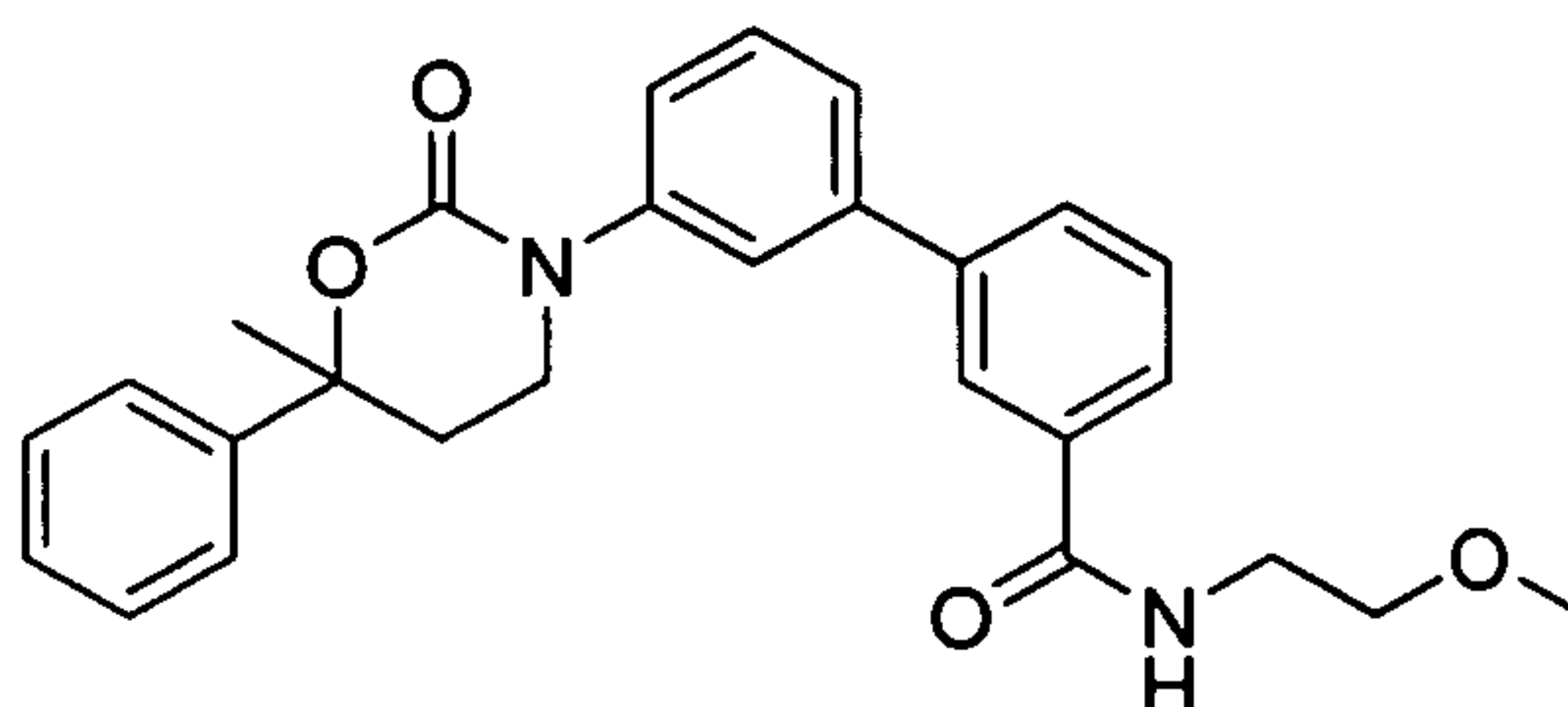
- 128 -



The title compound was prepared following procedures analogous to those in Example 9 using 3-cyanophenylboronic acid. LC-MS Method 3, t_R = 1.487 min, m/z = 369.1. ^1H NMR ($CDCl_3$) 1.72 (s, 3H), 2.32-2.58 (m, 2H), 3.25-3.38 (m, 1H), 3.45-3.57 (m, 1H), 7.12-7.18 (m, 1H), 7.25-7.32 (m, 2H), 7.33-7.42 (m, 6H), 7.42-7.50 (m, 1H), 7.52-7.58 (m, 1H), 7.66-7.75 (m, 2H).

EXAMPLE 18

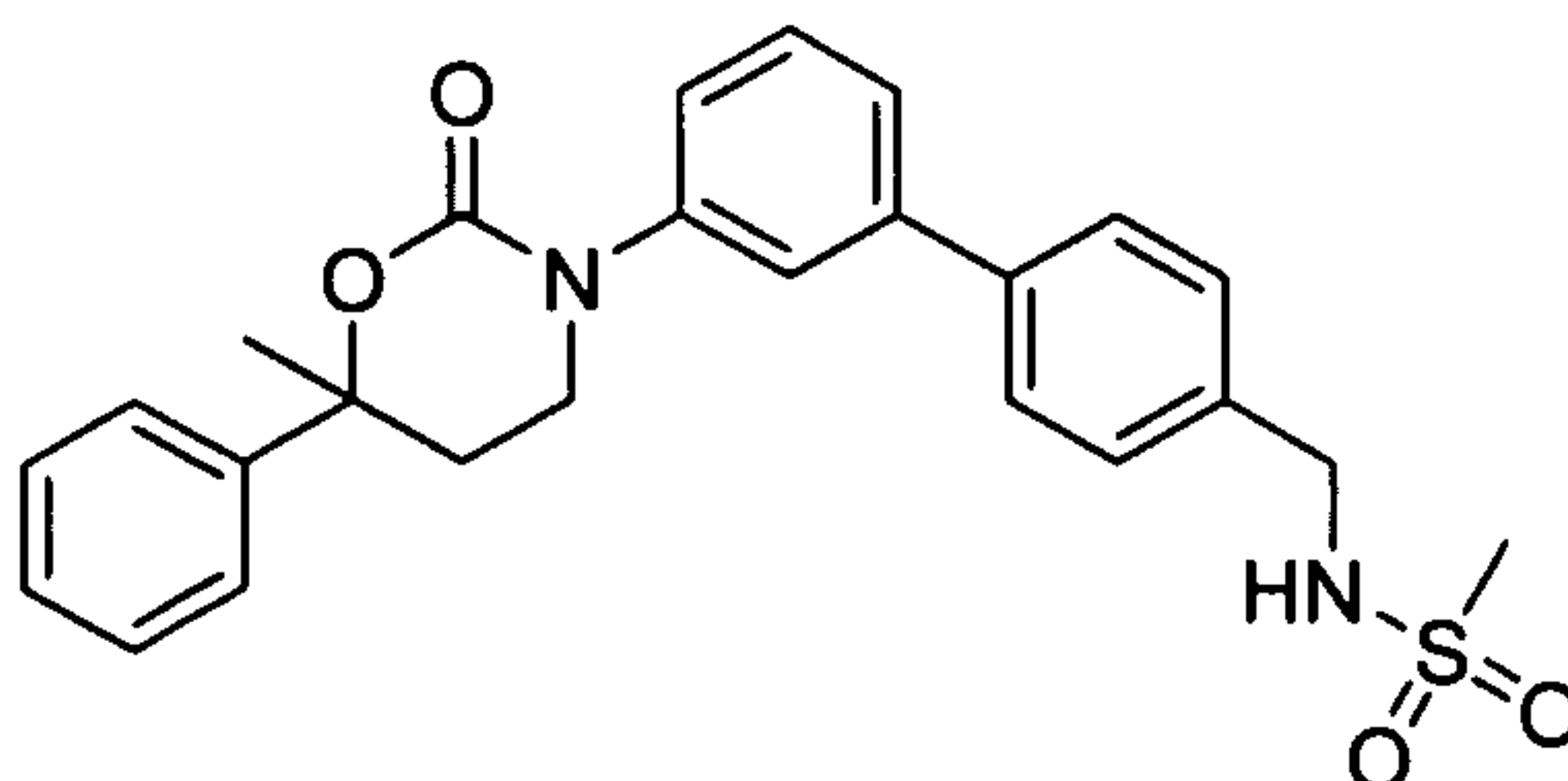
N-(2-methoxyethyl)-3'--(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-carboxamide



The title compound was prepared following procedures analogous to those in Example 9 using 3-(2-methoxyethylcarbamoyl)phenylboronic acid. LC-MS Method 3, t_R = 1.328 min, m/z = 445.2. ^1H NMR ($CDCl_3$) 1.70 (s, 3H), 2.45 (m, 2H), 3.27 (m, 1H), 3.33 (s, 3H), 3.50 (m, 3H), 3.65 (m, 2H), 6.52 (m, 1H), 7.10 (m, 1H), 7.30-7.47 (m, 10H), 7.60 (m, 1H), 7.68 (m, 1H), 7.90 (s, 1H).

EXAMPLE 19

N-((3'--(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-yl)methyl)methanesulfonamide



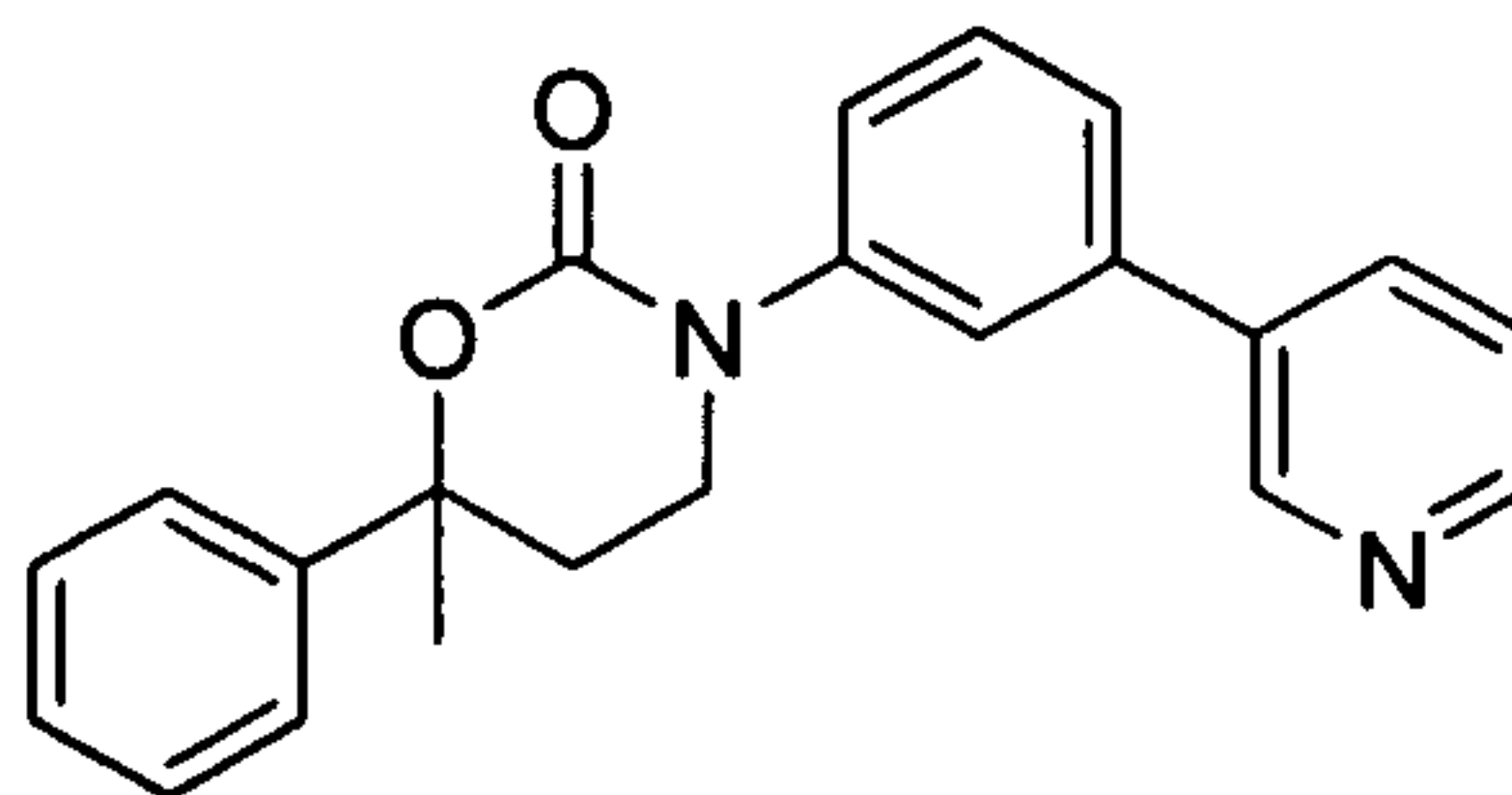
The title compound was prepared following procedures analogous to those in Example 9 using 4-(methylsulfonamidomethyl)phenylboronic acid. LC-MS Method 3, t_R = 1.19 min, m/z = 450.9. ^1H NMR ($CDCl_3$) 1.70 (s, 3H), 2.35-2.60 (m, 2H), 2.95 (s,

- 129 -

3H), 3.35 (m, 1H), 3.60 (m, 1H), 4.40 (m, 2H), 4.65 (b, 1H), 6.95-7.20 (m, 3H), 7.30-7.60 (m, 11H).

EXAMPLE 20

6-methyl-6-phenyl-3-(3-(pyridin-3-yl)phenyl)-1,3-oxazinan-2-one



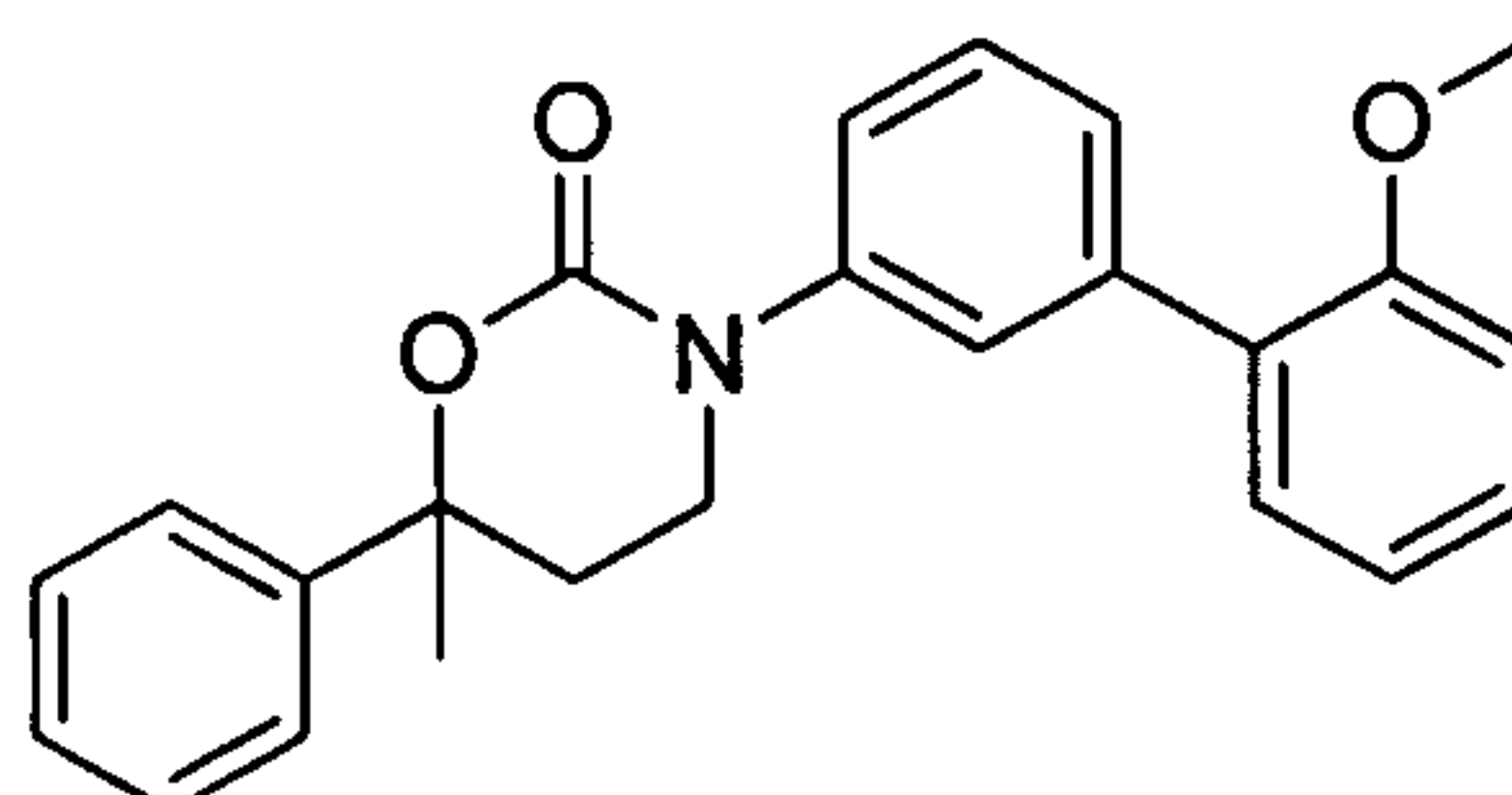
5

The title compound was prepared following procedures analogous to those in Example 9 using 3-pyridylboronic acid. LC-MS Method 2, t_R = 1.819 min, m/z = 345.1. ^1H NMR (CDCl_3) 1.80 (s, 3H), 2.45-2.65 (m, 2H), 3.40 (m, 1H), 3.62 (m, 1H), 7.30-7.60 (m, 8H), 7.85 (m, 1H), 8.40 (m, 1H), 8.75 (m, 1H), 9.00 (m, 1H), 9.30-9.50 (b, 2H).

10

EXAMPLE 21

3-(2'-methoxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



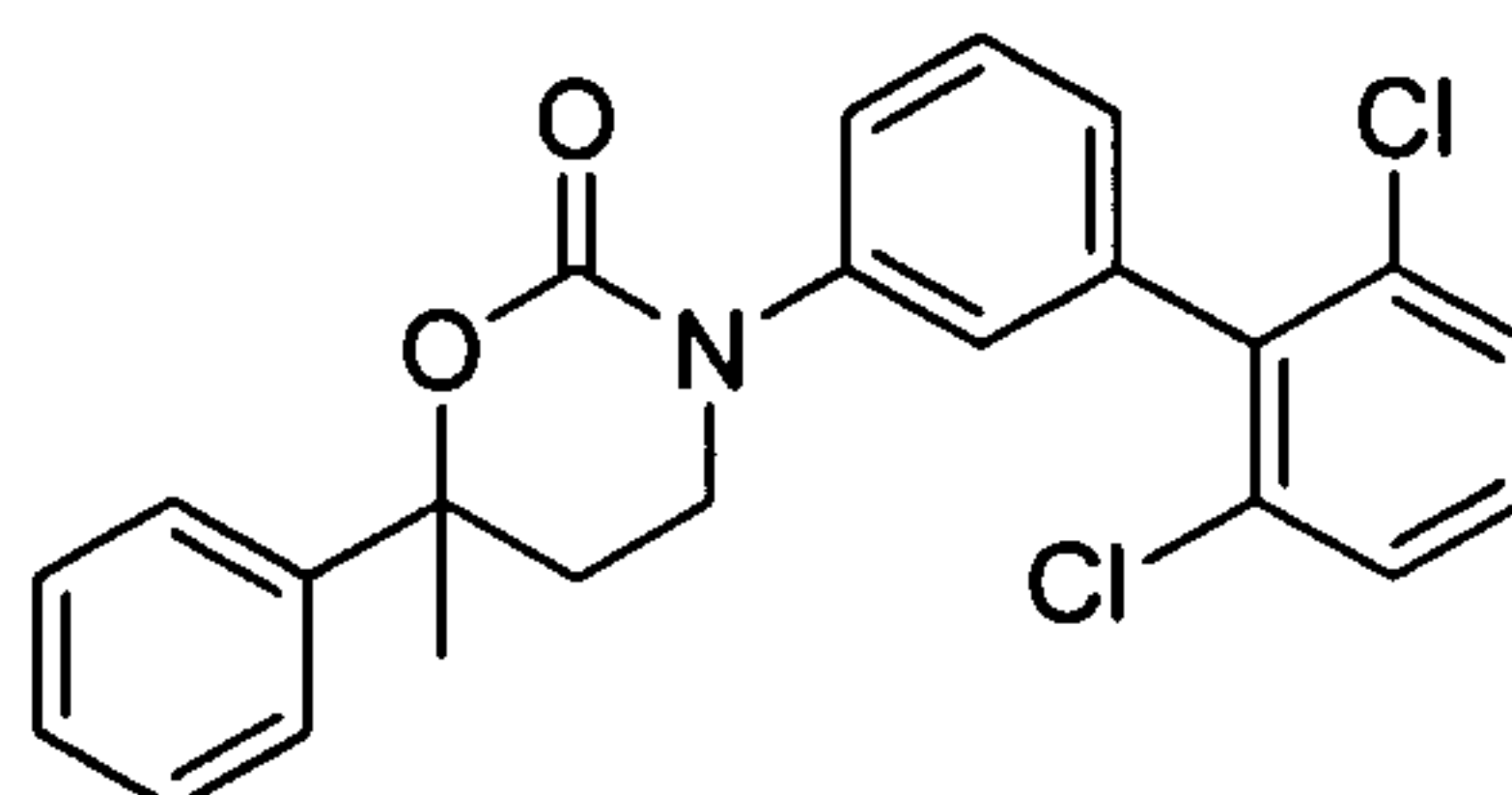
15

The title compound was prepared following procedures analogous to those in Example 9 using 2-methoxyphenylboronic acid. LC-MS Method 3, t_R = 1.55 min, m/z = 374.1. ^1H NMR (CDCl_3) 1.69 (s, 3H), 2.36 (m, 1H), 2.46 (m, 1H), 3.31 (m, 1H), 3.52 (m, 1H), 4.5 (m, 1H), 5.17 (m, 1H), 7.06 (m, 1H), 7.12 (m, 1H), 7.18 (m, 1H), 7.28 (m, 3H), 7.33 (m, 2H), 7.38 (m, 4H), 7.45 (m, 1H).

20

EXAMPLE 22

3-(2',6'-dichlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those in Example 9 using 2,6-dichlorophenylboronic acid. LC-MS Method 3, t_R = 1.676 min, m/z = 412. ^1H NMR (CDCl_3) 1.69 (s, 3H), 2.36 (m, 1H), 2.45 (m, 1H), 3.30 (m, 1H),

25

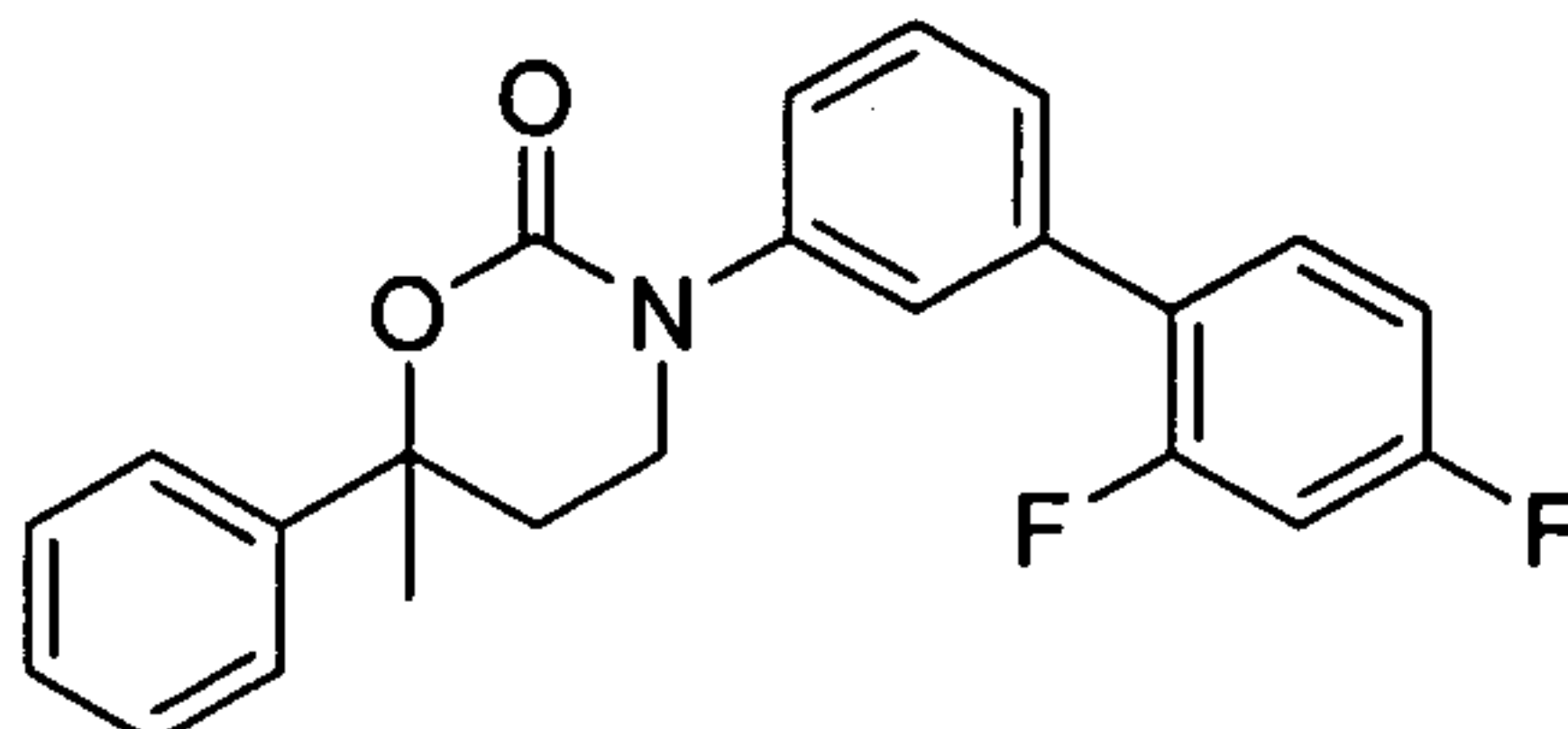
- 130 -

3.50 (m, 1H), 7.05 (m, 2H), 7.16 (m, 1H), 7.25 (m, 2H), 7.30 (m, 1H), 7.32 (m, 1H), 7.40 (m, 5H).

5

EXAMPLE 23

3-(2',4'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

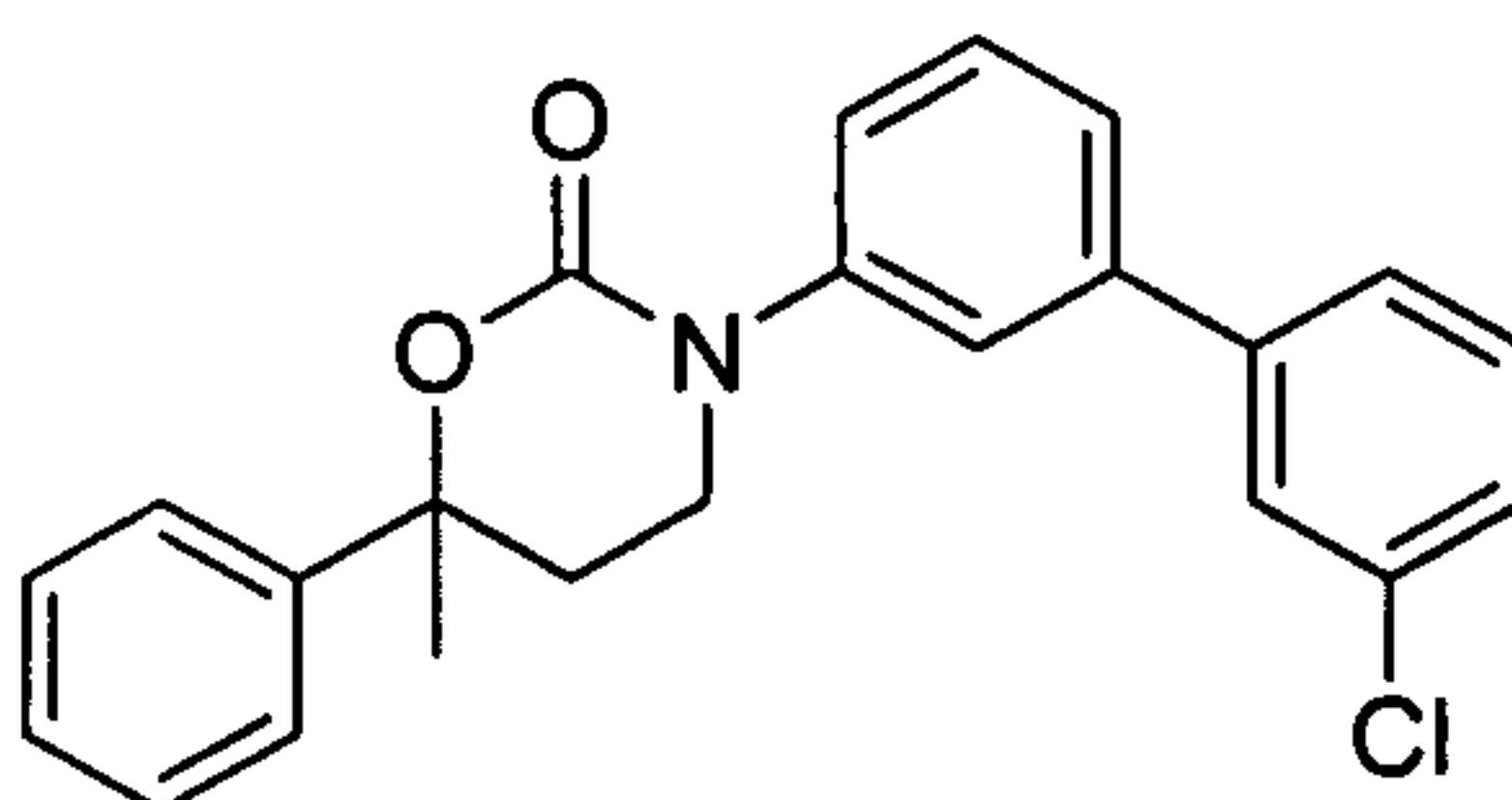


The title compound was prepared following procedures analogous to those in Example 9 using 2,4-difluorophenylboronic acid. LC-MS Method 3, t_R = 1.595 min, m/z = 380.1. ^1H NMR ($CDCl_3$) 1.69 (s, 3H), 2.30-2.50 (m, 2H), 3.28 (m, 1H), 3.50 (m, 1H), 6.86 (m, 2H), 7.13 (m, 1H), 7.21 (m, 1H), 7.28 (m, 3H), 7.35 (m, 5H).

15

EXAMPLE 24

3-(3'-chlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

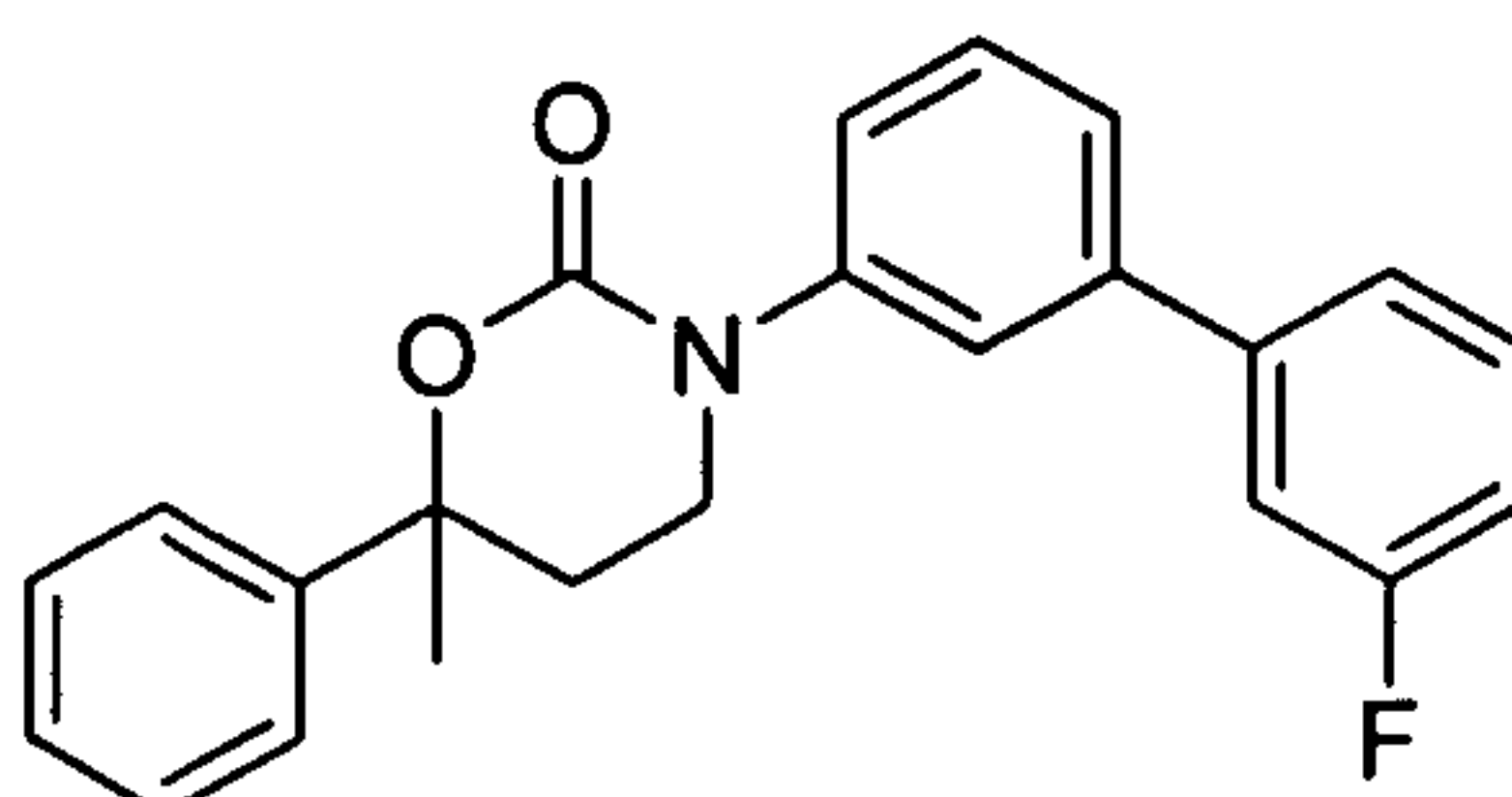


The title compound was prepared following procedures analogous to those in Example 9 using 3-chlorophenylboronic acid. LC-MS Method 3, t_R = 1.67 min, m/z = 378. ^1H NMR ($CDCl_3$) (s, 3H), 2.36 (m, 1H), 2.48(m, 1H), 3.28 (m, 1H), 3.49 (m, 1H), 7.12 (m, 1H), 7.27 (m, 4H), 7.32 (m, 3H), 7.38 (m, 4H), 7.42 (m, 1H).

20

EXAMPLE 25

3-(3'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



25

The title compound was prepared following procedures analogous to those in Example 9 using 3-fluorophenylboronic acid. LC-MS Method 3, t_R = 1.69 min, m/z =

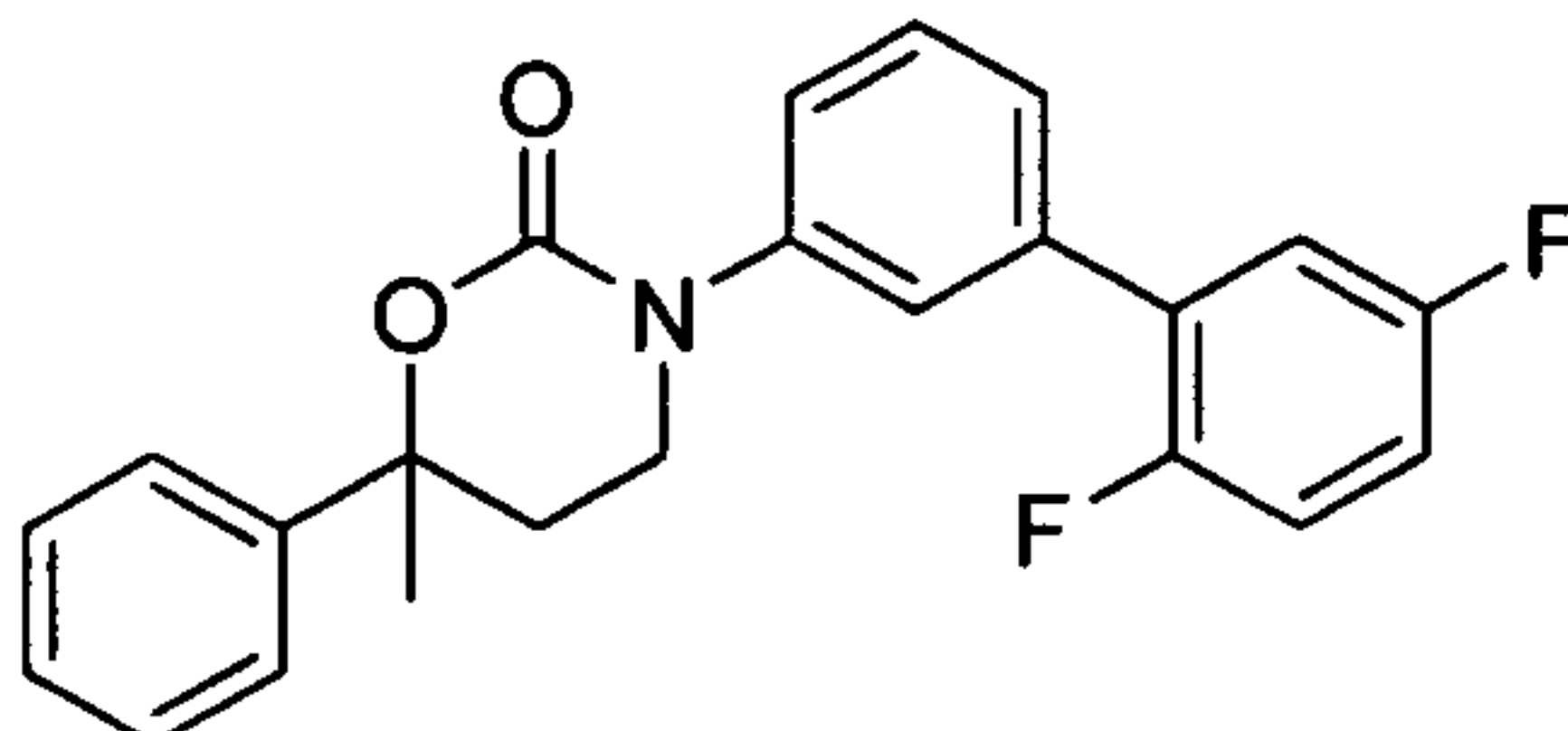
- 131 -

362.1. ¹H NMR (CDCl₃) 1.68 (s, 3H), 2.46 (m, 1H), 2.57(m, 1H), 3.38 (m, 1H), 3.62 (m, 1H), 7.06 (m,1H), 7.17 (m, 1H), 7.23 (m, 1H), 7.32 (m, 2H), 7.38 (m,2H), 7.48 (m, 6H).

5

EXAMPLE 26

3-(2',5'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

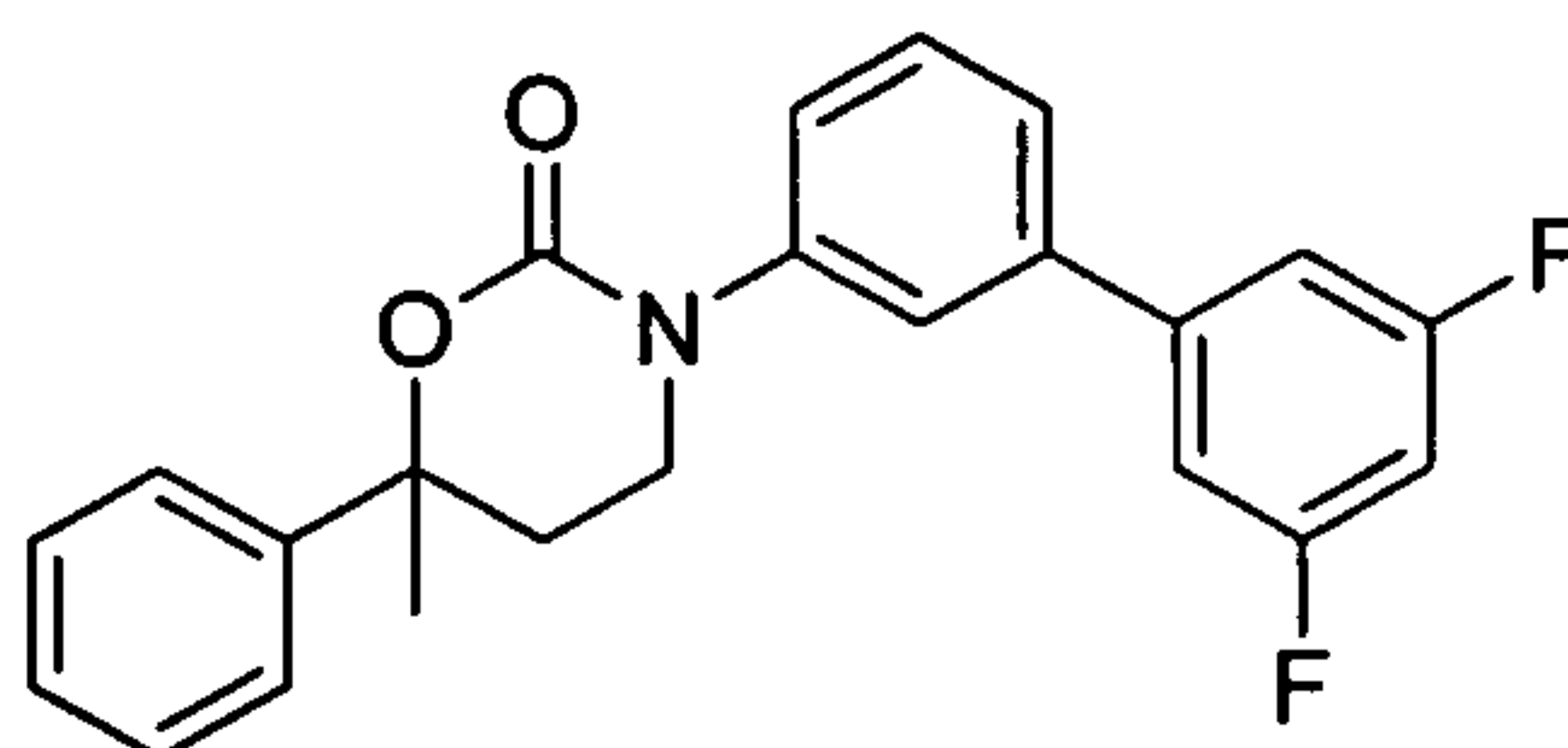


The title compound was prepared following procedures analogous to those in Example 9 using 2,5-difluorophenylboronic acid. LC-MS Method 3, t_R = 1.686 min, m/z = 380.1. ¹H NMR (CDCl₃) 1.77 (s, 3H), 2.42 (m, 1H), 2.55 (m, 1H), 3.35 (m, 1H), 3.58 (m, 1H), 6.98 (m, 1H), 7.08 (m, 2H), 7.23 (m, 1H), 7.35 (m, 2H), 7.43 (m, 6H).

15

EXAMPLE 27

3-(3',5'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

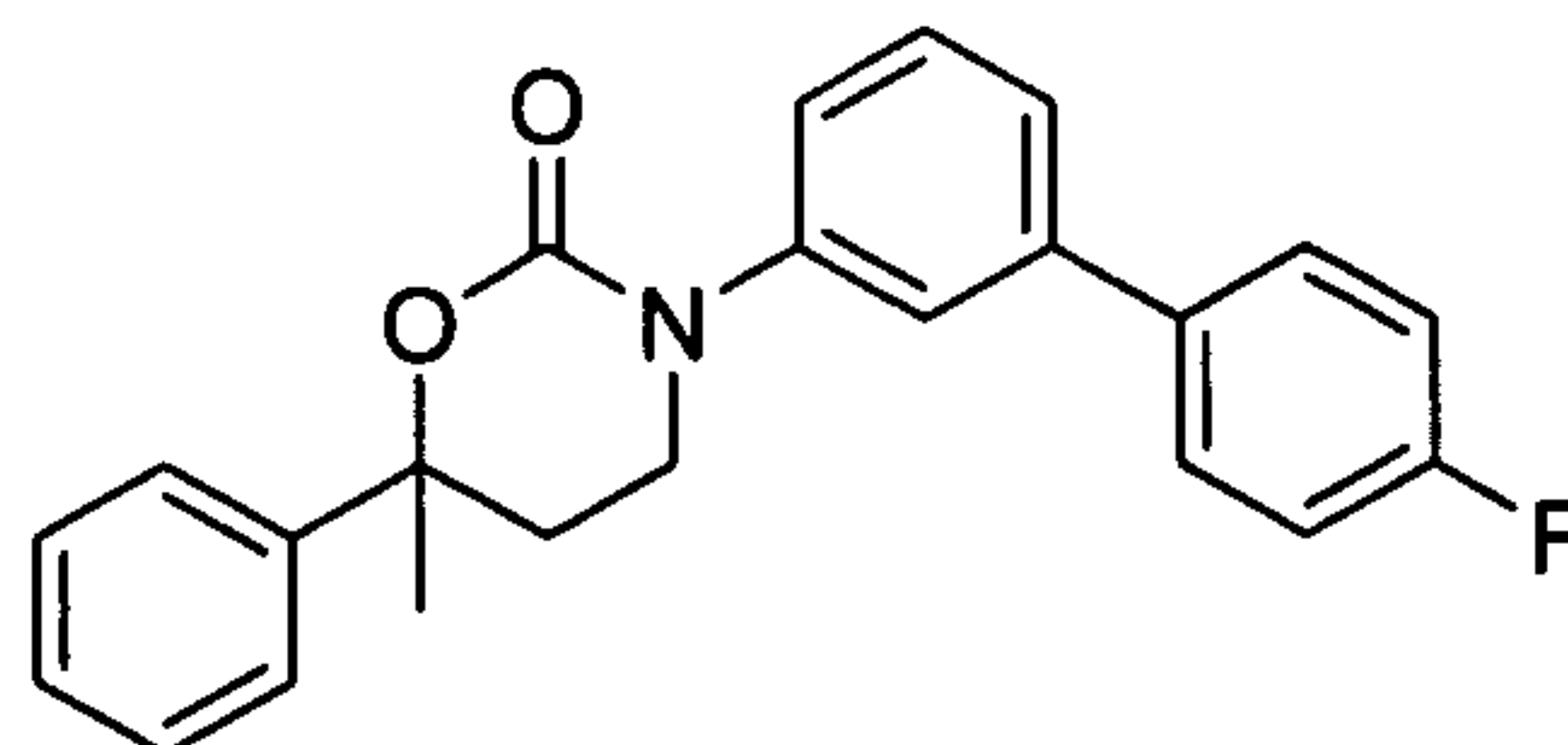


The title compound was prepared following procedures analogous to those in Example 9 using 3,5-difluorophenylboronic acid. LC-MS Method 3, t_R = 1.468 min, m/z = 379.9. ¹H NMR (CDCl₃) 1.78 (s, 3H), 2.42 (m, 1H), 2.56 (m, 1H), 3.37(m, 1H), 3.58 (m, 1H), 6.78 (m, 1H), 7.03 (m, 2H), 7.23 (m, 1H), 7.32 (m, 1H), 7.38 (m, 1H), 7.42 (m, 2H), 7.48(m, 4H).

20

EXAMPLE 28

3-(4'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



25

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The title compound was prepared following procedures analogous to those in Example 9 using 4-fluorophenylboronic acid. LC-MS Method 3, $t_R = 1.38$ min, $m/z = 362.1$. ^1H NMR (CDCl_3) 1.77 (s, 3H), 2.42 (m, 1H), 2.55 (m, 1H), 3.35 (m, 1H), 3.58 (m, 1H), 7.13 (m, 3H), 7.32 (m, 1H), 7.36 (m, 1H), 7.39 (m, 2H), 7.48 (m, 6H).

5 Chiral preparative SFC using a ChiralCel-AS, 400×25 mm I.D, $20 \mu\text{m}$ (Daicel Chemical Industries, Ltd) column maintained at 35°C eluted with 60:40 supercritical CO_2 /0.1% diethylamine in MeOH at a flow rate of 70 mL min^{-1} and a nozzle pressure of 100 bar afforded the two enantiomers.

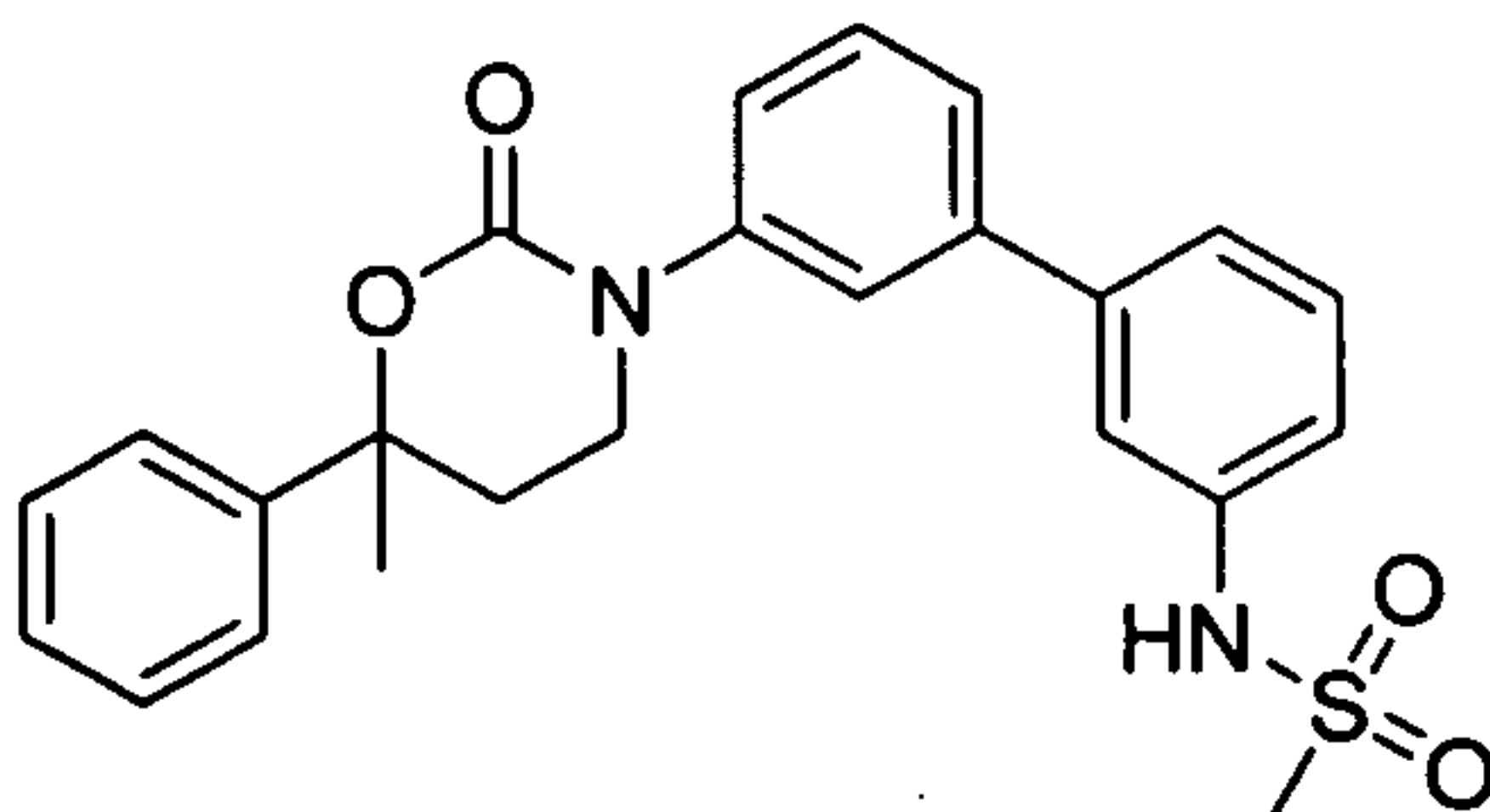
Isomer 1: LC-MS Method 3, $t_R = 1.38$ min, $m/z = 362.1$. ^1H NMR (CDCl_3)
10 1.81 (s, 3H), 2.41-2.50 (m, 2H), 3.35 (m, 1H), 3.51 (m, 1H), 7.15 (m, 3H), 7.33-7.52 (m, 10H).

Isomer 2: LC-MS Method 3, $t_R = 1.392$ min, $m/z = 362.1$. ^1H NMR (CDCl_3)
1.70 (s, 3H), 2.32-2.50 (m, 2H), 3.28 (m, 1H), 3.51 (m, 1H), 7.05 (m, 3H), 7.22-7.45(m, 10H).

15

EXAMPLE 29

N-(3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-yl)methanesulfonamide

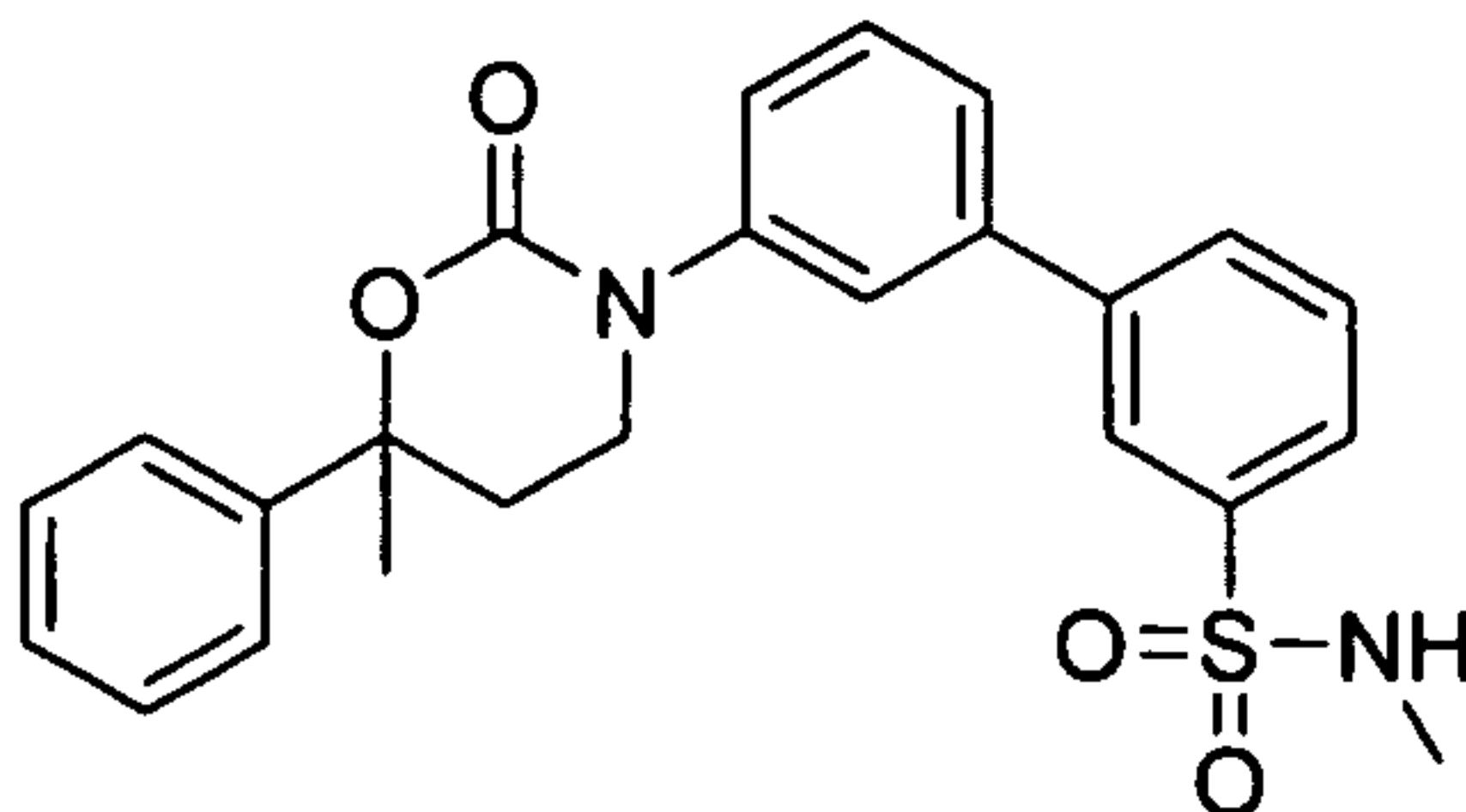


The title compound was prepared following procedures analogous to those in
20 Example 9 using 3-(methylsulfonylamino)phenylboronic acid. LC-MS Method 3, $t_R = 1.626$ min, $m/z = 437.1$. ^1H NMR (CDCl_3) 1.70 (s, 3H), 2.34-2.50 (m, 2H), 2.98 (s, 3H), 3.21 (m, 1H), 3.51 (m, 1H), 6.48 (m, 1H), 7.05 (m, 1H), 7.18 (m, 1H), 7.25-7.40 (m, 11H).

25

EXAMPLE 30

N-methyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-sulfonamide

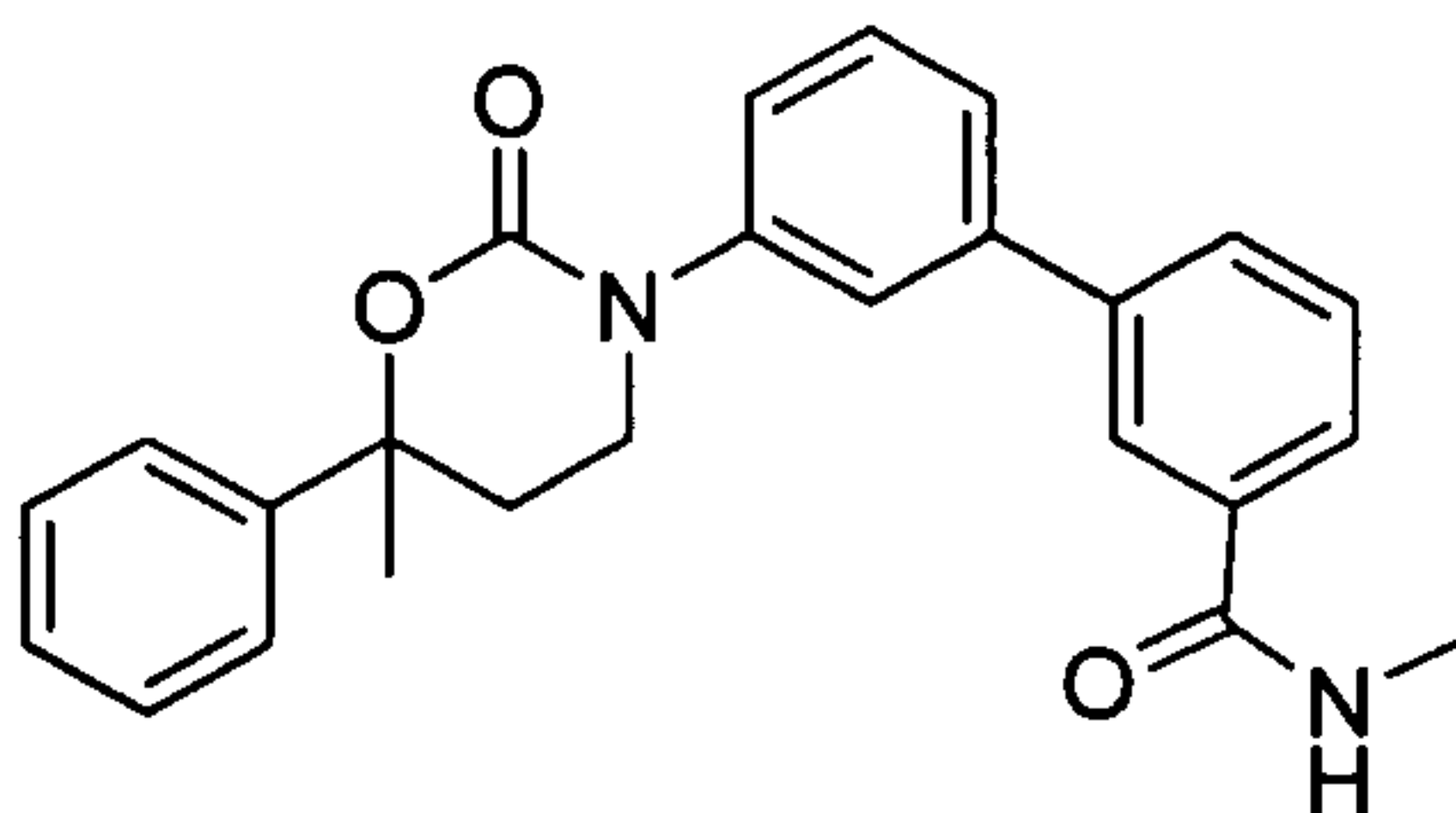


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The title compound was prepared following procedures analogous to those in Example 9 using 3-(methylaminosulfonyl)phenylboronic acid. LC-MS Method 3, t_R = 1.184 min, m/z = 437.1. ^1H NMR (CDCl_3) 1.11-1.13 (m, 6H), 1.70(m, 3H), 2.40-2.50 (m, 1H), 2.50-2.60 (m, 1H), 3.20-3.49 (s, 4H), 3.49-3.65 (m, 2H), 7.15-7.21 (m, 1H),
5 7.31-7.56 (m, 8H), 7.62-7.68(m, 2H), 7.90-7.96(m, 2H).

EXAMPLE 31

N-methyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-carboxamide

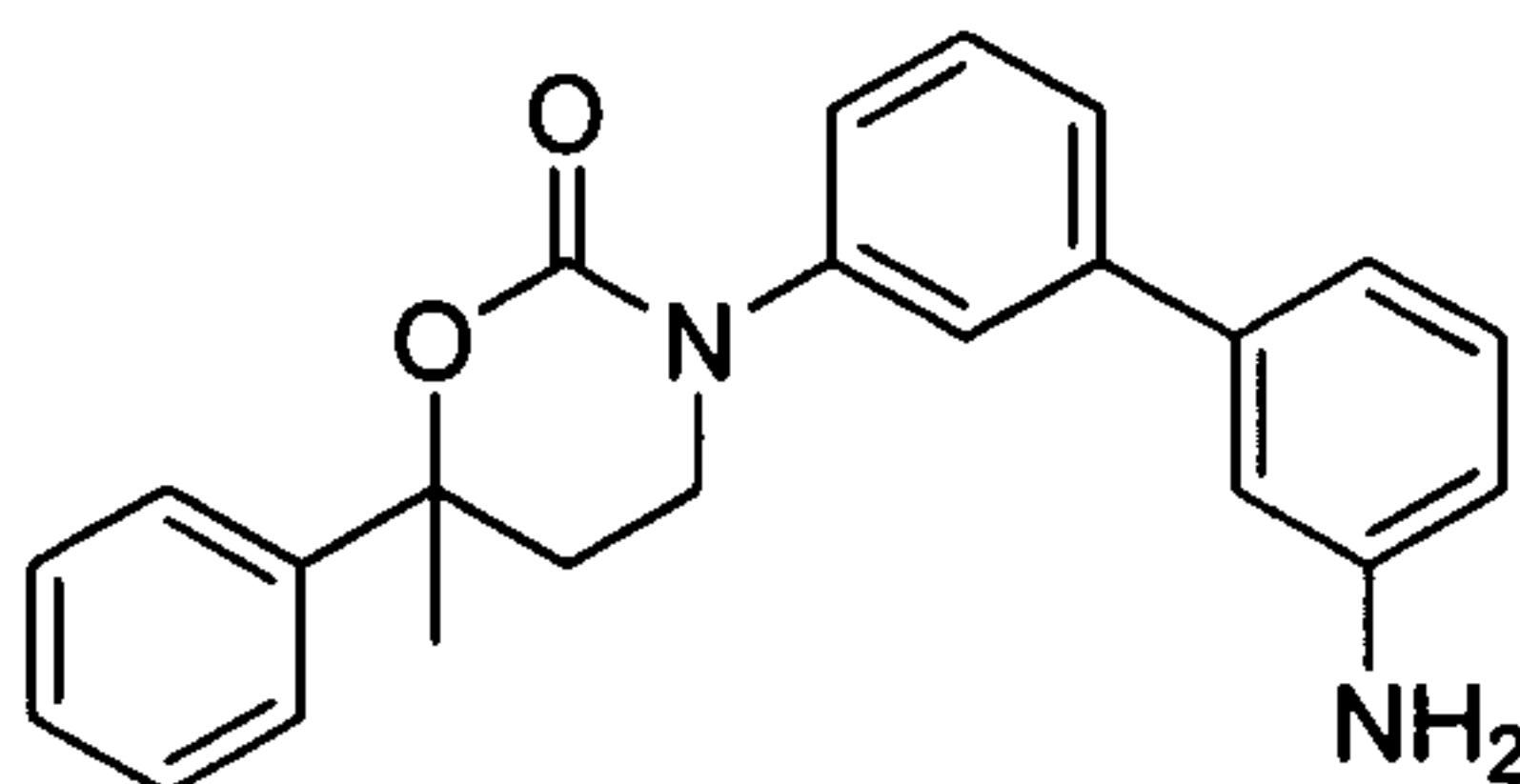


10

The title compound was prepared following procedures analogous to those in Example 9 using 3-(methylcarbamoyl)phenylboronic acid. LC-MS Method 3, t_R = 1.11 min, m/z = 401.1. ^1H NMR (CDCl_3) 1.70 (s, 3H), 2.35 (m, 1H), 2.46 (m, 1H), 2.95 (s, 3H), 3.30 (m, 1H), 3.50 (m, 1H), 6.45 (m, 1H), 7.17 (m, 1H), 7.30 (m, 2H),
15 7.38 (m, 6H), 7.55 (m, 1H), 7.65 (m, 1H), 7.80 (s, 1H).

EXAMPLE 32

3-(3'-aminobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



20

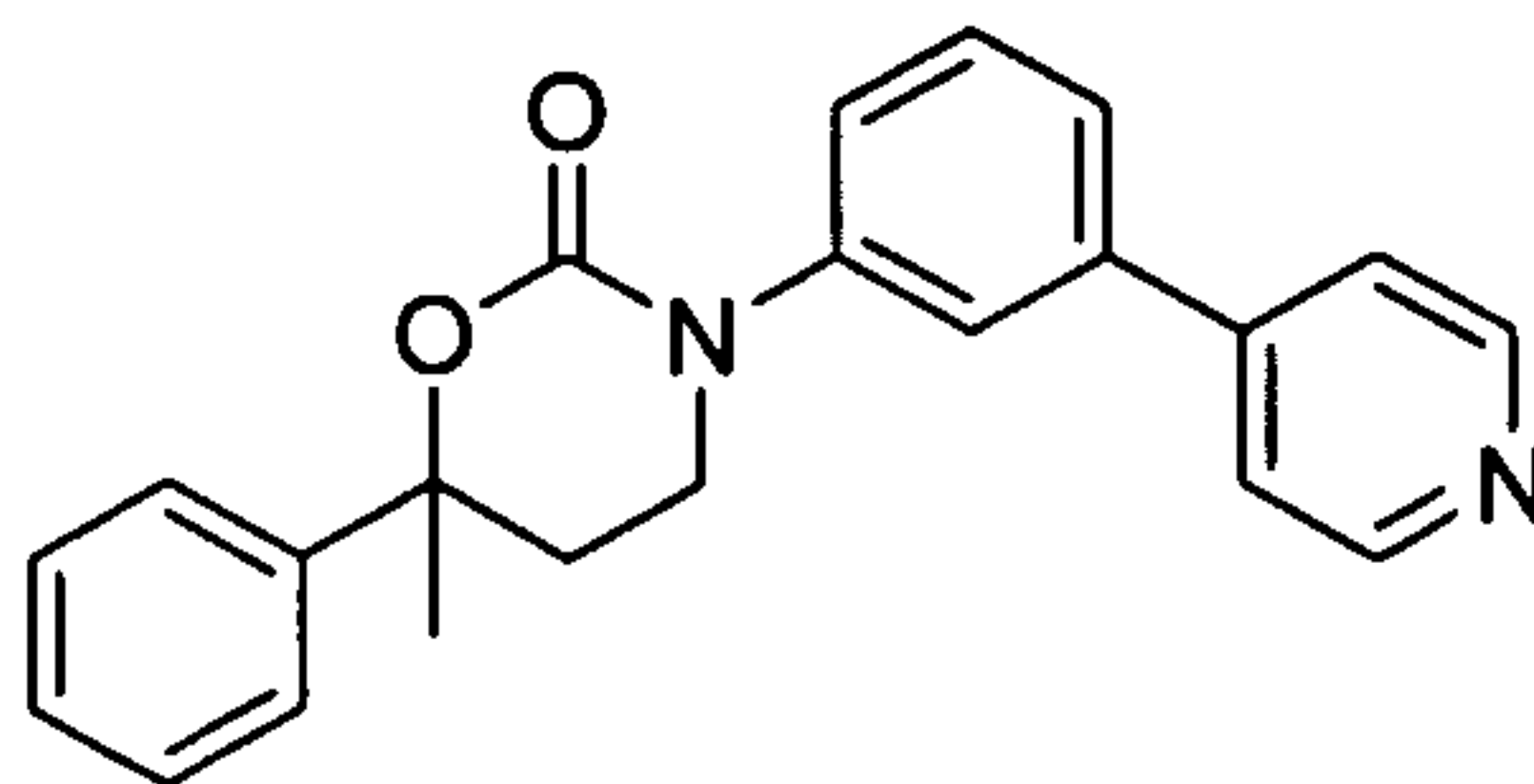
The title compound was prepared following procedures analogous to those in Example 9 using 3-aminophenylboronic acid. LC-MS Method 2, t_R = 1.761 min, m/z = 359.1. ^1H NMR (CDCl_3) 1.70 (s, 3H), 2.30-2.50 (m, 2H), 3.30 (m, 1H), 3.50 (m, 1H), 6.62 (m, 1H), 6.80-6.90 (m, 2H), 7.05-7.47 (m, 10H).

25

EXAMPLE 33

6-methyl-6-phenyl-3-(3-(pyridin-4-yl)phenyl)-1,3-oxazinan-2-one

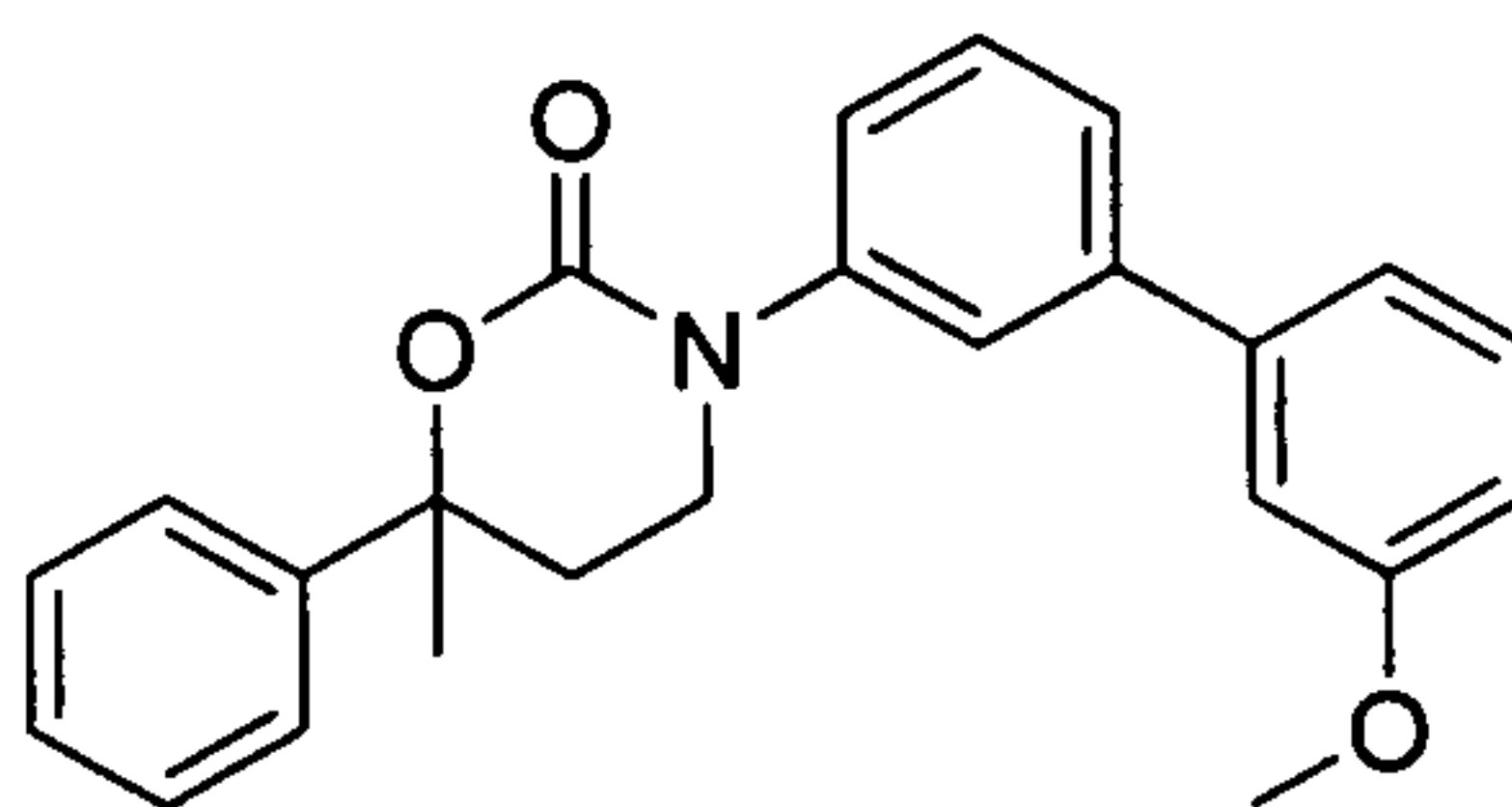
- 134 -



The title compound was prepared following procedures analogous to those in Example 9 using 4-pyridylboronic acid. LC-MS Method 2, t_R = 1.329 min, m/z = 345.1. ^1H NMR ($CDCl_3$) 1.70 (s, 3H), 2.30-2.50 (m, 2H), 3.30 (m, 1H), 3.50 (m, 1H), 4.10 (m, 2H), 7.27-7.50 (m, 9H), 8.60 (b, 1H).

EXAMPLE 34

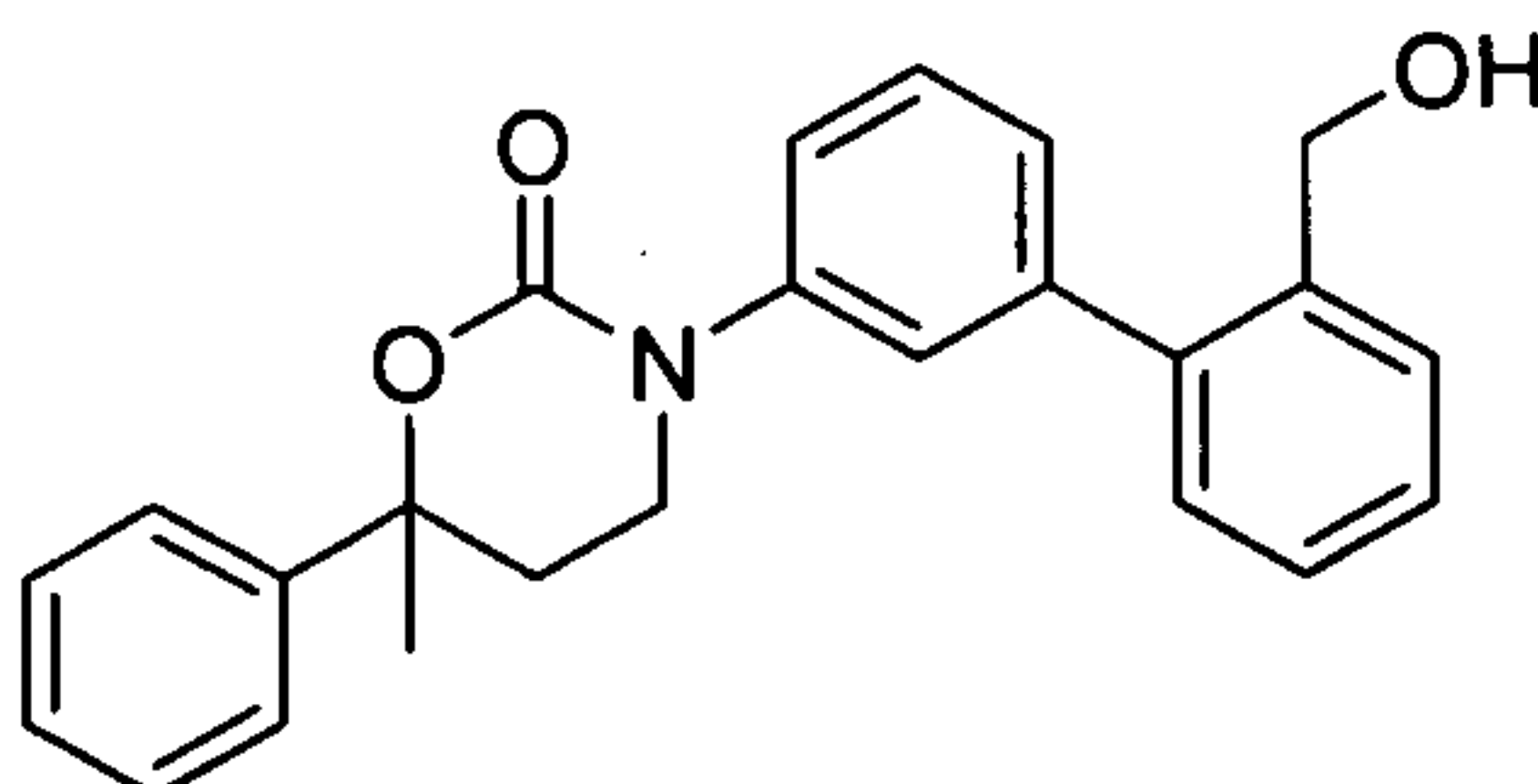
3-(3'-methoxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those in Example 9 using 3-methoxyphenylboronic acid. LC-MS Method 3, t_R = 1.392 min, m/z = 374.1. ^1H NMR ($CDCl_3$) 1.70 (s, 3H), 2.30-2.50 (m, 2H), 3.30 (m, 1H), 3.50 (m, 1H), 3.80 (s, 3H), 6.85 (m, 1H), 7.00-7.45 (m, 12H).

EXAMPLE 35

3-(2'-(hydroxymethyl)biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



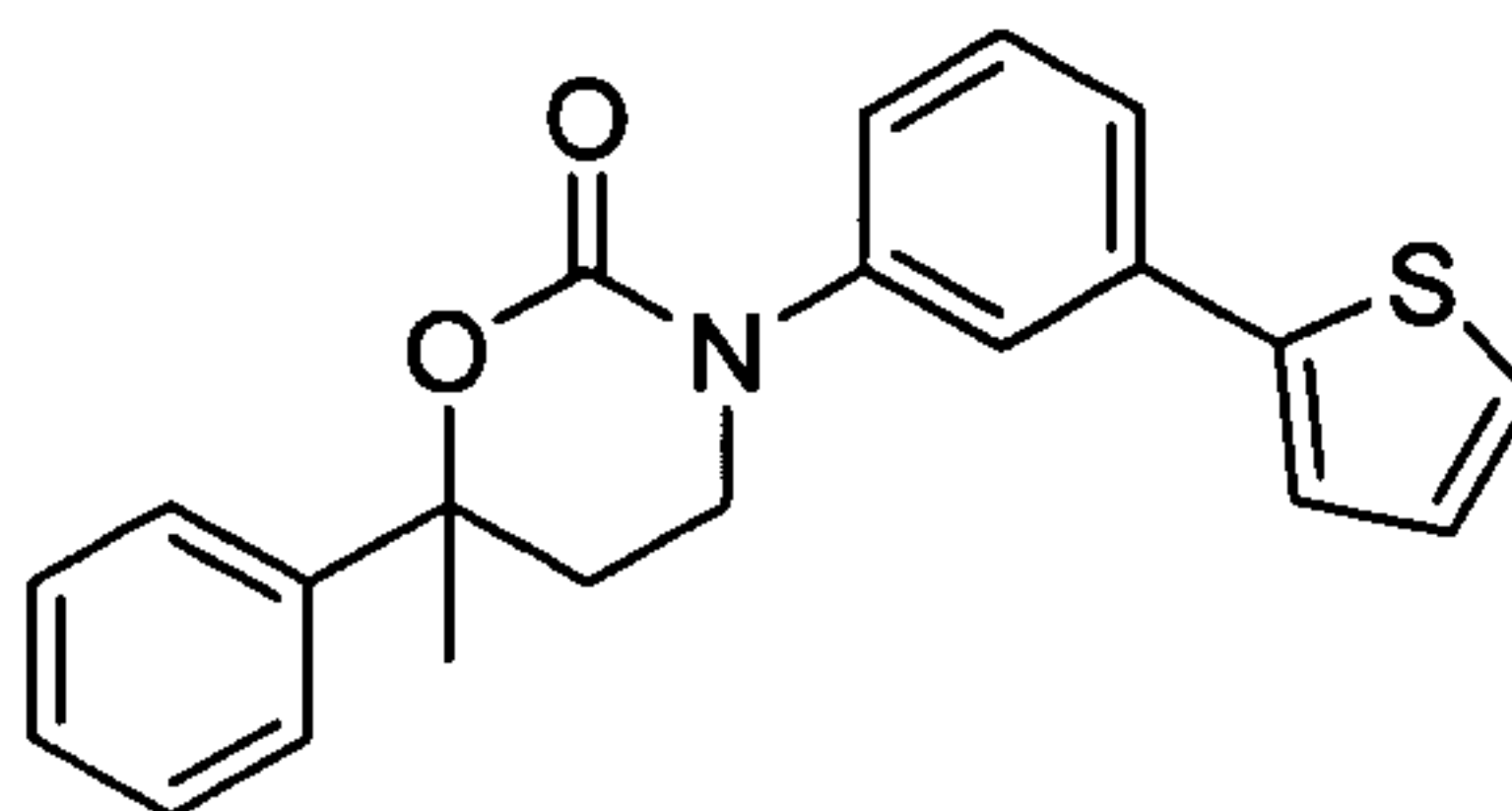
The title compound was prepared following procedures analogous to those in Example 9 using 2-hydroxymethylphenylboronic acid. LC-MS Method 3, t_R = 1.375 min, m/z = 769.3. ^1H NMR ($CDCl_3$) 1.69 (s, 3H), 2.36 (m, 1H), 2.46 (m, 1H), 3.31 (m, 1H), 3.52 (m, 1H), 4.5 (m, 1H), 5.17 (m, 1H), 7.06 (m, 1H), 7.12 (m, 1H), 7.18 (m, 1H), 7.28 (m, 3H), 7.33 (m, 2H), 7.38 (m, 4H), 7.45 (m, 1H).

EXAMPLE 36

6-methyl-6-phenyl-3-(3-(thiophen-2-yl)phenyl)-1,3-oxazinan-2-one

25

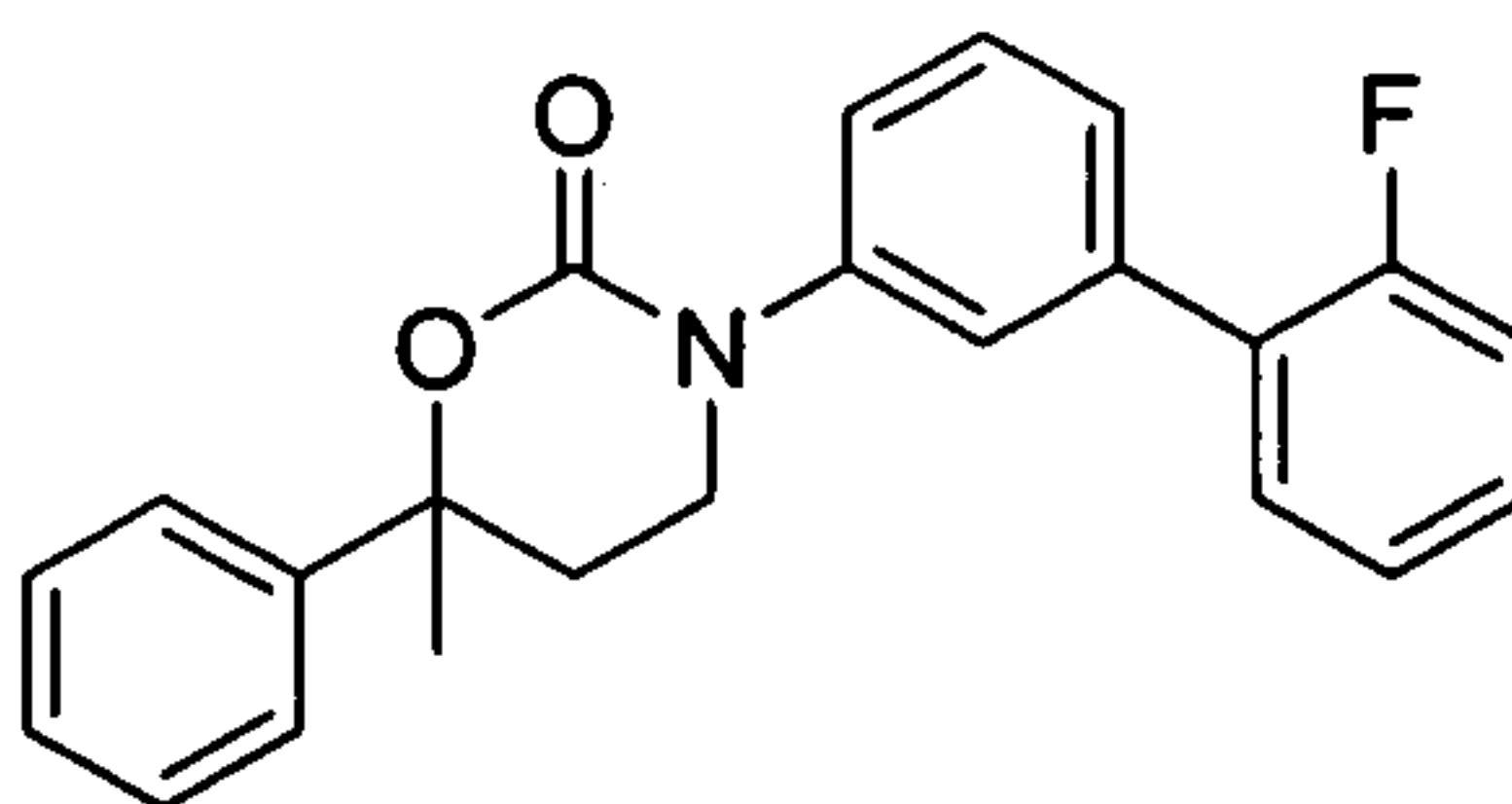
- 135 -



The title compound was prepared following procedures analogous to those in Example 9 using 2-thienylboronic acid. LC-MS Method 3, t_R = 1.721 min, m/z = 350. ^1H NMR ($CDCl_3$) 1.69 (s, 3H), 2.33-2.50 (m, 2H), 3.27 (m, 1H), 3.52 (m, 1H), 3.71 (s, 3H), 6.94 (m, 1H), 7.09 (m, 1H), 7.21-7.40 (m, 11H).

EXAMPLE 37

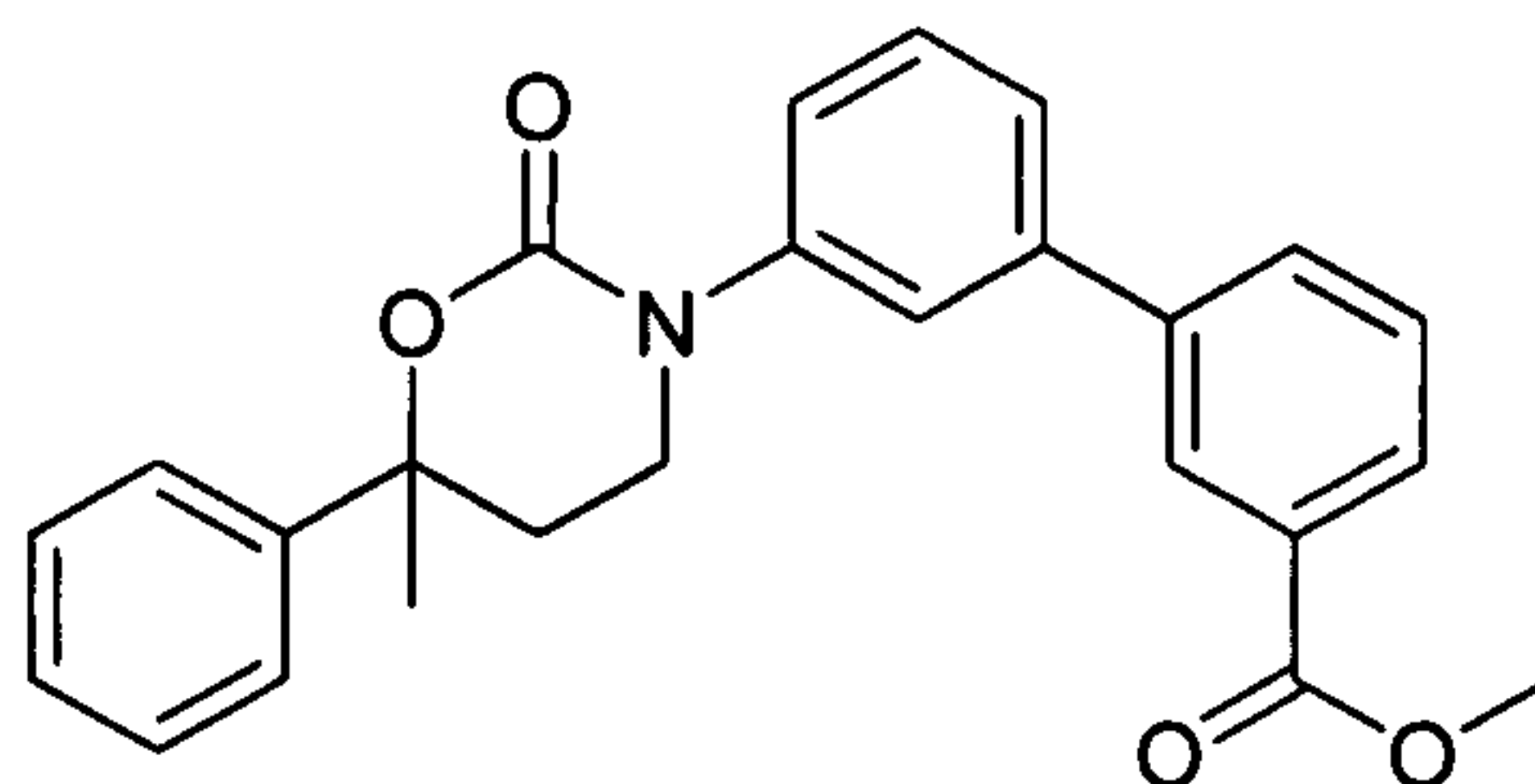
3-(2'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those in Example 9 using 2-fluorophenylboronic acid. LC-MS Method 3, t_R = 1.772 min, m/z = 362.1. ^1H NMR ($CDCl_3$) 1.15 (s, 3H), 2.30-2.53 (m, 2H), 3.30 (m, 1H), 3.50 (m, 1H), 7.08 (m, 3H), 7.25 (m, 2H), 7.32 (m, 3H), 7.38 (m, 5H).

EXAMPLE 38

methyl 3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-carboxylate

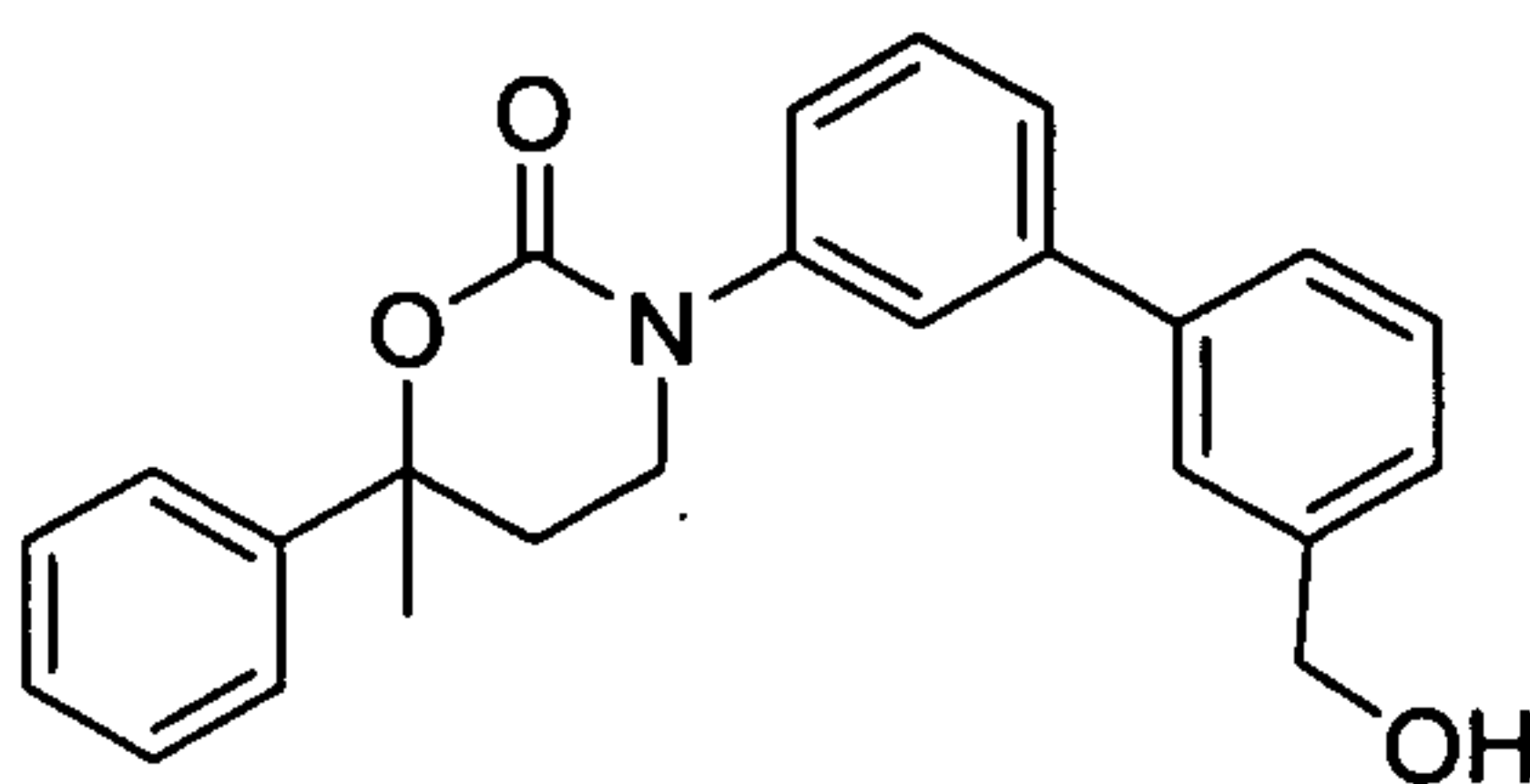


The title compound was prepared following procedures analogous to those in Example 9 using 3-methoxycarbonylphenylboronic acid. LC-MS Method 3, t_R = 1.745 min, m/z = 402.1. ^1H NMR ($CDCl_3$) 1.20 (s, 3H), 2.32-2.50 (m, 2H), 3.30 (m, 1H), 3.55 (m, 1H), 3.89 (s, 3H), 7.10 (m, 1H), 7.30-7.47 (m, 9H), 7.65 (m, 1H), 7.95 (m, 1H), 8.12 (m, 1H).

EXAMPLE 39

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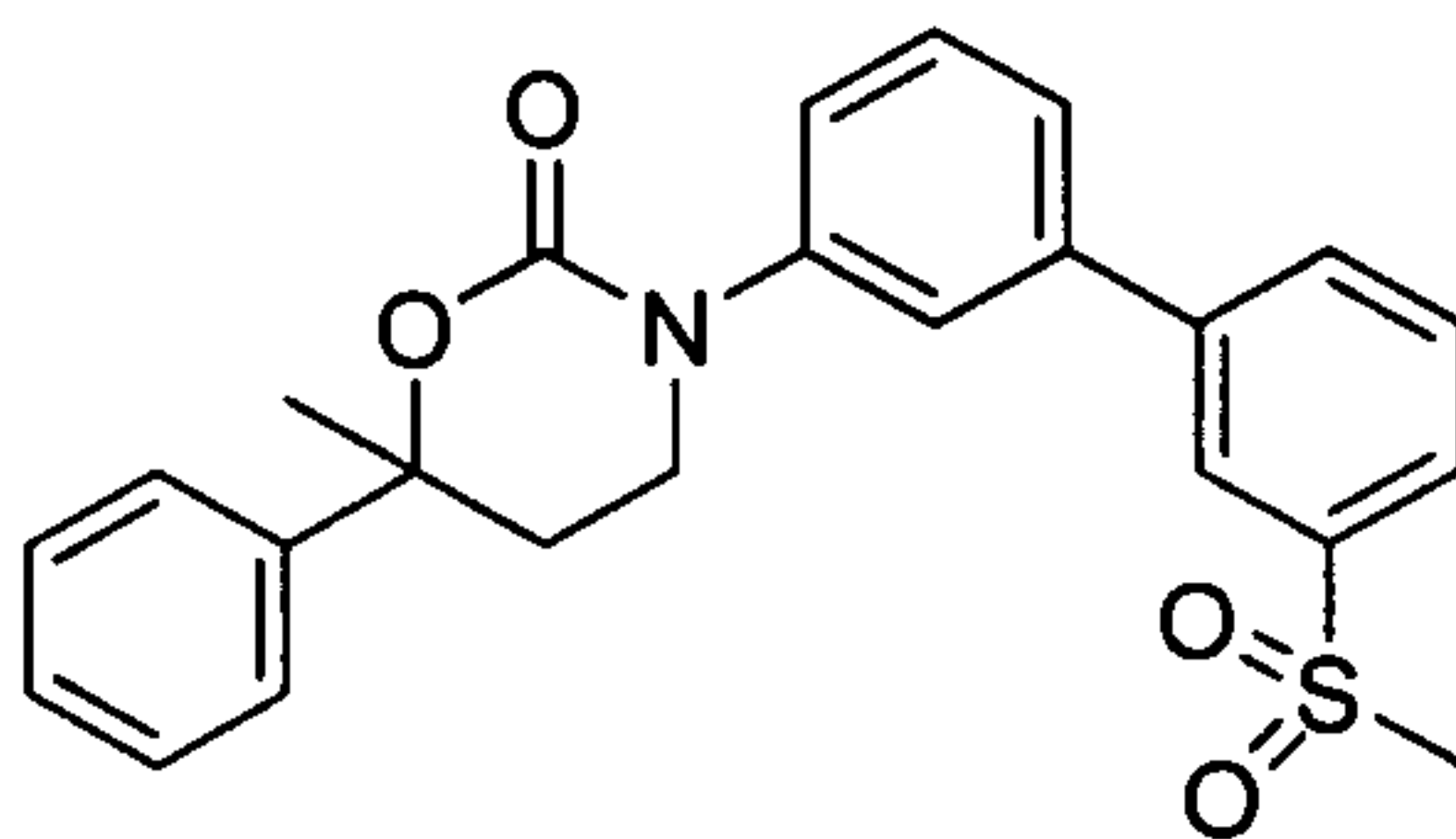
3-(3'-(hydroxymethyl)biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those in Example 9 using 3-hydroxymethylphenylboronic acid. LC-MS Method 3, t_R = 1.35 min, m/z = 374.1. ^1H NMR (CDCl_3) 1.70 (s, 3H), 2.30-2.50 (m, 2H), 3.30 (m, 1H), 4.70 (d, 2H), 7.05 (m, 1H), 7.27-7.55 (m, 13H).

EXAMPLE 40

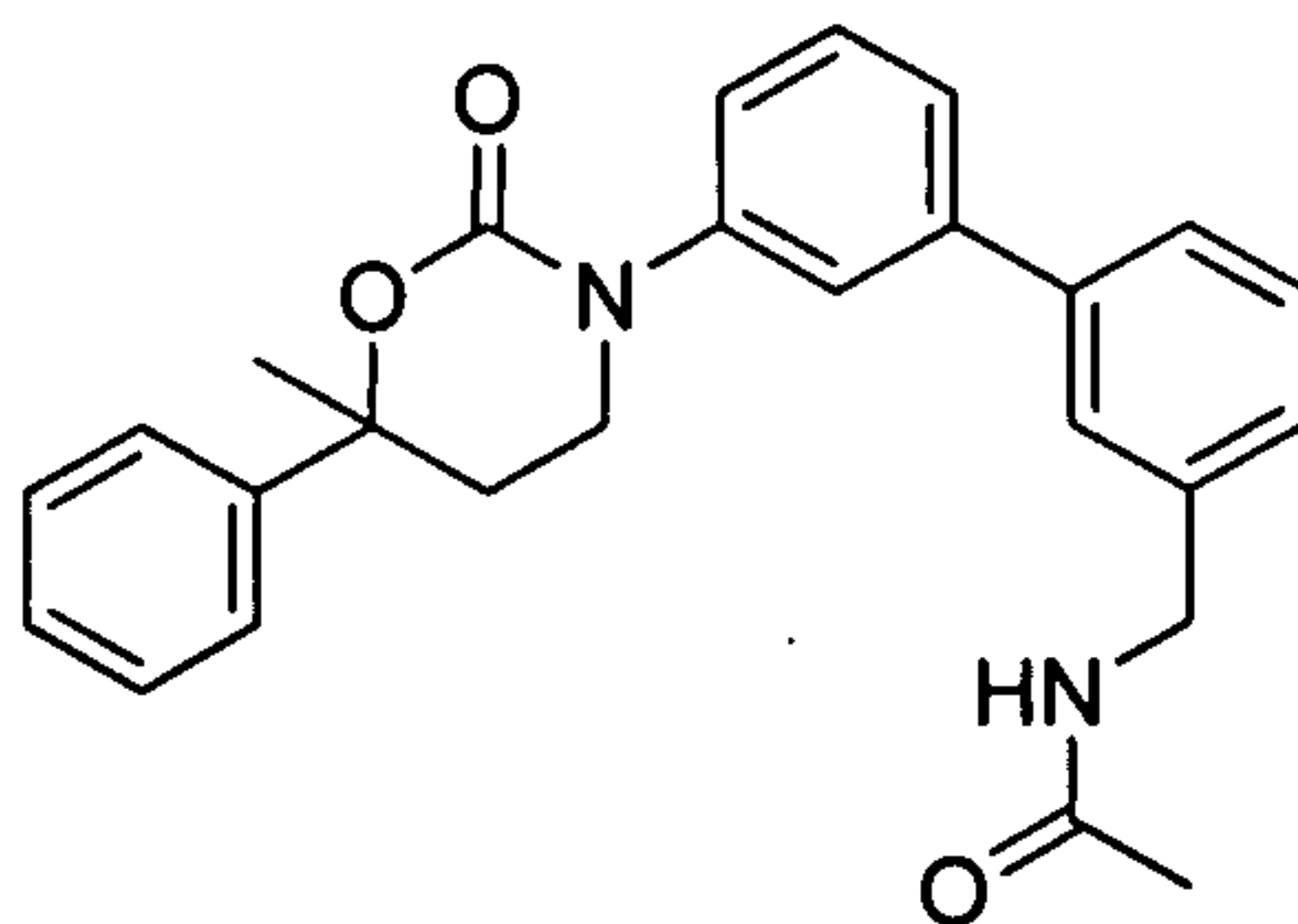
6-methyl-3-(3'-(methylsulfonyl)biphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those in Example 9 using 3-(methylsulfonyl)phenylboronic acid. LC-MS Method 3, t_R = 1.172 min, m/z = 422.1. ^1H NMR (CDCl_3) 1.71 (s, 3H), 2.37-2.44 (m, 1H), 2.46-2.52 (m, 1H), 3.02 (s, 3H), 3.27-3.35 (m, 1H), 3.51-3.58 (m, 1H), 7.11 (d, 1H), 7.26 (m, 1H), 7.35-7.42 (m, 6H), 7.52-7.58 (t, 2H), 7.75 (d, 1H), 7.88 (d, 1H), 8.01 (s, 1H).

EXAMPLE 41

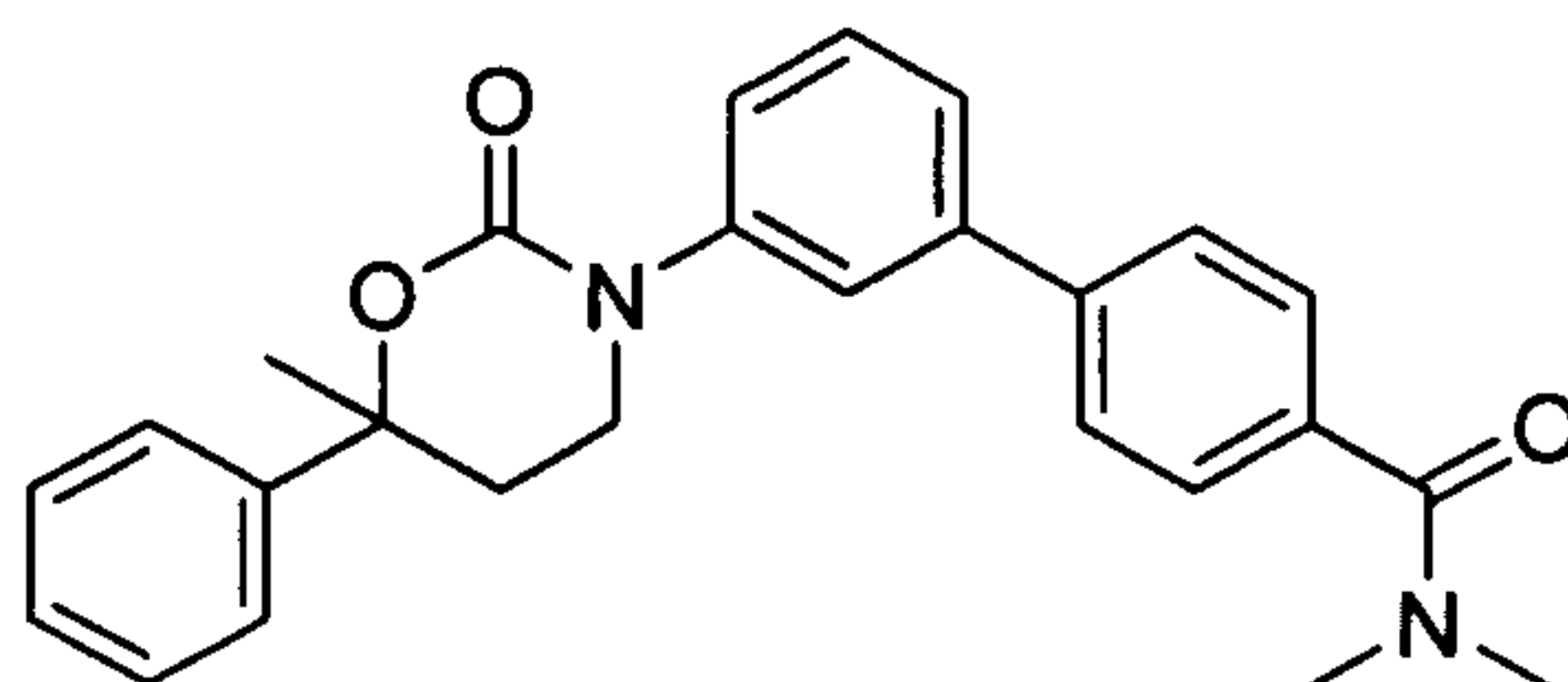
N-((3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-yl)methyl)acetamide



The title compound was prepared following procedures analogous to those in Example 9 using 3-(acetamidomethyl)phenylboronic acid. LC-MS Method 3, t_R = 1.329 min, m/z = 415.2. ^1H NMR (CDCl_3) 1.70 (s, 3H), 2.00 (s, 3H), 2.38 (m, 1H), 2.50 (m, 1H), 3.30 (m, 1H), 3.52 (m, 1H), 4.40 (m, 2H), 6.35 (m, 1H), 7.27-7.62 (m, 19H).

EXAMPLE 42

N,N-dimethyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-carboxamide

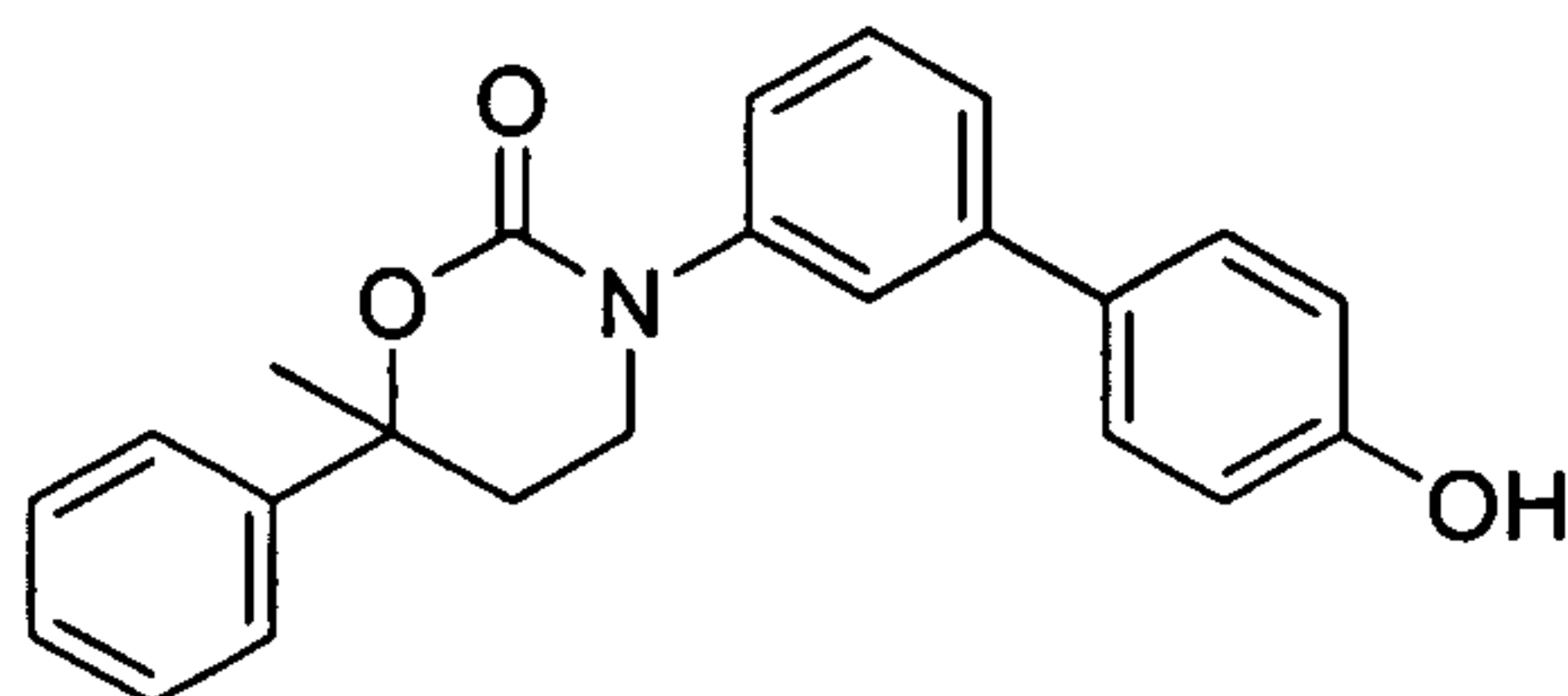


5 The title compound was prepared following procedures analogous to those in Example 9 using 4-(dimethylcarbamoyl)phenylboronic acid. LC-MS Method 3, t_R = 1.157 min, m/z = 415.1. ^1H NMR ($CDCl_3$) 1.70 (s, 2H), 2.30-2.50 (m, 2H), 2.85 (m, 1H), 2.97 (s, 3H), 3.10 (s, 3H), 3.30 (m, 1H), 3.50 (m, 1H), 7.00-7.60 (m, 14H).

10

EXAMPLE 43

3-(4'-hydroxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

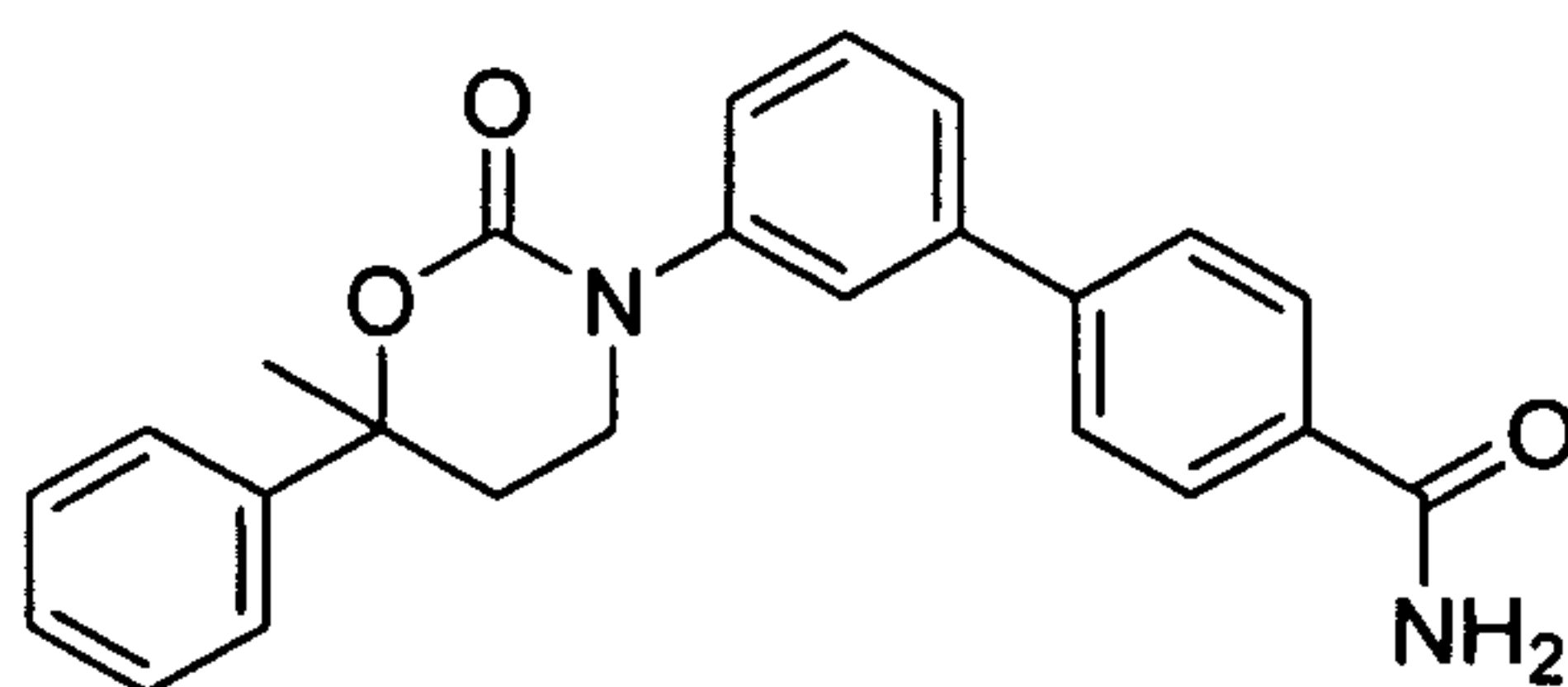


15

The title compound was prepared following procedures analogous to those in Example 9 using 4-hydroxyphenylboronic acid. LC-MS Method 3, t_R = 1.381 min, m/z = 360.1. ^1H NMR ($CDCl_3$) 1.70 (s, 3H), 2.35-2.50 (m, 2H), 3.30 (m, 1H), 3.50 (m, 1H), 6.80 (m, 2H), 7.0 (m, 1H), 7.20-7.65 (m, 12H).

EXAMPLE 44

3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-carboxamide



20

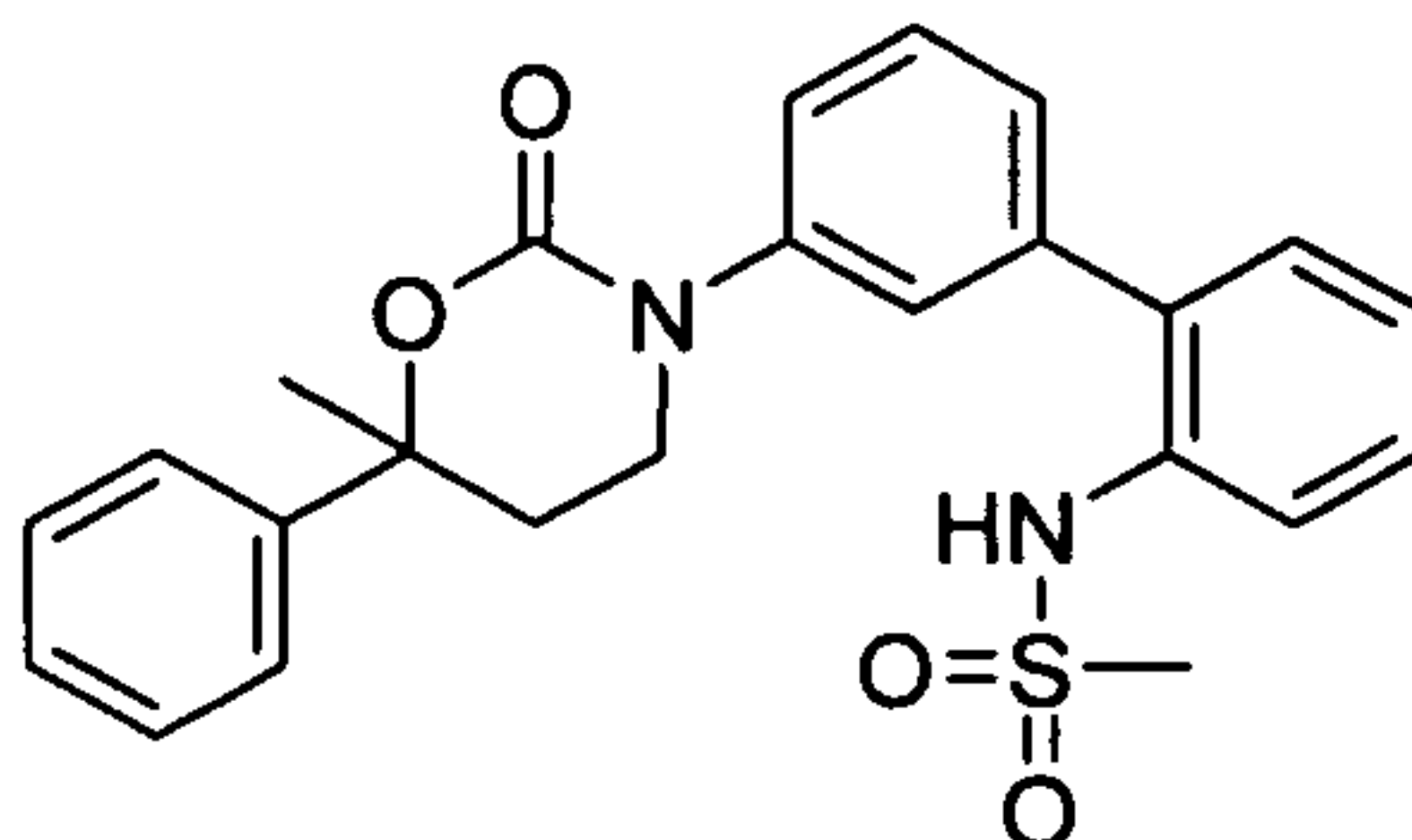
25

The title compound was prepared following procedures analogous to those in Example 9 using 4-(carbamoyl)phenylboronic acid. LC-MS Method 2, t_R = 1.999 min, m/z = 386.9. ^1H NMR ($CDCl_3$) 1.79 (s, 3H), 1.930 (s, 3H), 2.46 (m, 1H), 2.52 (m, 1H), 3.38 (m, 1H), 3.62 (m, 1H), 6.46 (m, 1H), 7.26 (m, 1H), 7.2 (m, 1H), 7.38 (m, 2H), 7.43 (m, 5H), 7.48 (m, 1H), 7.13 (m, 2H), 7.17 (m, 1H), 7.88 (m, 1H).

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EXAMPLE 45

N-(3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-2-yl)methanesulfonamide

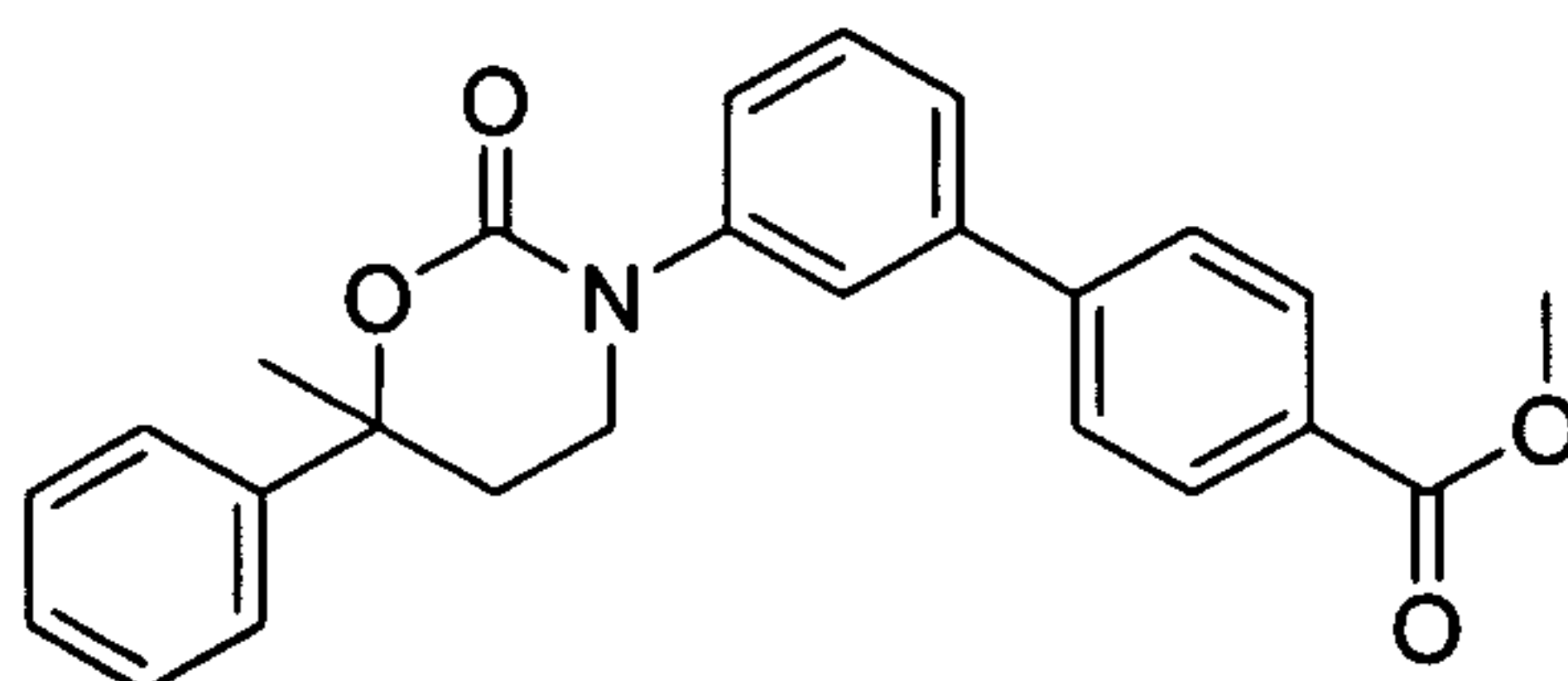


The title compound was prepared following procedures analogous to those in Example 9 using 2-(methylsulfonylamino)phenylboronic acid. LC-MS Method 3, t_R = 1.167 min, m/z = 437.1. ^1H NMR (CDCl_3) 1.69 (s, 3H), 2.32-2.41 (m, 1H), 2.46-2.52 (m, 1H), 2.86 (s, 2H), 3.30-3.40 (m, 1H), 3.40-3.60 (m, 1H), 6.50 (s, 1H), 7.10-7.18 (m, 4H), 7.20-7.40 (m, 8H), 7.51-7.59 (m, 1H).

10

EXAMPLE 46

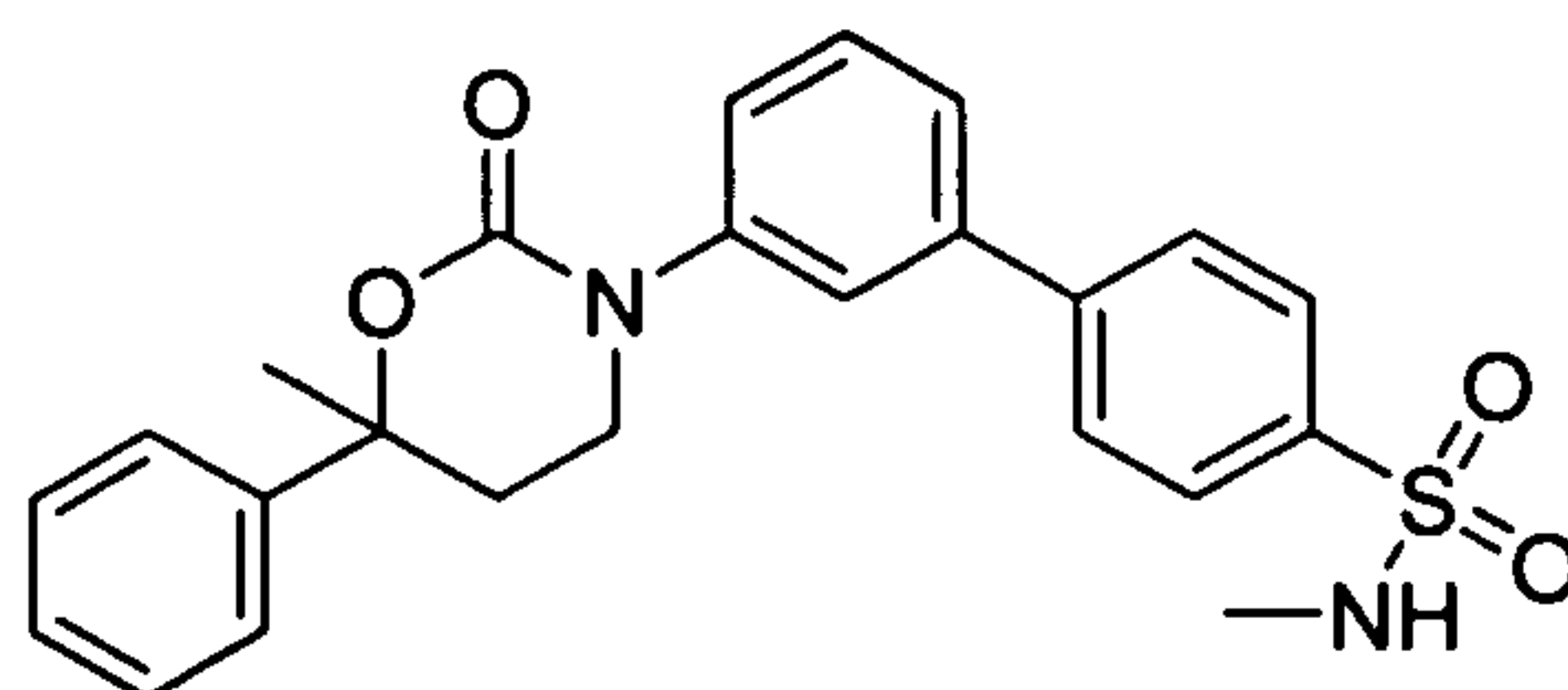
methyl 3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-carboxylate



The title compound was prepared following procedures analogous to those in Example 9 using 4-(methoxycarbonyl)phenylboronic acid. LC-MS Method 3, t_R = 1.359 min, m/z = 402.1. ^1H NMR (CDCl_3) 1.80 (s, 3H), 2.42-2.62 (m, 2H), 3.38-3.44 (m, 1H), 3.60 (m, 1H), 3.95 (s, 3H), 7.19 (d, 1H), 7.34-7.53 (m, 8H), 7.60 (d, 2H), 8.10 (d, 2H).

EXAMPLE 47

20 N-methyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-sulfonamide



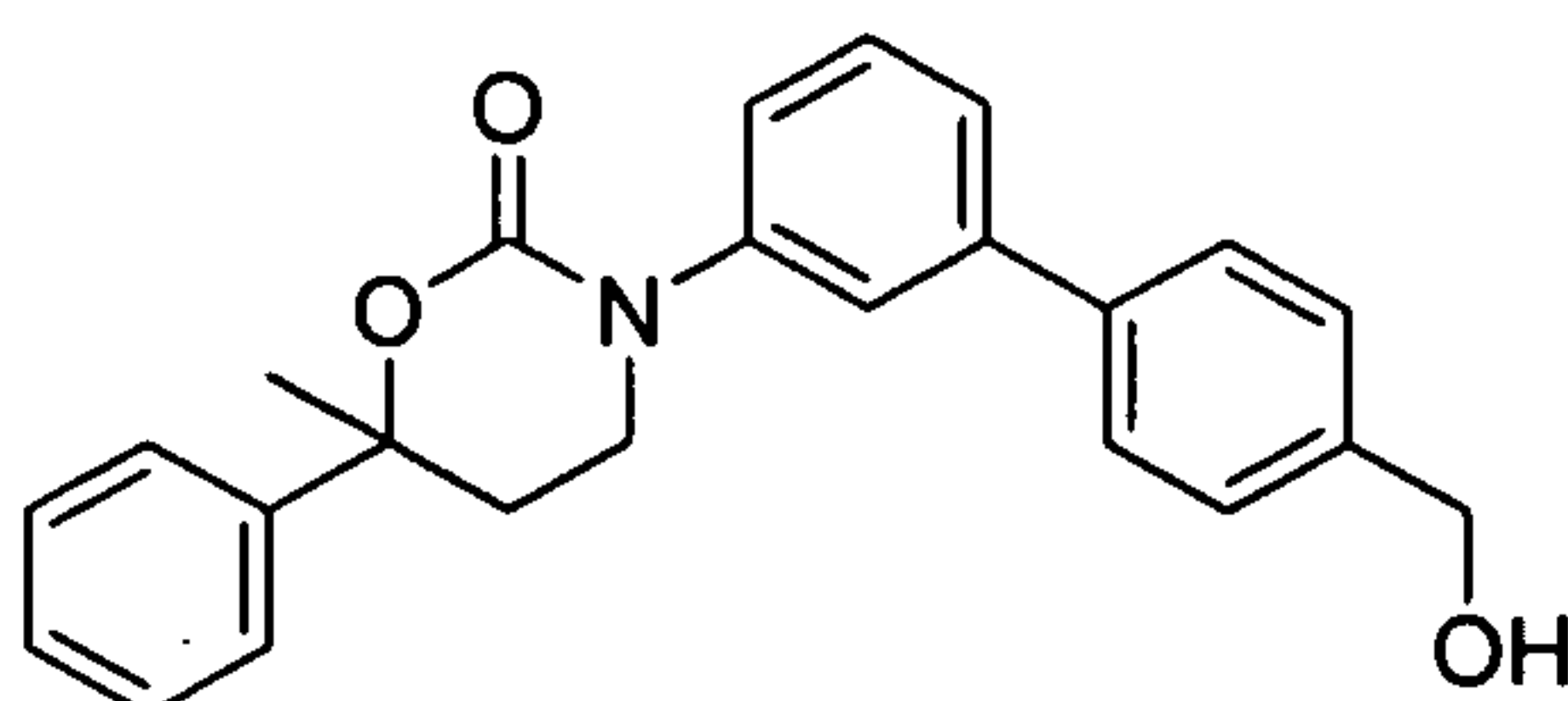
The title compound was prepared following procedures analogous to those in Example 9 using 4-(methylaminosulfonyl)phenylboronic acid. LC-MS Method 3, t_R = 1.403 min, m/z = 437.1. ^1H NMR (CDCl_3) 1.70 (s, 3H), 2.40-2.50 (m, 1H), 2.50-2.60

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(m, 1H), 3.20 (s, 3H), 3.32-3.42 (m, 1H), 3.52-3.62 (m, 1H), 7.15-7.20 (m, 1H), 7.30-7.50 (m, 8H), 7.60-7.70 (m, 2H), 7.86-7.95(m, 2H).

EXAMPLE 48

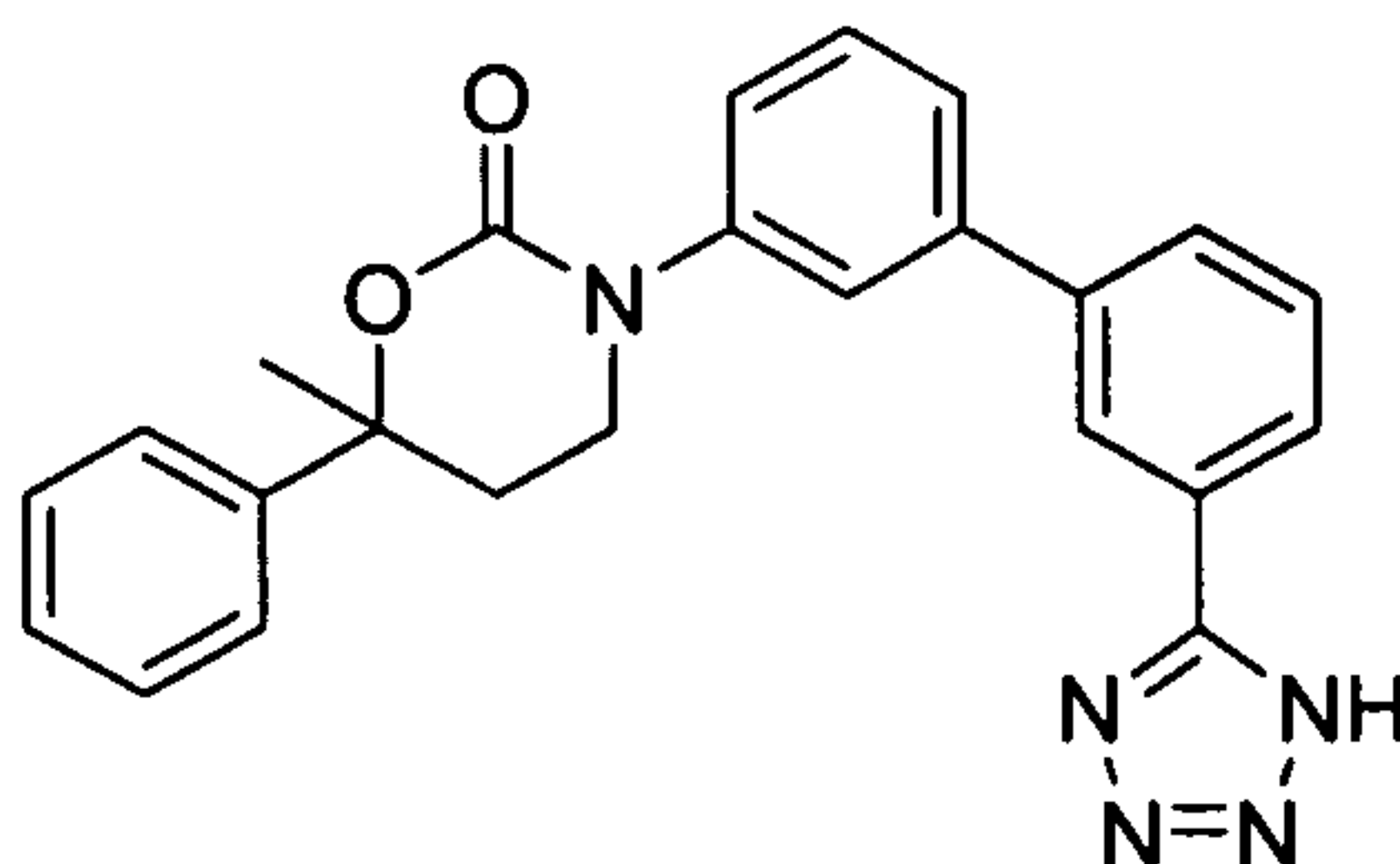
5 3-(4'-(hydroxymethyl)biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those in Example 9 using 4-(hydroxymethyl)phenylboronic acid. LC-MS Method 3, t_R = 1.123 min, m/z = 374.1. ^1H NMR ($CDCl_3$) 1.80 (s, 3H), 2.40-2.60 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 4.75 (d, 2H), 7.15 (m, 1H), 7.34-7.62 (m, 13H).

EXAMPLE 49

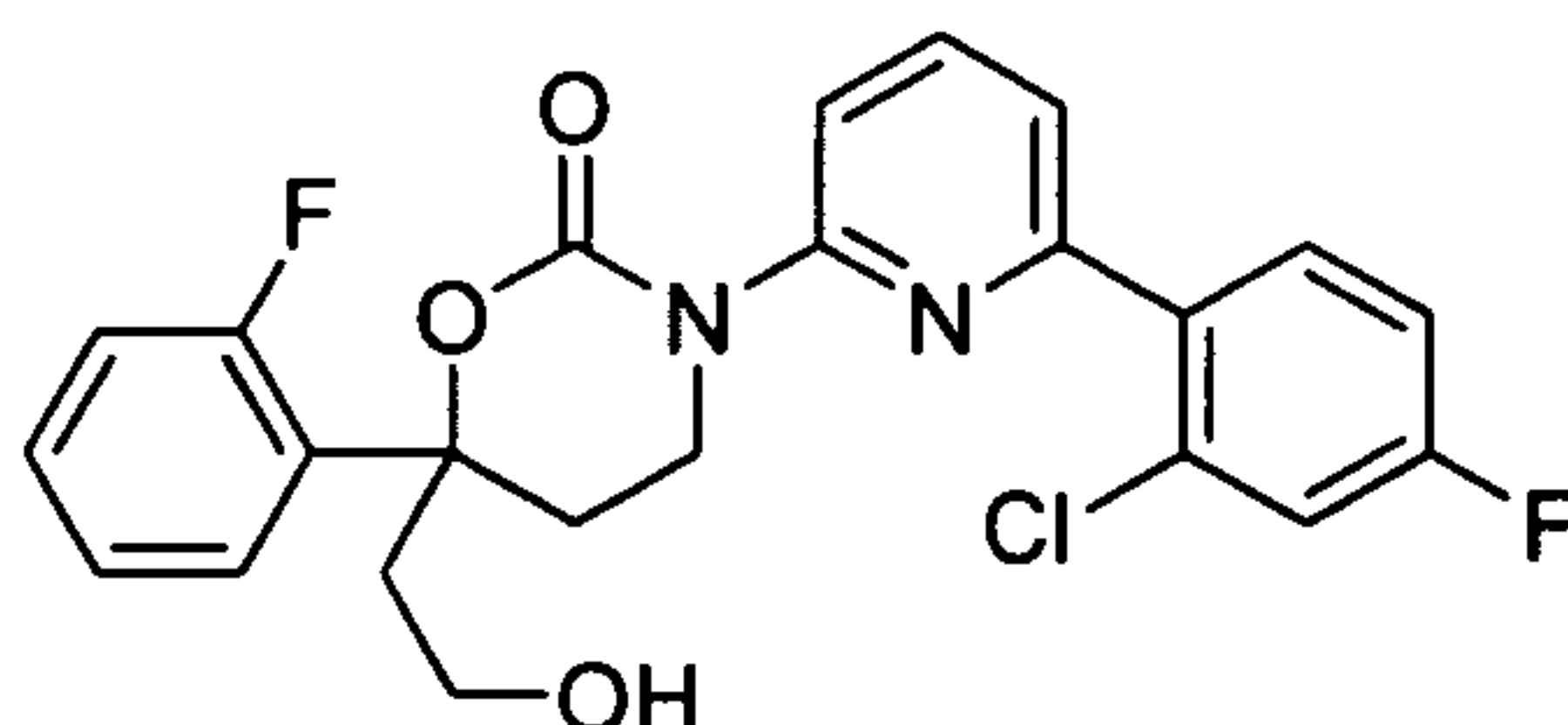
3-(3'-(1H-tetrazol-5-yl)biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those in Example 9 using 3-(2H-tetrazol-5-yl)phenylboronic acid. LC-MS Method 3, t_R = 1.341 min, m/z = 412.2. ^1H NMR ($CDCl_3$) 1.85 (s, 3H), 2.50-2.70 (m, 2H), 3.40 (m, 1H), 3.65 (m, 1H), 7.05 (d, 1H), 7.20-7.35 (m, 3H), 7.40-7.50 (m, 3H), 7.52 (m, 4H), 7.80 (s, 1H), 7.90 (d, 1H).

EXAMPLE 50

3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one



The title compound was prepared by application of procedures analogous to those described in Example 63 using *o*-fluoroacetophenone in Step 1 and 2-amino-6-

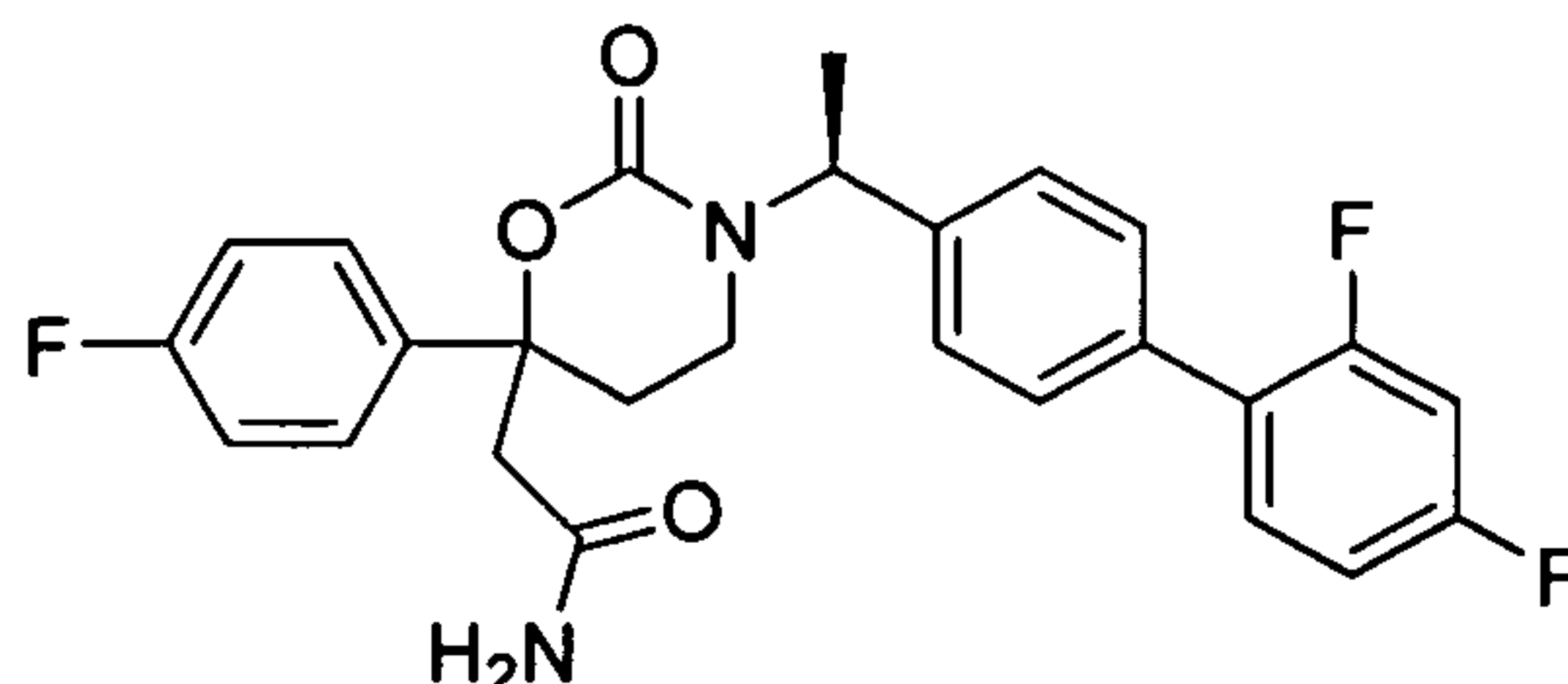
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bromopyridine in Step 2, followed by Example 74 and Example 75 Step 1 using 2-chloro-4-fluorophenylboronic acid. LC-MS Method 3, $t_R = 1.381$ min, $m/z = 444.11$. ^1H NMR (CD_3OD) $\delta=2.20$ - 2.60 (m, 3H), 2.75 (dd, 1H), 3.42 (m, 2H), 3.72 (m, 1H), 4.15 (m, 1H), 7.03-7.30 (m, 4H), 7.42 (m, 3H), 7.55 (m, 1H), 7.75 (m, 2H).

5

EXAMPLE 51

2-(3-((1S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetamide



The title compound was prepared from 3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one by application of procedures analogous to those described in Example 70 followed by Example 76. Two isomers were isolated.

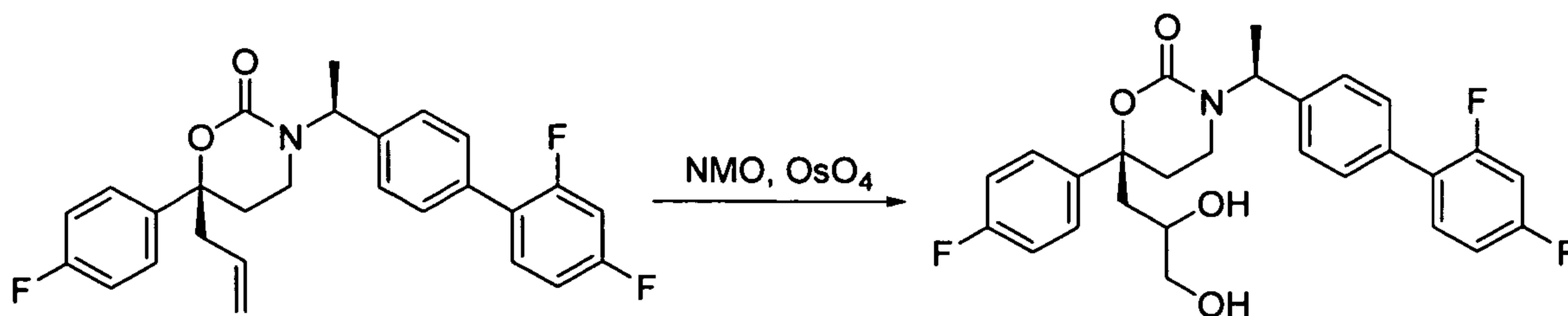
Isomer 1: 2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetamide LC-MS Method 1, $t_R = 1.71$ min, $m/z = 469$. ^1H NMR ($CDCl_3$) 7.25-7.33 (m, 5H), 6.86-7.06 (m, 6H), 5.66 (q, 1H), 2.95-2.99 (m, 1H), 2.83 (d, 1H), 2.72 (d, 1H), 2.30-2.50 (m, 3H), 2.55 (d, 3H).

Isomer 2: 2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetamide LC-MS Method 1 $t_R = 1.75$ min, $m/z = 469$ (M+1); ^1H NMR ($CDCl_3$) 7.49-6.88 (m, 11H), 6.19 (br s, 1H), 5.75 (q, $J = 6.8$ Hz, 1H), 5.46 (br s, 1H), 2.85-2.69 (m, 4H), 2.43-2.38 (m, 1H), 2.29-2.21 (m, 1H), 1.33 (d, $J = 6.8$ Hz, 3H).

25

EXAMPLE 52

(6S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one



A mixture of (*R*)-6-allyl-3-((*S*)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (1.2722 g, 2.82 mmol), 4-methylmorpholine *N*-oxide monohydrate (0.8926 g, 6.60 mmol), and OsO₄ (2.5 wt.% solution in *t*-BuOH, 0.2800 g, 0.0275 mmol) in CH₂Cl₂ (25 mL) was stirred at rt for 16 h. The mixture was treated with EtOAc and washed with 0.5 *N* HCl, brine, dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give 1.3462 g of the crude diol as a foam. The crude diol was directly used in the next step without further purification. LC-MS *t*_R = 1.71 min in 3 min chromatography, *m/z* 486 (MH⁺).

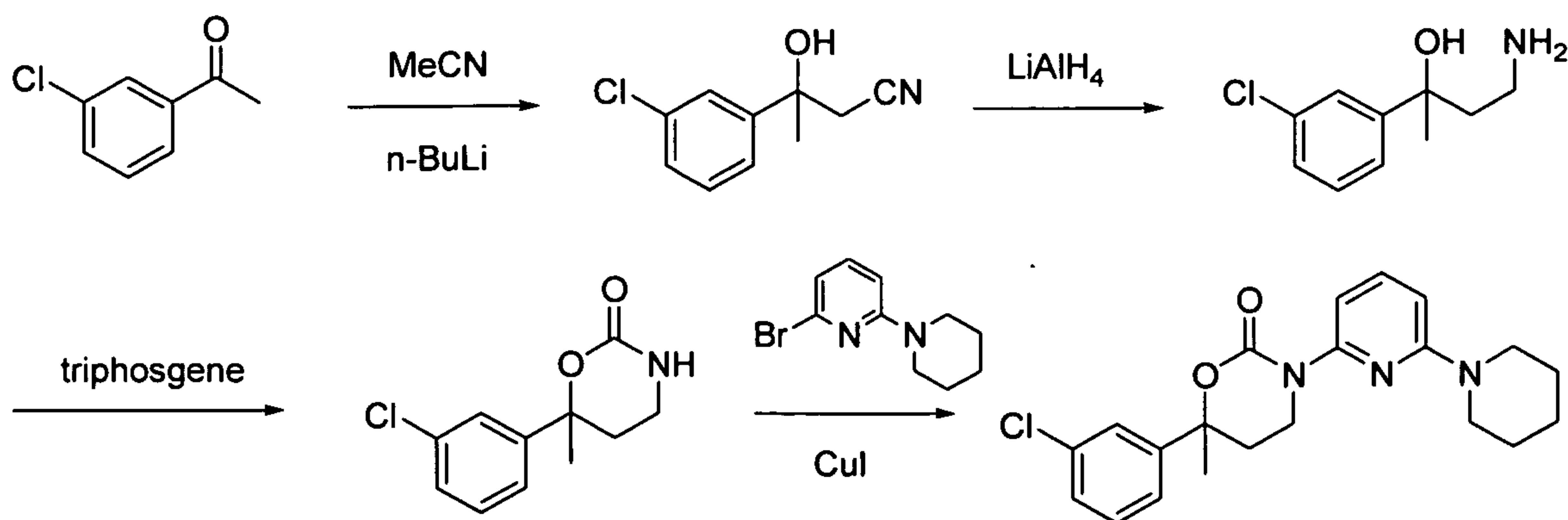
Analytical samples were purified by reversed-phase HPLC (SunFireTM Prep C₁₈ OBDTM 5μm 19 × 50 mm column, 10% → 90% CH₃CN/H₂O, 0.1% CF₃COOH over 8 min and then 90% CH₃CN/H₂O, 0.1% CF₃COOH over 2 min, flow rate 20 mL/min) to afford two diastereoisomers.

Isomer 1: (6*S*)-3-((*S*)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 1, *t*_R = 1.7 min, *m/z* = 486. ¹H NMR (CD₃OD) 7.35-7.29 (m, 3H), 7.18 (d, *J* = 7.0 Hz, 2H), 7.04-6.88 (m, 6H), 5.48 (q, *J* = 7.0 Hz, 1H), 3.36-3.27 (m, 3H), 3.09-3.04 (m, 1H), 2.67-2.61 (m, 1H), 2.37-2.30 (m, 1H), 2.23-2.15 (m, 1H), 2.02-1.91 (m, 2H), 1.47 (d, *J* = 7.0 Hz, 3H).

Isomer 2: (6*S*)-3-((*S*)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 1, *t*_R = 1.71 min, *m/z* = 486. ¹H NMR (CD₃OD) 7.36-7.19 (m, 5H), 7.04-6.91 (m, 6H), 5.51 (q, *J* = 7.0 Hz, 1H), 3.76-3.71 (m, 1H), 3.06-3.01 (m, 1H), 2.44-2.37 (m, 2H), 2.25-2.18 (m, 1H), 1.98 (dd, *J* = 14.9, 2.6 Hz, 1H), 1.84 (dd, *J* = 15.2, 7.9 Hz, 1H), 1.48 (d, *J* = 7.0 Hz, 3H).

EXAMPLE 53

6-(3-chlorophenyl)-6-methyl-3-(6-(piperidin-1-yl)pyridin-2-yl)-1,3-oxazinan-2-one



Step 1. 3-(3-chlorophenyl)-3-hydroxybutanenitrile

Dry THF (15 mL) was cooled to -78 °C and 2.5M *n*-BuLi (5.18mL, 2.0 equiv.) was added. A solution of acetonitrile (680 µL, 2.0 equiv.) in dry THF (2 mL) was added dropwise over 2 min. The mixture was stirred at -78 °C for 1 h. A solution of 3-chloroacetophenone (835µL, 6.468 mmol) in dry THF (2 mL) was added dropwise over 2 min. 30 min. The mixture was stirred at -78°C for 30 min. and was warmed to rt slowly. After being stirred at rt for 15 min., the mixture was quenched with water (10 mL), diluted by ether (20 mL), washed with 2% aq HCl (15 mL). The aqueous layer was extracted with ether (2 x 10mL). The combined organic layers were washed with satd aq NaHCO₃ (5 mL) and brine (10 mL), and dried over Na₂SO₄. After filtration and concentration, the crude product (1.4g, quant. yield) was used for next step without further purification. LC-MS Method 1 *t_R* = 1.40 min., *m/z* = 219, 221 (M+Na).

Step 2. 4-amino-2-(3-chlorophenyl)butan-2-ol

A solution of 3-(3-chlorophenyl)-3-hydroxybutanenitrile (400 mg, 2.04 mmol) in dry THF (10 mL) was cooled to 0 °C. LiAlH₄ powder (155 mg, 2 equiv.) was added. After 5 min, the mixture was warmed to rt and stirred for 4 h. The mixture was then heated to reflux for 6 h. The mixture was diluted with 1 M aq NaOH (30 mL) and extracted with CH₂Cl₂ (2 x 100 mL). The combined CH₂Cl₂ extracts were washed with brine, dried over Na₂SO₄ and concentrated to afford crude 4-amino-2-(3-chlorophenyl)butan-2-ol (550 mg, quant) which was used without purification. LC-MS Method 1, *t_R* = 0.88 min, *m/z* = 200, 202.

Step 3. 6-(3-chlorophenyl)-6-methyl-1,3-oxazinan-2-one

A stirred solution of crude 4-amino-2-(3-chlorophenyl)butan-2-ol (550 mg) and *i*-Pr₂NEt (1 mL, 5.5 mmol) in CH₂Cl₂ was cooled in an ice bath and solid triphosgene (286 mg, 0.96 mmol) was added. The ice bath was allowed to melt and the mixture was stirred overnight at rt. The mixture was diluted with ether (150 mL), washed with 5% aq HCl (50 mL) and satd aq NaHCO₃ (50 mL) and dried over MgSO₄. Removal of the solvent left a brown oil (590 mg) which was purified by chromatography on a 12-g silica cartridge eluted with a 0 - 100% EtOAc in hexanes gradient to afford 6-(3-chlorophenyl)-6-methyl-1,3-oxazinan-2-one (57 mg).

Step 4. 6-(3-chlorophenyl)-6-methyl-3-(6-(piperidin-1-yl)pyridin-2-yl)-1,3-oxazinan-2-one

A mixture of 6-(3-chlorophenyl)-6-methyl-1,3-oxazinan-2-one (28 mg, 0.12 mmol), 2-bromo-6-piperidinopyridine (33 mg, 0.14 mmol), CuI (7 mg, 0.037 mmol),

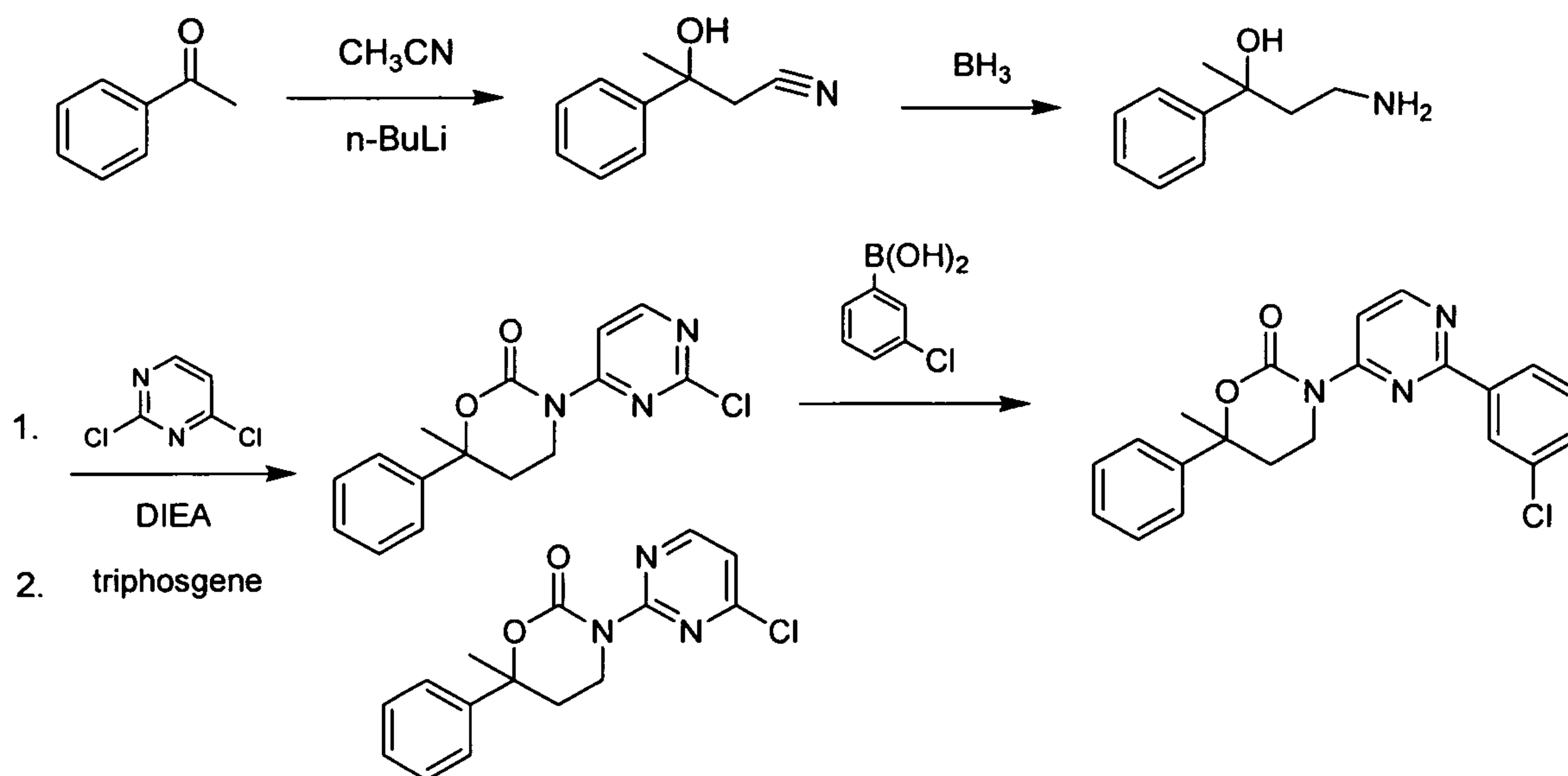
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powdered K₂CO₃ (19 mg, 0.14 mmol) and CH₂Cl₂ (0.25 mL) was heated to 130 °C under a stream of N₂ such that the CH₂Cl₂ evaporated. The vessel was sealed and the mixture was heated at 130 °C for 1 h under N₂. The residue was dissolved in MeCN (0.5 mL) and DMSO (0.5 mL) and purified by prep HPLC to afford 6-(3-chlorophenyl)-6-methyl-3-(6-(piperidin-1-yl)pyridin-2-yl)-1,3-oxazinan-2-one (20 mg) as a brown oil. LC-MS Method 1, t_R = 2.08 min, m/z = 386, 388. ¹H NMR (CDCl₃) 1.62 (6H), 1.73 (s, 3H), 2.35 (m, 1H), 2.48 (m, 1H), 3.43 (5H), 4.11 (m, 1H), 6.50 (d, 1H), 7.20-7.60 (6H).

10

EXAMPLE 54

3-(2-(3-chlorophenyl)pyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



Step 1. 3-hydroxy-3-phenylbutanenitrile

Dry THF was cooled to -20 °C and 2.5 M n-BuLi (100 mL, 0.25 mol) was added. A solution of CH₃CN (11.25 g, 0.25 mol) in dry THF was added dropwise over 10 min. Then the mixture was stirred for 1 h at -20 °C and a solution of acetophenone (30 g, 0.25 mol) in THF was added dropwise over 10 min. The mixture was stirred at -20 °C for 15 min and warmed to rt over 15 min. Aq NH₄Cl was added to quench the reaction. The solution was extracted with EtOAc. The organic layer washed with brine, dried over anhydrous Na₂SO₄ and concentrated to give 3-hydroxy-3-phenylbutanenitrile (30 g, yield 75%). ¹H NMR (CDCl₃, 400 MHz): δ=1.76 (s, 3H), 2.83 (s, 2H), 7.34 (m, 1H), 7.41 (m, 2H), 7.5 (m, 2H).

Step 2. 4-amino-2-phenylbutan-2-ol

To a solution of 3-hydroxy-3-phenylbutanenitrile (1 g, 6.2 mmol) in THF (10 mL) was added dropwise BH₃.Me₂S (32 mL, 62 mmol) under a N₂ atmosphere. The

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mixture was stirred at rt overnight. The reaction was quenched with MeOH (10 mL). The mixture was concentrated to give crude 4-amino-2-phenylbutan-2-ol (1.2 g, crude), which was used in the next step without further purification.

Step 3. 4-(2-chloropyrimidin-4-ylamino)-2-phenylbutan-2-ol

5 To a solution of 4-amino-2-phenylbutan-2-ol (1.2 g, 0.0072 mmol) and DIEA in CH₂Cl₂ (15 ml) was added dropwise a solution of 2,4-dichloro-pyrimidine (980 mg, 0.0072 mmol) in CH₂Cl₂ slowly at 0 °C under N₂. The mixture was stirred at rt overnight. The mixture was concentrated to give the crude product, which was purified by preparative TLC to afford a mixture of 4-(2-chloro-pyrimidin-4-ylamino)-2-phenylbutan-2-ol and 4-(4-chloropyrimidin-2-ylamino)-2-phenylbutan-2-ol (450 mg, 23%). ¹H NMR (CDCl₃, 400 MHz): δ=1.55 (s, 3H), 2.05 (m, 2H), 3.03 (m, 2H), 3.6 (m, 1H), 6.02 (m, 2H), 7.28 (m, 1H), 7.28 (m, 2H), 7.28 (m, 2H).

Step 4. 3-(2-chloropyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

15 To a solution of 4-(4-chloro-pyrimidin-2-ylamino)-2-phenylbutan-2-ol (450 mg, 1.6 mmol) and Et₃N (508 mg, 4.8 mmol) in CH₂Cl₂ (2 ml) was added dropwise a solution of triphosgene (159 mg, 0.54 mmol) in CH₂Cl₂ slowly at 0 °C under nitrogen atmosphere. The mixture was stirred at rt overnight. The mixture was concentrated to give the crude product, which was purified by TLC and preparative HPLC to afford 3-(2-chloropyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (250 mg, 52%) ¹H NMR (CDCl₃, 400 MHz): δ=1.73 (s, 3H), 2.38 (m, 1H), 2.63 (m, 1H), 3.49 (m, 1H), 4.2 (m, 1H), 7.36 (m, 5H), 8.28 (m, 1H), 8.52 (m, 1H) and 3-(4-chloropyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (20 mg, 9%) [Example 57]. ¹H NMR (CDCl₃, 400 MHz): δ=1.73 (s, 3H), 2.4 (m, 1H), 2.58 (m, 1H), 3.47 (m, 1H), 4.13 (m, 1H), 7.06 (m, 5H), 7.16-7.55 (m, 5H), 8.54 (m, 1H).

25 Step 5. 3-(2-chloropyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

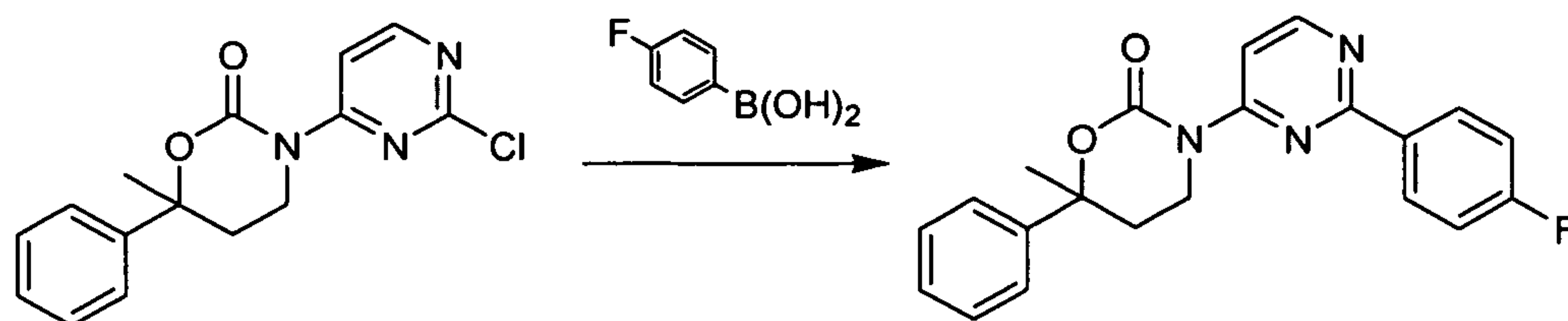
To a solution of 3-(2-chloropyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (100 mg, 0.33 mmol) and 3-chlorophenylboronic acid (0.53 mmol) in 2M aq K₂CO₃ (1 mL, 2 mmol) and 1,4-dioxane (3 mL) was slowly added Pd(Ph₃)₂Cl₂ (20 mg, 10%) at 0 °C under N₂. The mixture was refluxed overnight. The mixture was concentrated to give crude product, which was purified by TLC and preparative HPLC to afford 3-(2-chloropyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (13 mg). ¹H NMR (CDCl₃, 400 MHz): δ=1.78 (s, 3H), 2.43 (m, 1H), 2.57 (m, 1H), 3.6 (m, 1H), 4.4 (m, 1H), 7.3-7.5 (m, 6H), 8.2-8.4 (m, 3H), 8.65 (m, 1H). LC-MS Method 3, t_R = 1.655 min, m/z = 380.

35

EXAMPLE 55

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3-(2-(4-fluorophenyl)pyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

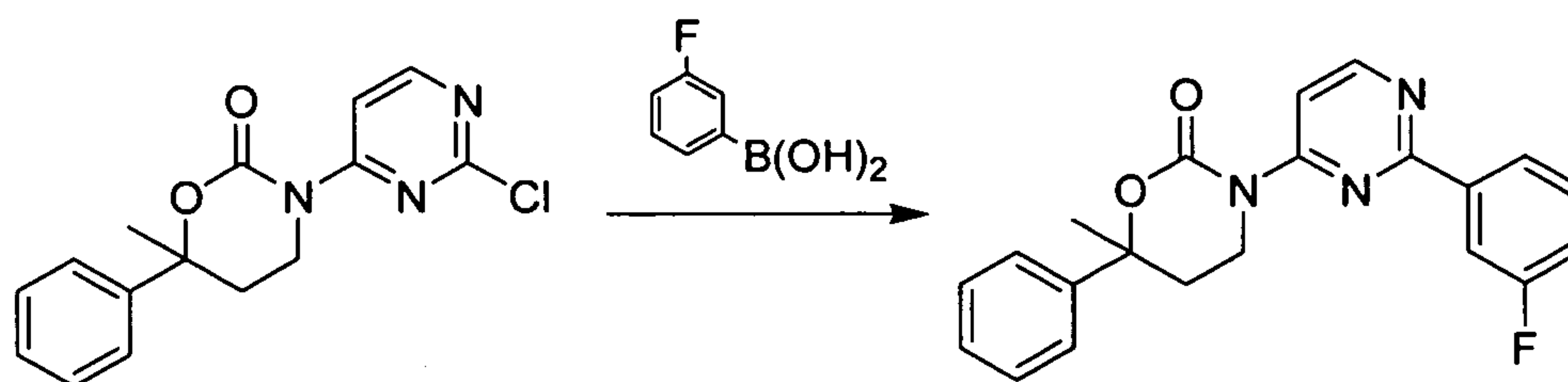


To a solution of 3-(2-chloropyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (50 mg, 0.165 mmol) and 4-fluorophenylboronic acid (32 mg, 0.33 mmol), K_2CO_3 (0.5 mL, 2 M) in 1,4-dioxane (1.5 ml) at 0 °C under N_2 was slowly added $Pd(Ph_3)_2Cl_2$ (10 mg, 20%). The mixture was refluxed overnight. The mixture was concentrated to give the crude product, which was purified by TLC and preparative HPLC to afford 3-(2-(4-fluorophenyl)pyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (15 mg, yield 25%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.75 (s, 3H), 2.4 (m, 1H), 2.54 (m, 1H), 3.6 (m, 1H), 4.4 (m, 1H), 7.1 (m, 2H), 7.25-7.4 (m, 5H), 8.08 (m, 1H), 8.34 (m, 2H), 8.62 (m, 1H). LC-MS Method 3, t_R = 1.519 min, m/z = 364.1. ^1H NMR ($CDCl_3$) 1.80 (s, 3H), 2.40 (m, 1H), 2.60-2.70 (d, 1H), 3.60 (m, 1H), 4.40 (t, 1H), 7.10 (t, 2H), 7.20-7.45 (m, 5H), 8.17 (d, 1H), 8.35 (t, 2H), 8.65 (d, 1H).

15

EXAMPLE 56

3-(2-(3-fluorophenyl)pyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



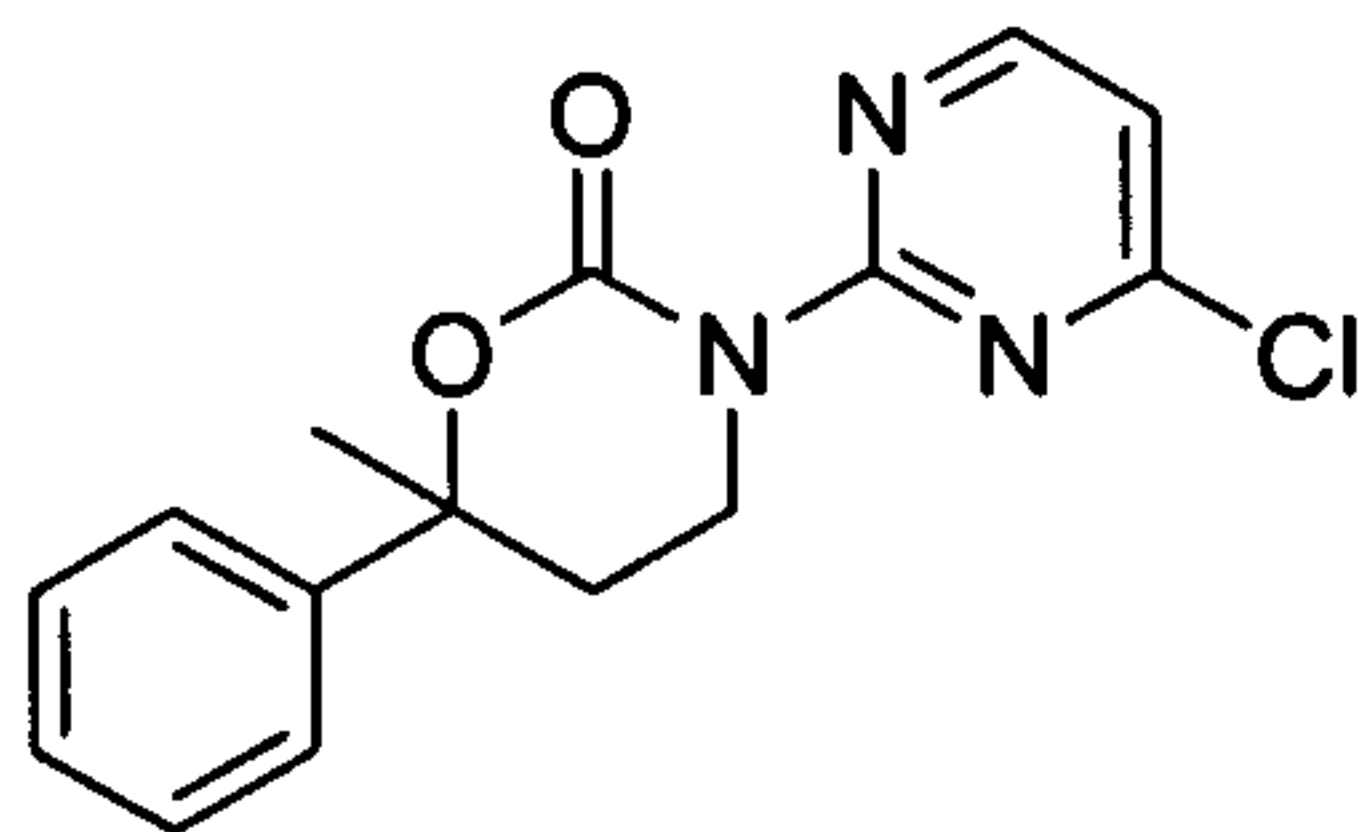
To a solution of 3-(2-chloropyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (100 mg, 0.33 mmol) and 3-fluorophenylboronic acid (80 mg, 0.53 mmol), K_2CO_3 (1 mL, 2 M) in 1,4-dioxane (3 ml) at 0 °C under N_2 was slowly added $Pd(Ph_3)_2Cl_2$ (20 mg, 20%). The mixture was refluxed overnight. The mixture was concentrated to give the crude product, which was purified by TLC and preparative HPLC to afford 3-(2-(3-fluorophenyl)pyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (20 mg, yield 17%). ^1H NMR ($CDCl_3$, 400 MHz): δ =1.71 (s, 3H), 2.37 (m, 1H), 2.6 (m, 1H), 3.54 (m, 1H), 4.34 (m, 1H), 7.08 (m, 1H), 7.25 (m, 1H), 7.34 (m, 5H), 7.96 (m, 1H), 8.09 (m, 1H), 8.16 (m, 1H), 8.6 (m, 1H). LC-MS Method 3, t_R = 1.46 min, m/z = 364.

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EXAMPLE 57

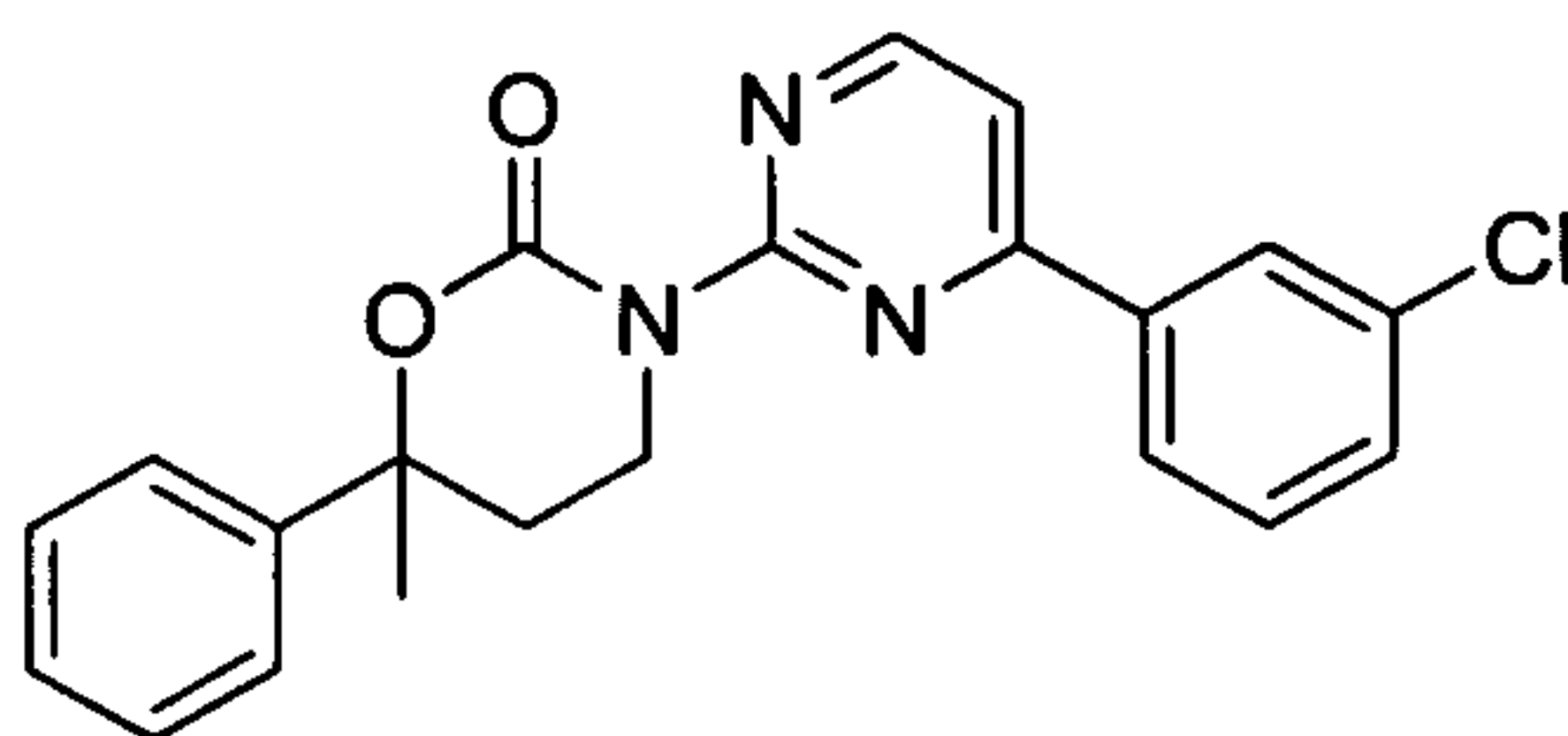
3-(4-chloropyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was isolated as described in Example 54 Step 3. LC-MS
 5 Method 3, $t_R = 1.007$ min, $m/z = 304$. ^1H NMR ($CDCl_3$) 1.73 (s, 3H), 2.4 (m, 1H), 2.58 (m, 1H), 3.47 (m, 1H), 4.13 (m, 1H), 7.06 (m, 5H), 7.16-7.55 (m, 5H), 8.54 (m, 1H).

EXAMPLE 58

3-(4-(3-chlorophenyl)pyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

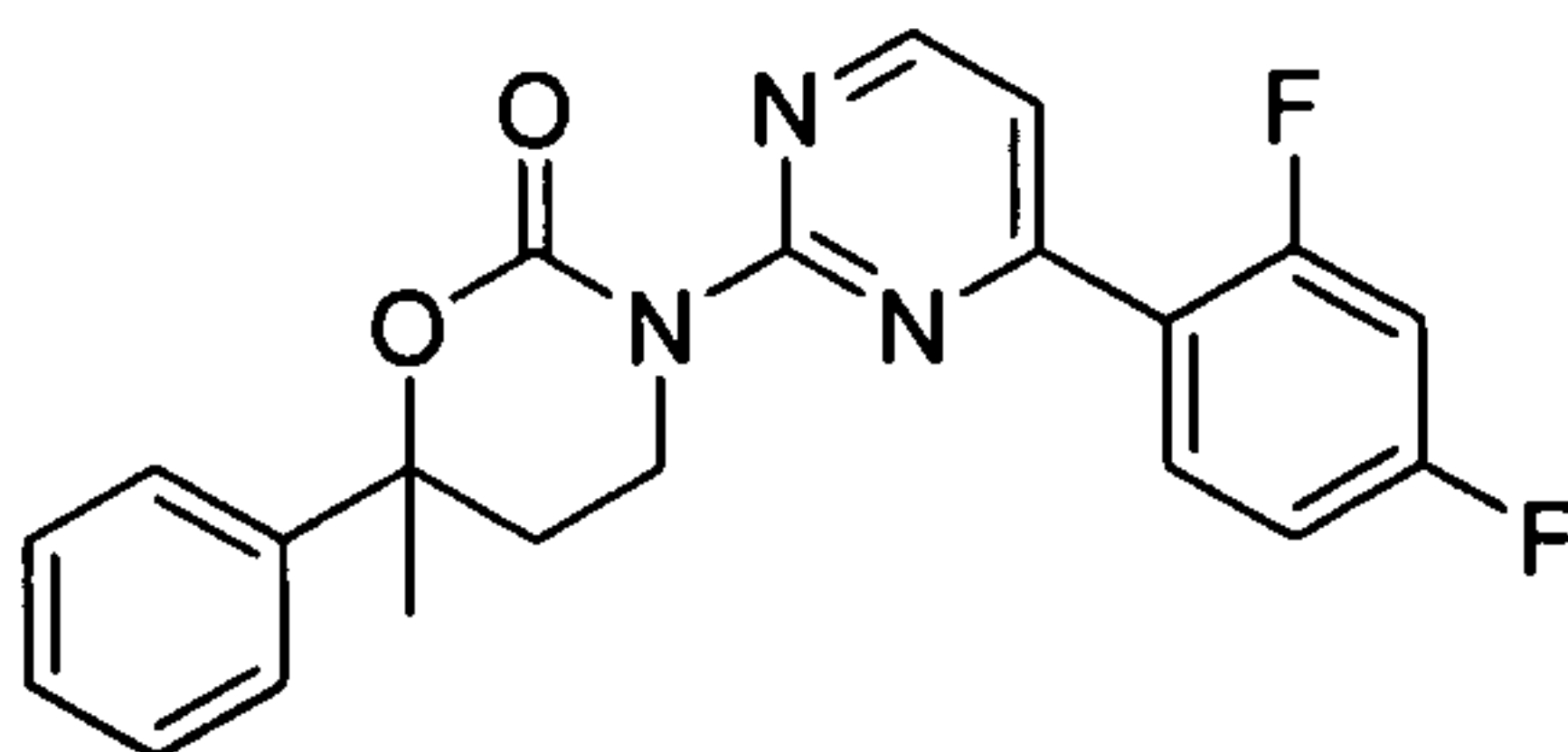


10

The title compound was prepared following procedures analogous to those in
 Example 56 using 3-(4-chloropyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one
 and 3-chlorophenylboronic acid. LC-MS Method 3, $t_R = 1.354$ min, $m/z = 781.1$. ^1H
 NMR ($CDCl_3$) 1.80 (s, 3H), 2.48-2.53 (m, 1H), 2.62-2.71 (m, 1H), 3.55-3.67 (m, 1H),
 15 4.30-4.40 (m, 1H), 7.30-7.60 (m, 8H), 7.90-7.95 (m, 1H), 8.05 (s, 1H), 8.80-8.85 (m,
 1H).

EXAMPLE 59

3-(4-(2,4-difluorophenyl)pyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

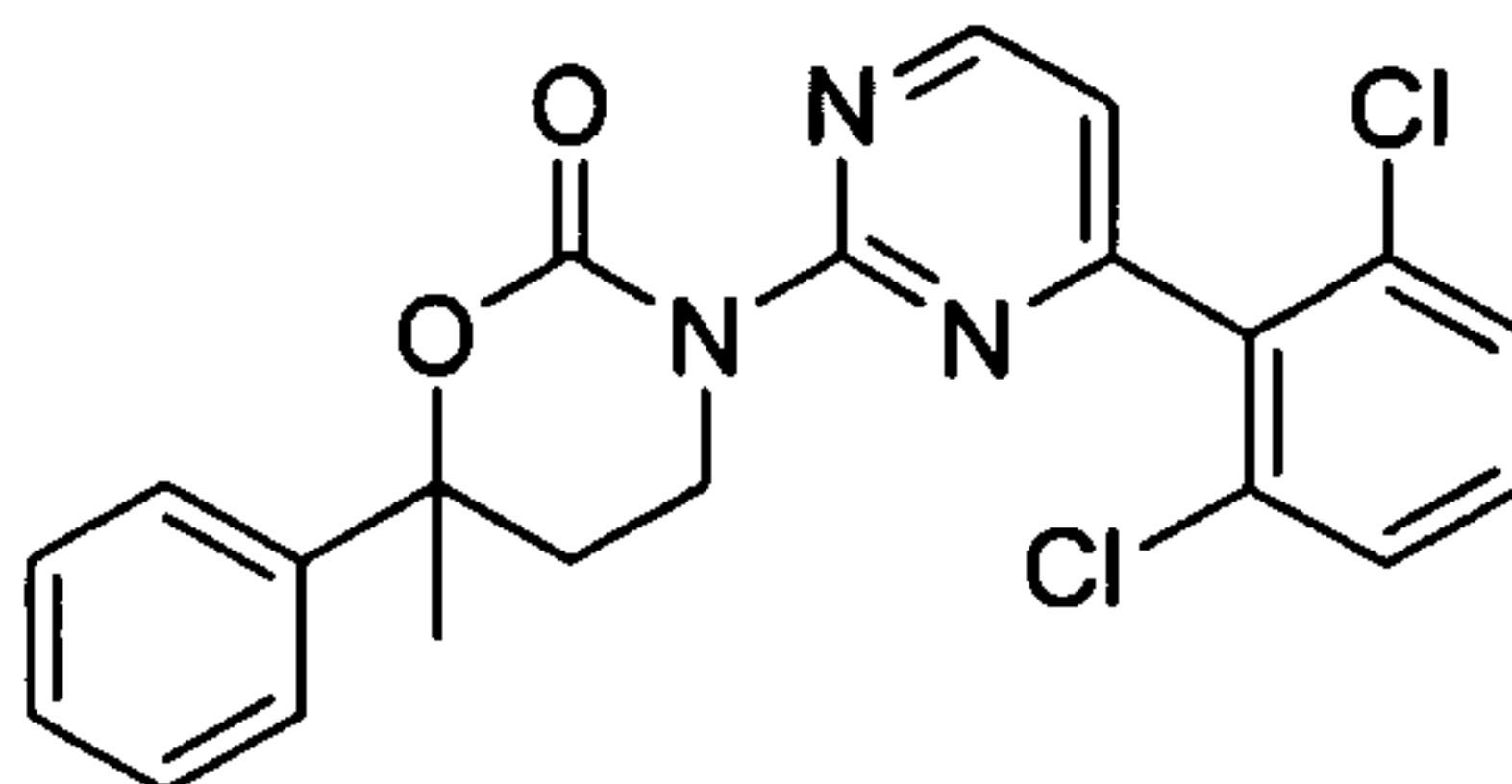


20

The title compound was prepared following procedures analogous to those in
 Example 56 using 3-(4-chloropyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one
 and 2,4-difluorophenylboronic acid. LC-MS Method 3, $t_R = 1.238$ min, $m/z = 785$. ^1H
 NMR ($CDCl_3$) 1.80 (s, 3H), 2.48-2.53 (m, 1H), 2.62-2.71 (m, 1H), 3.58-3.67 (m, 1H),
 25 4.35-4.45 (m, 1H), 6.93-7.08 (m, 2H), 7.30-7.48 (m, 5H), 7.62-7.65 (m, 1H), 8.15-
 8.23 (m, 1H), 8.78-8.81 (m, 1H).

EXAMPLE 60

3-(4-(2,6-dichlorophenyl)pyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

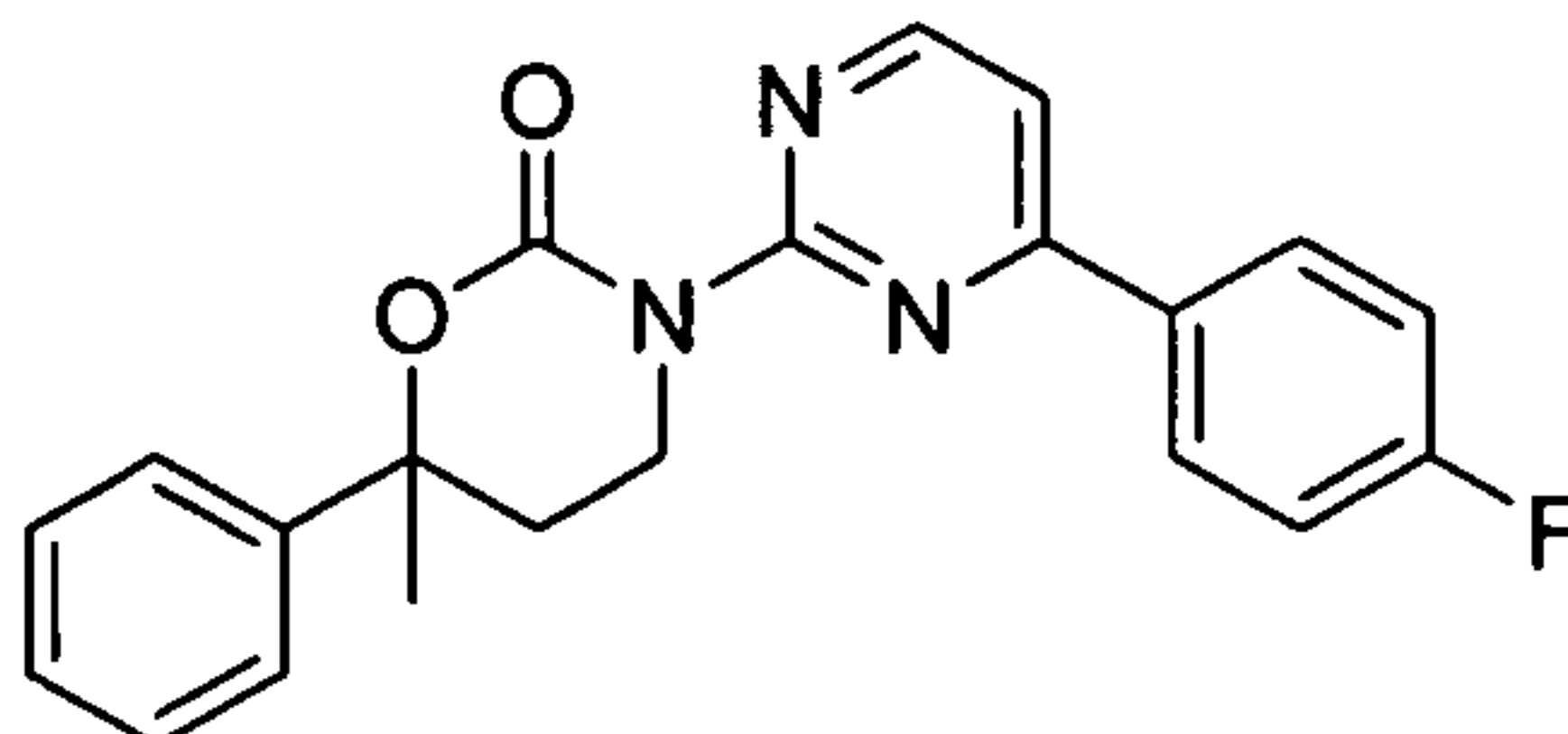


5 The title compound was prepared following procedures analogous to those in Example 56 using 3-(4-chloropyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one and 2,6-dichlorophenylboronic acid. LC-MS Method 3, $t_R = 1.317$ min, $m/z = 414$. ^1H NMR ($CDCl_3$) 1.70 (s, 3H), 2.30-2.40 (m, 1H), 2.48-2.52 (m, 1H), 3.47-3.51 (m, 1H), 4.10-4.15 (m, 1H), 7.10-7.40 (m, 10H), 8.78-8.79 (m, 1H).

10

EXAMPLE 61

3-(4-(4-fluorophenyl)pyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

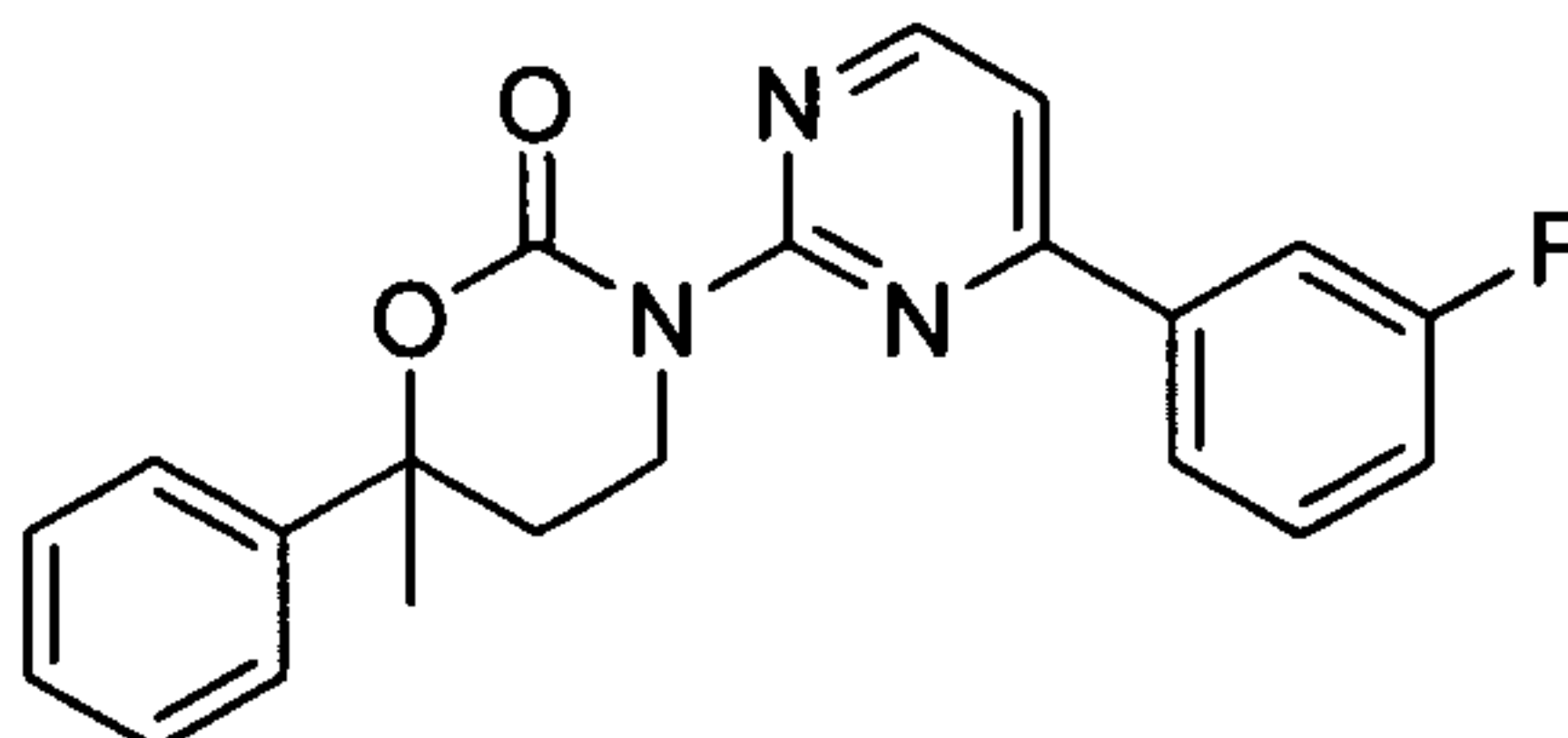


15 The title compound was prepared following procedures analogous to those in Example 56 using 3-(4-chloropyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one and 4-fluorophenylboronic acid. LC-MS Method 3, $t_R = 1.193$ min, $m/z = 363.9$. ^1H NMR ($CDCl_3$) 1.60 (s, 1H), 1.80 (s, 3H), 2.48-2.53 (m, 1H), 2.62-2.71 (m, 1H), 3.60-3.67 (m, 1H), 4.30-4.40 (m, 1H), 7.20-7.55 (m, 10H), 7.60-7.62 (m, 1H), 8.05-8.15 (m, 3H), 8.80-8.85 (m, 1H).

20

EXAMPLE 62

3-(4-(3-fluorophenyl)pyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



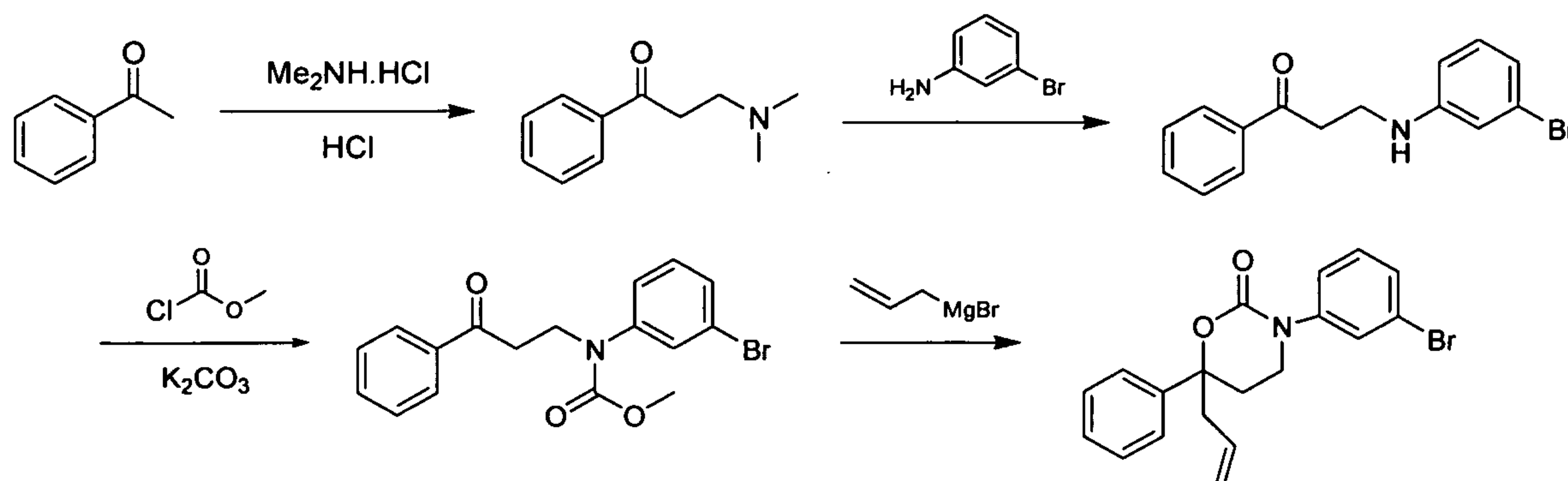
25 The title compound was prepared following procedures analogous to those in Example 56 using 3-(4-chloropyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one and 3-fluorophenylboronic acid. LC-MS Method 3, $t_R = 1.215$ min, $m/z = 749$. ^1H

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NMR (CDCl₃) 1.80 (s, 3H), 2.48-2.53 (m, 1H), 2.62-2.71 (m, 1H), 3.58-3.67 (m, 1H), 4.30-4.40 (m, 1H), 7.30-7.65 (m, 10H), 7.80-7.90 (m, 2H), 8.90-8.95 (m, 1H).

EXAMPLE 63

5 6-allyl-3-(3-bromophenyl)-6-phenyl-1,3-oxazinan-2-one



Step 1. 3-(dimethylamino)-1-phenylpropan-1-one

The solution of acetophenone (30 g, 0.25 mol) and Me₂NH.HCl (0.28 mol) in EtOH (400 mL) was heated at 70 °C overnight. The resulting mixture was concentrated and the residue was washed with EtOAc to give 3-(dimethylamino)-1-phenylpropan-1-one (17.7 g, 40%). ¹H NMR (400MHz, CDCl₃): δ=2.36 (m, 6H), 2.74 (m, 2H), 3.14 (m, 2H), 7.43 (m, 2H), 7.52 (m, 1H), 7.94 (m, 2H).

Step 2. 3-(3-bromophenylamino)-1-phenylpropan-1-one

A mixture of 3-(dimethylamino)-1-phenylpropan-1-one (0.1 mol) and 3-bromoaniline (0.1 mol) in 1:1 EtOH/H₂O (100 mL) was heated at 80 °C overnight. The resulting mixture was concentrated and the residue was washed with H₂O and then EtOH several times to give 3-(3-bromophenylamino)-1-phenylpropan-1-one (27 g, 90%). ¹H NMR (400MHz, CDCl₃): δ=3.52 (m, 2H), 4.33 (m, 2H), 4.51 (m, 1H), 6.8 (m, 1H), 7.05 (m, 2H), 7.28 (m, 1H), 7.72 (m, 2H), 7.80 (m, 1H), 8.2 (m, 2H).

20 Step 3. Methyl 3-bromophenyl(3-oxo-3-phenylpropyl)carbamate

To the solution of 3-(3-bromophenylamino)-1-phenylpropan-1-one (0.03 mol) in anhydrous THF (30 mL) was added K₂CO₃ (0.06 mol) and methyl chloroformate (0.033 mol) at 0 °C under N₂ atmosphere. Then the reaction mixture was stirred at rt for 2 h. The resulting mixture was filtered and the filtrate was concentrated. The residue was washed with H₂O, 1N HCl and brine and then extracted with EtOAc. The combined organic layers were concentrated to give crude product, which was purified by column chromatography to afford methyl 3-bromophenyl(3-oxo-3-phenylpropyl)carbamate (30.5 g, 95%). ¹H NMR (400MHz, CDCl₃): δ=3.22 (m, 2H), 3.62 (s, 3H), 4.02 (m, 2H), 7.05-7.20 (m, 2H), 7.3-7.5 (m, 4H), 7.8 (m, 1H).

30 Step 4. 6-allyl-3-(3-bromophenyl)-6-phenyl-1,3-oxazinan-2-one

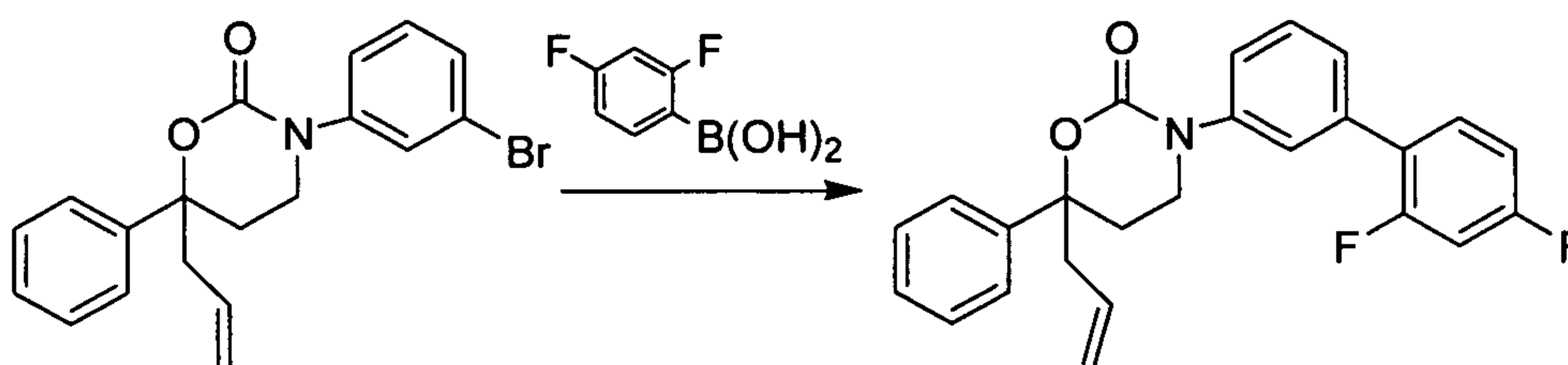
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To a solution of methyl 3-bromophenyl(3-oxo-3-phenylpropyl)carbamate (250 mg, 0.69 mmol) in dry THF (2 mL) was added dropwise 1 M allylmagnesium bromide (10 mL) -78 °C. The reaction mixture was stirred at rt for 3 h. The resulting mixture was quenched with sattd aq NH₄Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to give 6-allyl-3-(3-bromophenyl)-6-phenyl-1,3-oxazinan-2-one (120 mg, 47%). ¹H NMR (400MHz, CDCl₃): δ=2.48 (m, 2H), 2.55-2.7 (m, 2H), 3.23 (m, 1H), 3.51 (m, 1H), 5.04 (m, 2H), 5.72 (m, 1H), 7.01 (m, 1H), 7.11 (m, 1H), 7.23 (m, 1H), 7.3 (m, 1H), 7.35 (m, 6H).

10

EXAMPLE 64

6-allyl-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one



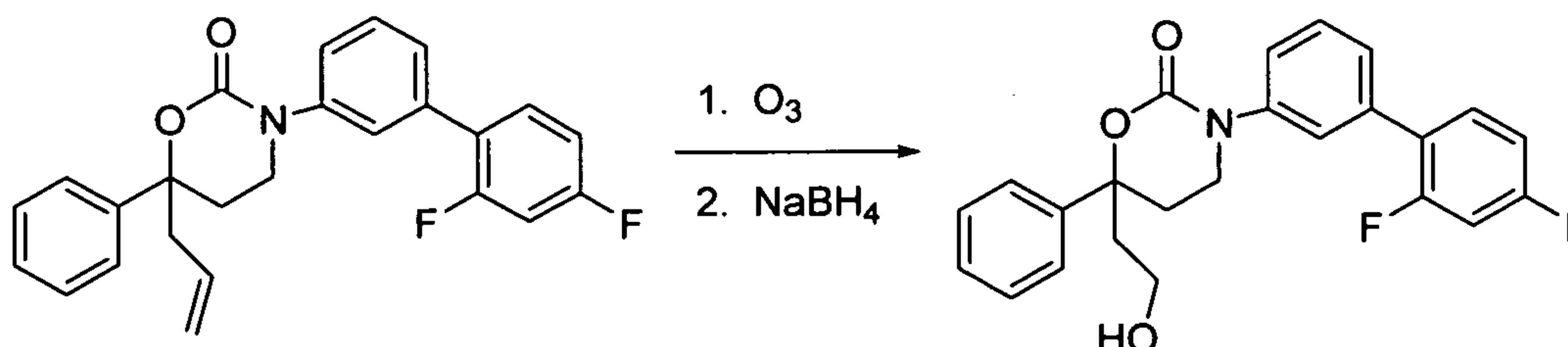
Step 1. 6-allyl-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one

To a solution of 6-allyl-3-(3-bromophenyl)-6-phenyl-1,3-oxazinan-2-one (50 mg, 0.134 mmol) and 2,4-difluorophenylboronic acid (40 mg, 0.215 mmol), K₂CO₃ (0.5 mL, 2 M) in 1,4-dioxane (1.5 ml) was slowly added Pd(Ph₃)₂Cl₂ (10 mg, 20%) at 0 °C under N₂. The mixture was refluxed overnight. The mixture was concentrated to give the crude product, which was purified by TLC and preparative HPLC to afford 6-allyl-3-(2',4'- difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one (10 mg, 18%). ¹H NMR (400MHz, CDCl₃): δ=2.40 (m, 2H), 2.55-2.72 (m, 2H), 3.26 (m, 1H), 3.47 (m, 1H), 5.05 (m, 2H), 5.76 (m, 1H), 6.76-6.90 (m, 2H), 7.04 (m, 1H), 7.28 (m, 4H), 7.36 (m, 2H).

25

EXAMPLE 65

3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one



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Step 1. 3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one

A solution of 6-allyl-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one (600 mg, 1.47 mmol) in dry CH₂Cl₂ (10 mL) was treated with ozone at -78 °C until the mixture turned blue. The system was then flushed with oxygen to remove excess ozone. NaBH₄ (450 mg, 11.7 mmol) was added to the mixture in portions at -20 °C. The mixture was stirred overnight at rt. The mixture was quenched with water and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x). The organic layers were combined, washed with brine, dried over anhydrous Na₂SO₄ and concentrated to give 3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one (150 mg, 25%). ¹H NMR (400MHz, CDCl₃): δ=2.12-2.35 (m, 2H), 2.51(m, 2H), 3.26 (m, 1H), 3.47-3.6 (m, 2H), 4.25 (m, 1H), 6.83 (m, 2H), 7.06 (m, 1H), 7.26-7.51 (m, 8H).

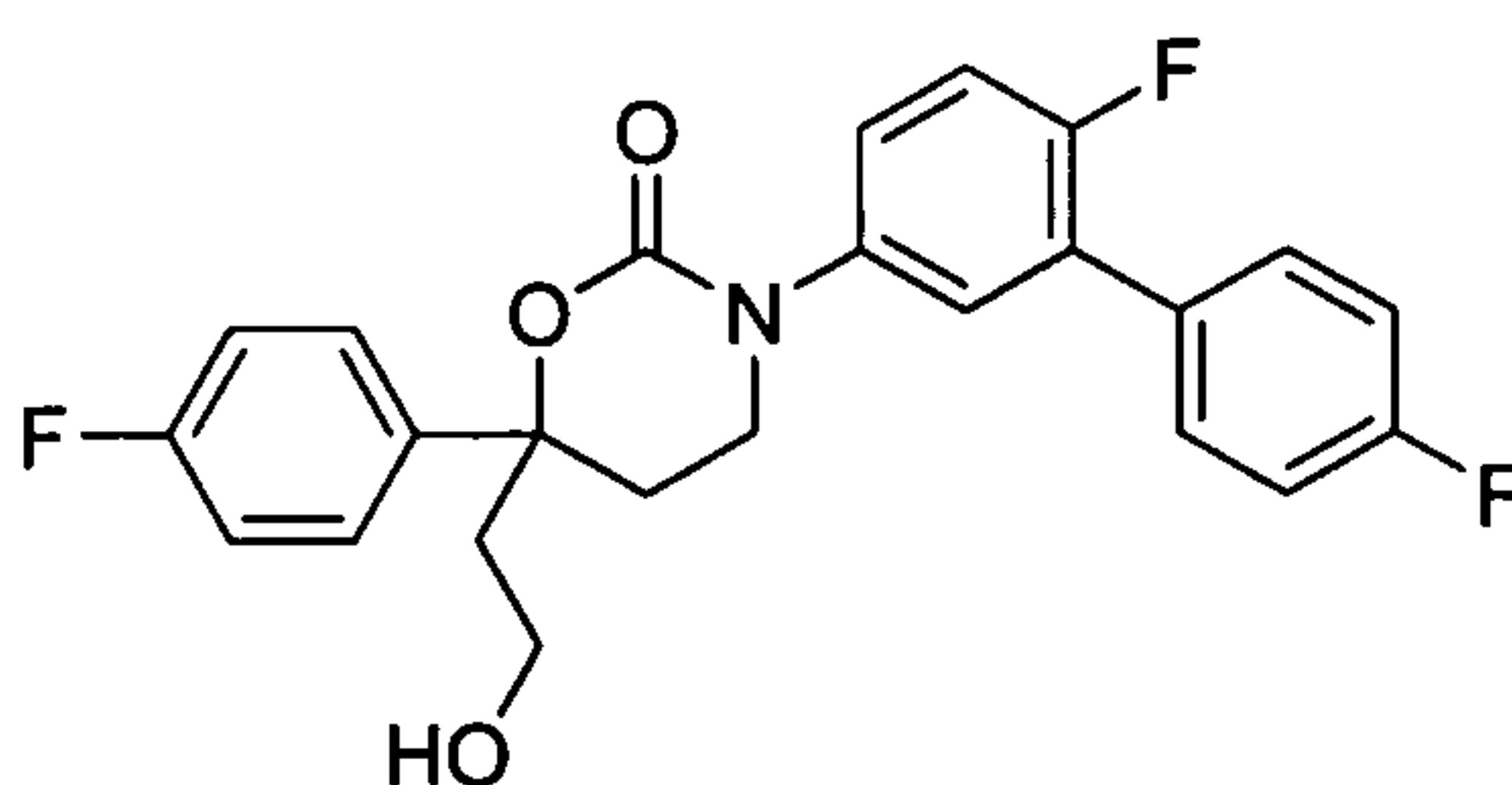
Preparative HPLC on a Chiralpak IA, 4.6x250 mm, 5 micron column eluted with 10% EtOH in hexanes at a flow rate of 1 mL min⁻¹ afforded two isomers.

Isomer 1: LC-MS Method 1, t_R = min, m/z = 410 (M+1). ¹H NMR (CDCl₃) 7.47-7.33 (m, 8H), 7.27-7.26 (m, 1H), 7.16-7.13 (m, 1H), 6.96-6.86 (m, 2H), 3.86-3.80 (m, 1H), 3.64-3.61 (m, 1H), 3.58-3.53 (m, 1H), 3.35-3.28 (m, 1H), 2.58-2.52 (m, 2H), 2.37-2.23 (m, 2H).

Isomer 2 was not characterized.

EXAMPLE 66

3-(4',6-difluorobiphenyl-3-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one



25

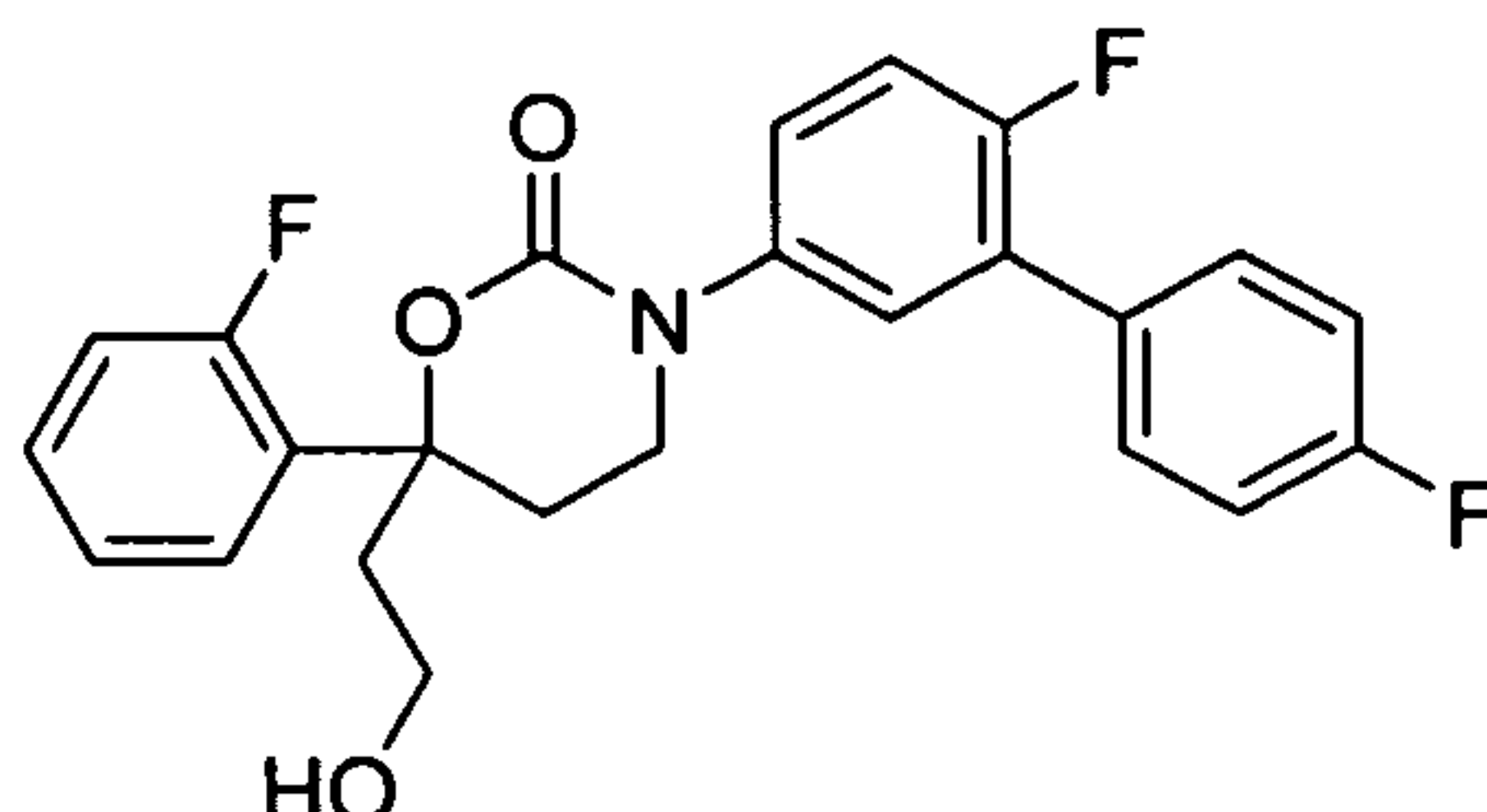
The title compound was prepared by application of procedures analogous to those described in Example 63 using *p*-fluoroacetophenone in Step 1 and 3-bromo-4-fluoroaniline in Step 2 followed by procedures analogous to those described in Example 64 using 4-fluorophenylboronic acid followed by procedures analogous to those described in Example 65. LC-MS Method 3, t_R = 1.234 min, m/z = 428. ¹H NMR (CDCl₃) 1.62-1.70 (m, 1H), 2.2-2.38 (m, 2H), 2.5-2.6 (m, 2H), 3.22-3.35 (m, 1H), 3.50-3.65 (m, 2H), 3.80-3.90 (m, 1H), 7.05-7.2 (m, 7H), 7.5-7.6 (m, 4H).

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EXAMPLE 67

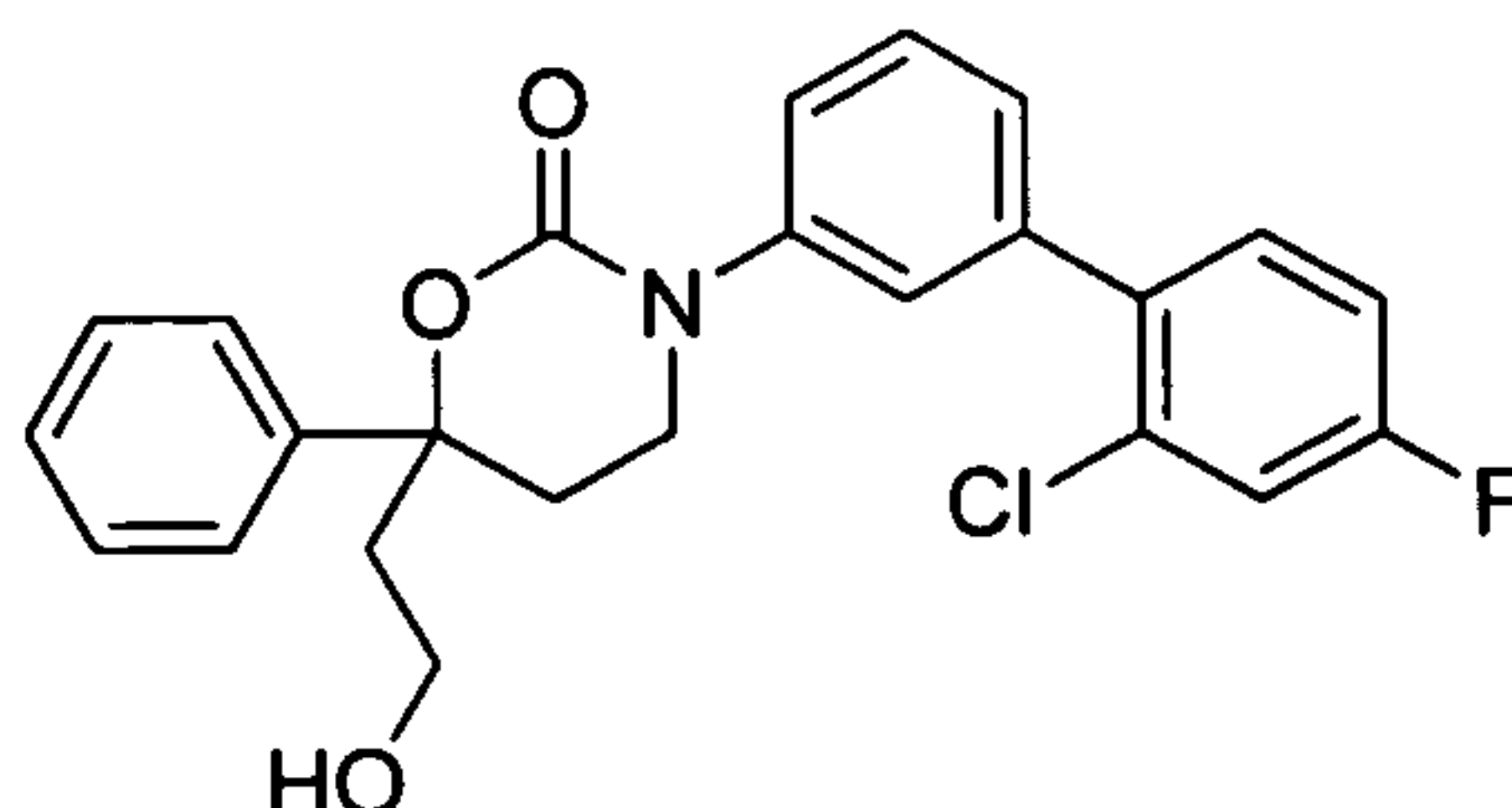
3-(4',6-difluorobiphenyl-3-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one



The title compound was prepared by application of procedures analogous to those described in Example 63 using *o*-fluoroacetophenone in Step 1 and 3-bromo-4-fluoroaniline in Step 2 followed by procedures analogous to those described in Example 64 using 4-fluorophenylboronic acid followed by procedures analogous to those described in Example 65. LC-MS Method 3, $t_R = 1.263$ min, $m/z = 428.1$. ^1H NMR ($CDCl_3$) 2.35-2.6 (m, 3H), 2.79-2.85 (m, 1H), 3.28-3.40 (m, 2H), 3.52-3.60 (m, 1H), 3.63-3.72 (m, 1H), 3.80-3.88 (m, 1H), 7.05-7.20 (m, 6H), 7.22-7.3 (m, 1H), 7.38-7.50 (m, 3H), 7.52-7.61 (m, 1H).

EXAMPLE 68

3-(2'-chloro-4'-fluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one

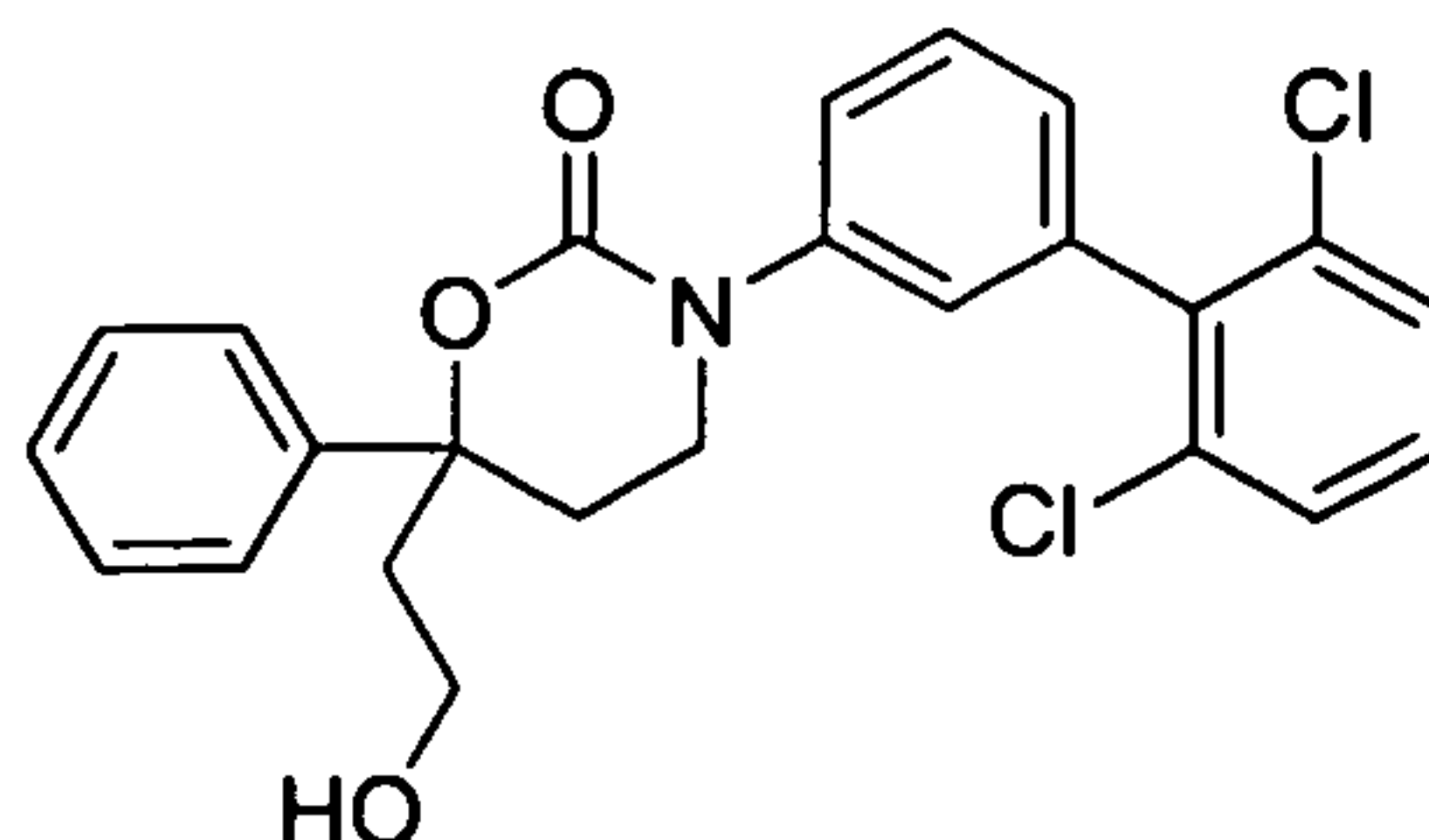


The title compound was prepared by application of procedures analogous to those described in Example 64 using 2-chloro-4-fluorophenylboronic acid in Step 1 followed by procedures analogous to those described in Example 65. LC-MS Method 3, $t_R = 1.268$ min, $m/z = 426$. ^1H NMR (CD_3OD) 2.2-2.30 (m, 2H), 2.45-2.60 (m, 1H), 2.60-2.70 (m, 1H), 3.15-3.25 (m, 1H), 3.3-3.40 (m, 1H), 3.5-3.65 (m, 1H), 3.65-3.77 (m, 1H), 7.0-7.2 (m, 3H), 7.3-7.48 (m, 9H).

EXAMPLE 69

3-(2',6'-dichlorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one

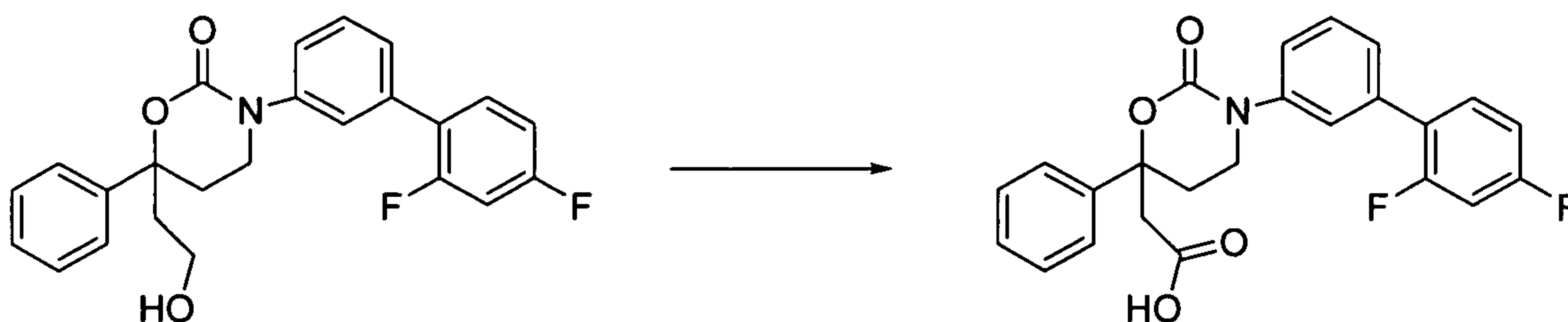
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The title compound was prepared by application of procedures analogous to those described in Example 64 using 2,6-dichlorophenylboronic acid in Step 1 followed by procedures analogous to those described in Example 65. LC-MS
 5 Method 3, $t_R = 1.28$ min, $m/z = 441.9$. ^1H NMR (CDCl_3) 2.26-2.44 (m, 2H), 2.60 (m, 2H), 3.37-3.48 (m, 1H), 3.60-3.70 (m, 1H), 3.88 (m, 1H), 7.11 (m, 1H), 7.19 (m, 1H), 7.29 (m, 1H), 7.45 (m, 4H), 7.50 (m, 4H).

EXAMPLE 70

10 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetic acid



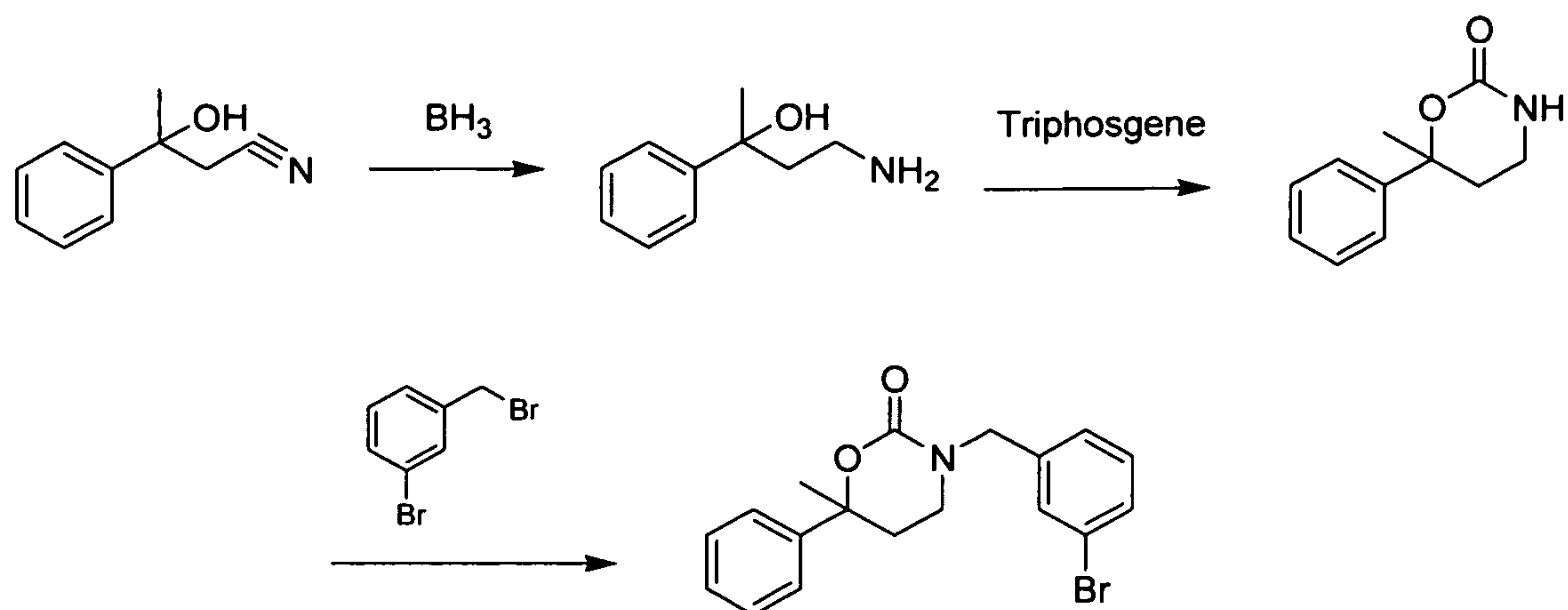
Step 1. 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetic acid

Jones reagent was prepared by addition of CrO_3 (1 g) to H_2SO_4 (1 mL) and addition of water to bring the total volume to 4 mL. 3-(2',4'-difluorobiphenyl-3-yl)-6-
 15 (2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one (100 mg, 0.24 mmol) was dissolved in acetone (2 mL), and cooled in an ice bath. Jones reagent (0.2 mL) was slowly added to the mixture and the reaction mixture was stirred overnight. Solvent was removed in *vacuo* and the obtained residue was purified by preparative HPLC to afford 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetic acid (20 mg,
 20 yield 19%). ^1H NMR (400MHz, CDCl_3): δ =2.7-2.9 (m, 4H), 3.55 (m, 2H), 6.86 (m, 2H), 7.05 (m, 1H), 7.19 (m, 1H), 7.33 (m, 5H), 7.44 (m, 3H).

EXAMPLE 71

3-(3-bromobenzyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

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Step 1. 4-amino-2-phenylbutan-2-ol

To a solution of 3-hydroxy-3-phenylbutanenitrile (13 g, 0.081 mol) in THF (150 mL) was added $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (2 M, 122 mL) at 0 °C. The mixture was refluxed overnight. The reaction mixture was quenched with MeOH and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to obtain crude . 4-amino-2-phenylbutan-2-ol (15 g, 100%). ^1H NMR (CDCl_3): 1.60 (s, 3H), 1.60 (s, 3H), 2.10-2.20 (m, 1H), 2.30-2.40 (m, 1H), 2.90-3.00 (m, 1H), 3.65-3.85 (m, 1H), 7.20-7.40 (m, 5H).

Step 2. 6-methyl-6-phenyl-1,3-oxazinan-2-one

A solution of 4-amino-2-phenylbutan-2-ol (5.0 g, 0.03 mol) in CH_2Cl_2 (50 mL) was added triphosgene (2.97 g, 0.01 mol) and Et_3N (9.09 g, 0.09 mol) at 0 °C. After stirring for 1 h, the mixture was diluted with water and extracted with CH_2Cl_2 . The organic layer was washed with brine, dried over Na_2SO_4 , concentrated and purified by chromatography to afford 6-methyl-6-phenyl-1,3-oxazinan-2-one (1.14 g, 20%). ^1H NMR (CDCl_3): 1.60 (s, 3H), 1.80-2.00 (m, 1H), 2.30-2.40 (m, 1H), 3.15-3.21 (m, 1H), 6.00 (s, 1H), 7.30-7.45 (m, 5H), 8.90-9.01 (m, 1H).

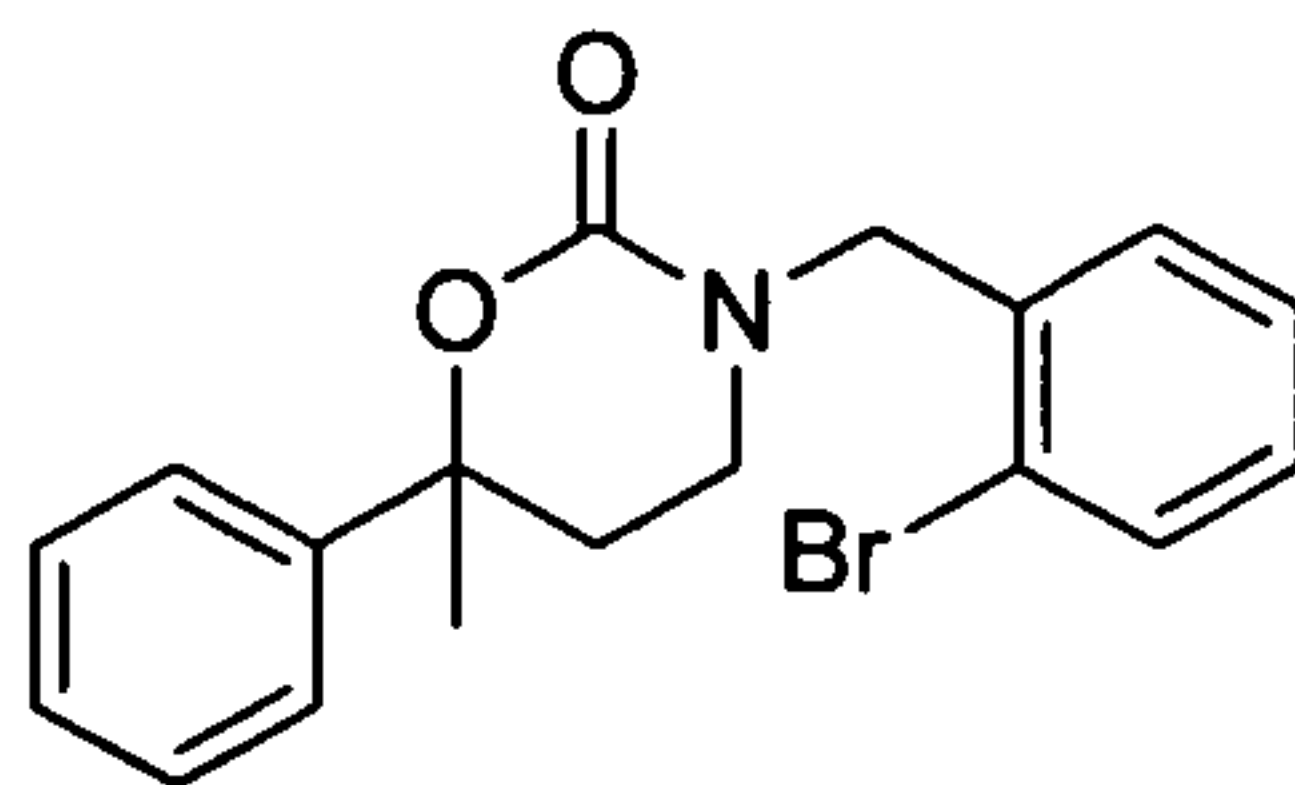
Step 3. 3-(3-bromobenzyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

A solution of 6-methyl-6-phenyl-1,3-oxazinan-2-one (500 mg, 2.62 mmol) and NaH (189 mg, 7.86 mmol) in dry THF (10 mL) was stirred for 1 h. A solution of *m*-bromobenzyl bromide (1.31 g, 5.24 mmol) in dry THF (3 mL) was added. The mixture was stirred overnight at rt. The reaction mixture was quenched water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , concentrated and purified by preparative TLC to afford 3-(3-bromobenzyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (300 mg, 32%). ^1H NMR (CDCl_3): 1.60-1.70 (s, 3H), 2.15-2.30 (m, 1H), 2.35-2.48 (m, 1H), 2.79-2.90 (m, 1H), 3.00-3.10 (m, 1H), 4.30-4.40 (m, 1H), 4.50-4.60 (m, 1H), 6.90-7.00 (m, 1H), 7.00-7.10 (m, 1H), 7.20-7.45 (m, 7H).

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EXAMPLE 72

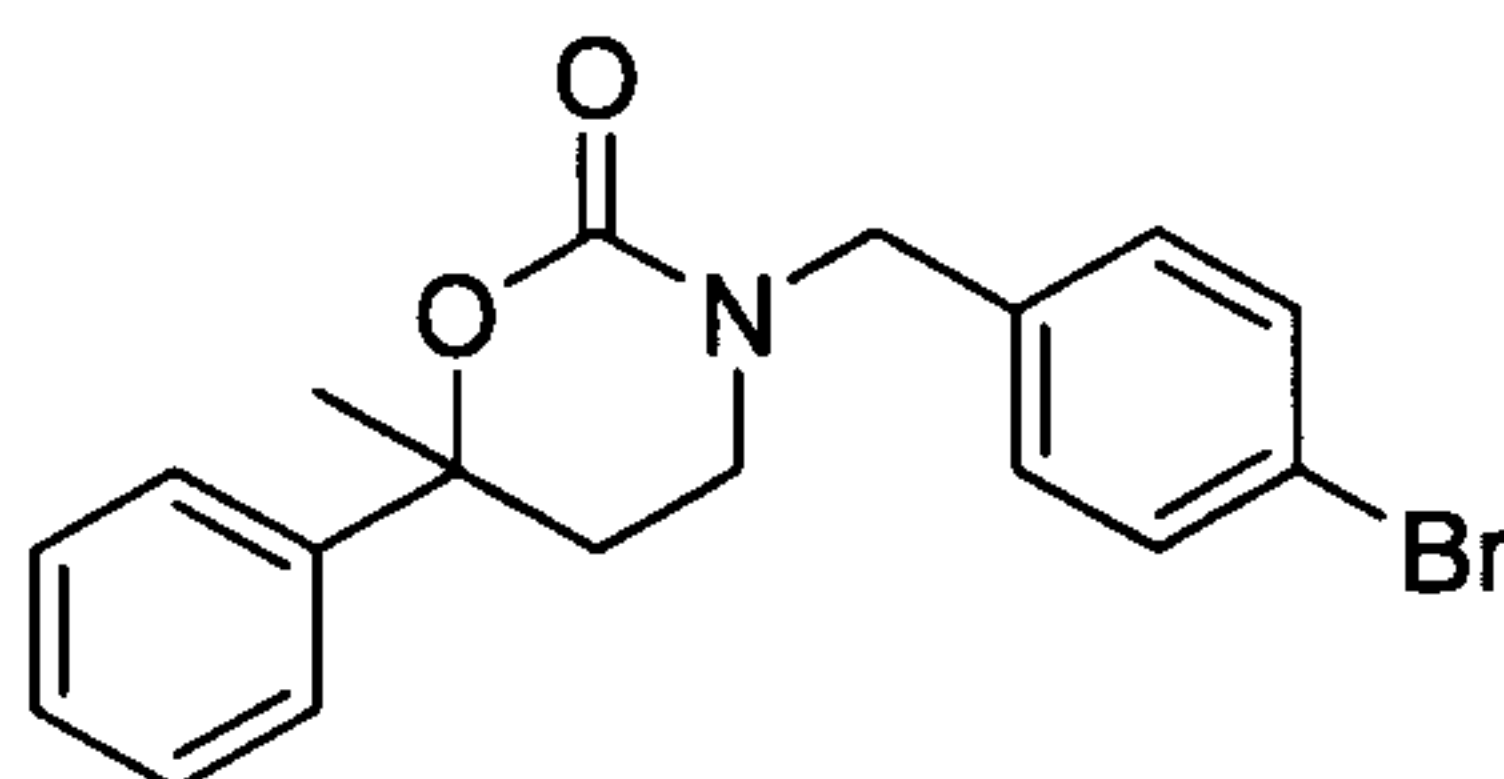
3-(2-bromobenzyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those described in Example 71 using *o*-bromobenzyl bromide in Step 3. LC-MS Method 3, $t_R = 1.305$ min, $m/z = 362$. ^1H NMR ($CDCl_3$) 1.60-1.65 (s, 3H), 2.15-2.26 (m, 1H), 2.30-2.40 (m, 1H), 2.81-2.92 (m, 1H), 3.00-3.08 (m, 1H), 4.45-4.65 (m, 2H), 6.80-6.90 (m, 1H), 7.00-7.10 (m, 1H), 7.21-7.38 (m, 5H), 7.40-7.45 (m, 1H).

EXAMPLE 73

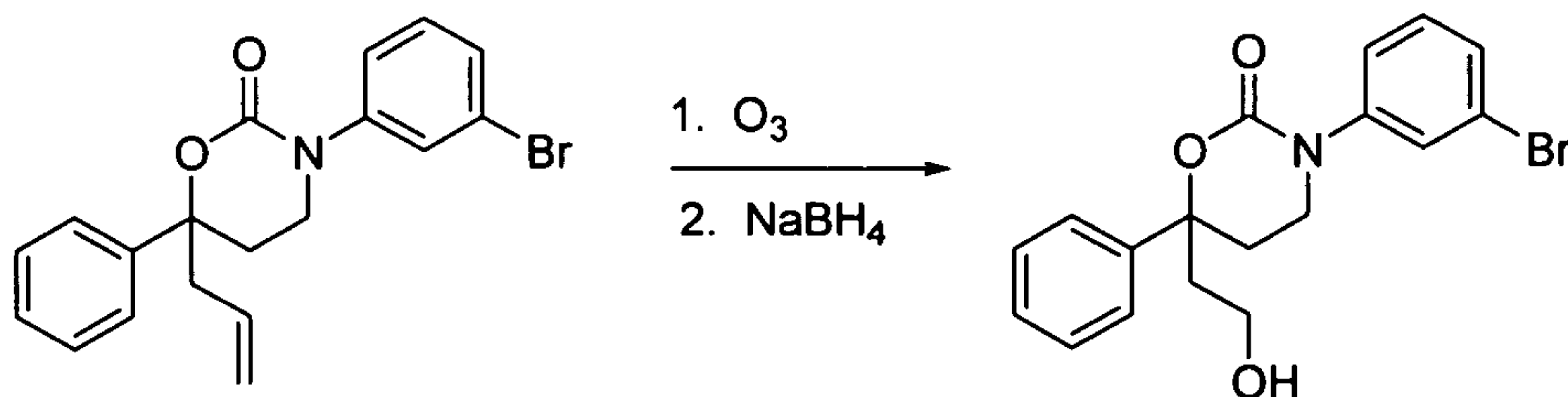
3-(4-bromobenzyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those described in Example 71 using *p*-bromobenzyl bromide in Step 3. LC-MS Method 3, $t_R = 1.317$ min, $m/z = 361.8$. ^1H NMR ($CDCl_3$) 1.55-1.65 (s, 3H), 2.10-2.20 (m, 1H), 2.30-2.40 (m, 1H), 2.79-2.80 (m, 1H), 2.90-3.00 (m, 1H), 4.25-4.50 (m, 2H), 6.80-6.90 (m, 1H), 7.21-7.38 (m, 7H).

EXAMPLE 74

3-(3-bromophenyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one



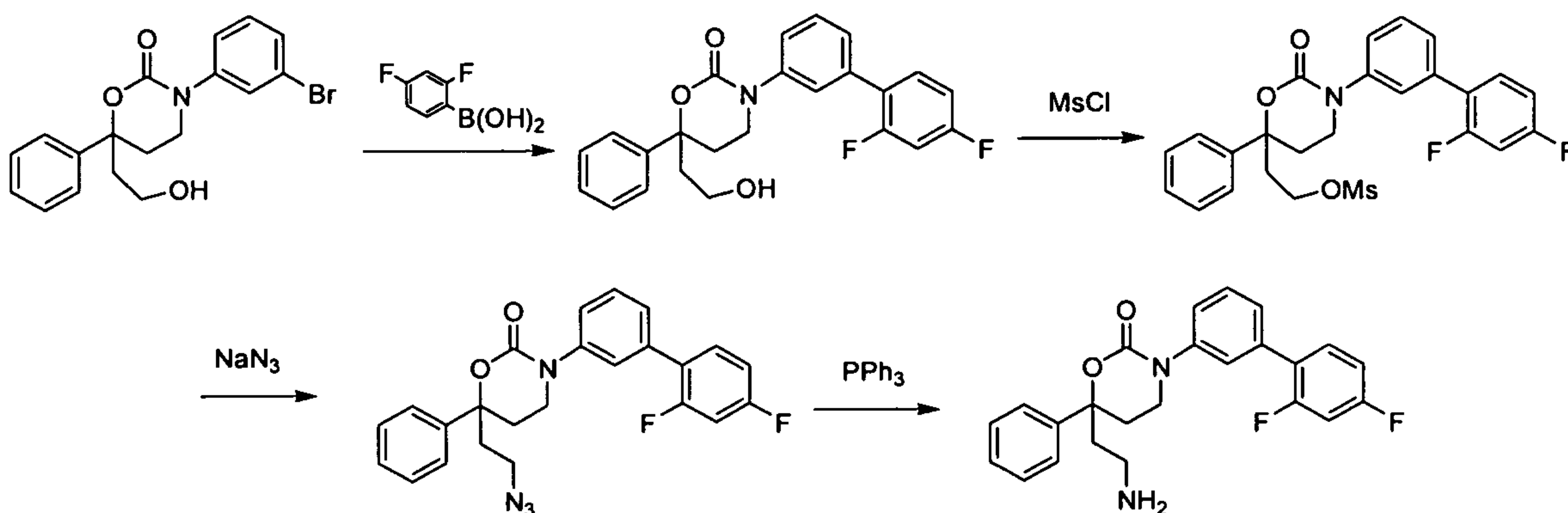
A solution of 6-allyl-3-(3-bromophenyl)-6-phenyl-1,3-oxazinan-2-one (200 mg, 0.54 mmol) in dry CH_2Cl_2 (10 mL) was treated with ozone at $-78^\circ C$ until the mixture turned blue. The system was then flushed with oxygen to remove excess ozone. $NaBH_4$ (207 mg, 5.4 mmol) was added to the mixture in portions at $-20^\circ C$. The mixture was stirred overnight at rt. The mixture was quenched with water and the

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layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give 3-(3-bromophenyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one (75 mg, 37%). ^1H NMR (400MHz, CDCl_3): δ =2.12-2.30 (m, 2H), 2.47 (m, 2H), 3.19 (m, 1H), 3.40 (m, 1H), 3.53 (m, 1H), 3.76 (m, 1H), 7.06 (m, 1H), 7.13 (m, 1H), 7.22 (m, 1H), 7.25-7.40 (m, 6H).

EXAMPLE 75

6-(2-aminoethyl)-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one



Step 1. 3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one

To a solution of 3-(3-bromophenyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one (200 mg, 0.538 mmol), 4-fluorophenylboronic acid (128 mg, 0.806 mmol), and aq. K_2CO_3 (1 mL, 2 M) in 1,4-dioxane (3 mL) was slowly added $\text{Pd}(\text{Ph}_3)_2\text{Cl}_2$ (20 mg, 10%) at 0 °C under N_2 . The mixture was refluxed overnight. The mixture was concentrated to give the crude product, which was purified by TLC and preparative HPLC to afford 3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one (200 mg, 91 %). ^1H -NMR (400MHz, CDCl_3): δ =2.12-2.35 (m, 2H), 2.51(m, 2H), 3.26 (m, 1H), 3.47-3.6 (m, 2H), 4.25 (m, 1H), 6.83 (m, 2H), 7.06 (m, 1H), 7.26-7.51 (m, 8H).

Step 2. 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl methanesulfonate

To a solution of 3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one (200 mg, 0.49 mmol) in dry CH_2Cl_2 (4 mL) was added Et_3N (0.234 mL, 1.46 mmol) at 0 ~ -5 °C. A solution of methanesulfonyl chloride (67 mg, 0.59 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise at the same temperature. After addition, the mixture was allowed to warm to rt gradually. When the reaction was complete, water (10 mL) was added and the mixture was extracted with CH_2Cl_2 .

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(3 x 10 mL). The combined organic layers were washed with 10% aq citric acid, satd aq NaHCO₃ and brine, then dried over Na₂SO₄, filtered and concentrated to give 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl methanesulfonate (230 mg, 97%), which was used in the next step without purification.

Step 3. 6-(2-azidoethyl)-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one

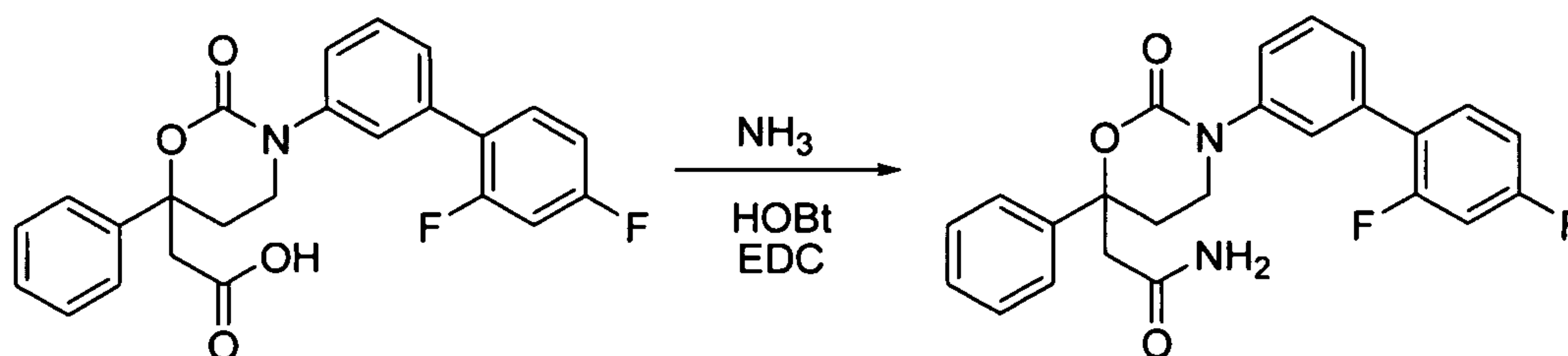
To a solution of 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl methanesulfonate (230 mg, 0.47 mmol) in anhydrous DMF (5 mL) was added NaN₃ (92 mg, 1.42 mmol). The reaction mixture was heated to 70 °C overnight. The reaction mixture was cooled to rt and diluted with EtOAc (30 mL), and water (20 mL). The organic phase was washed with water (3 x 20 mL), dried over Na₂SO₄ and evaporated to give 6-(2-azidoethyl)-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one (100 mg, 49%).

Step 4. 3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one

To a solution of 6-(2-azidoethyl)-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one (100 mg, 0.23 mmol) in 20:1 THF/H₂O (3 mL) was added PPh₃ (72 mg, 0.28 mmol). The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford 6-(2-aminoethyl)-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one (30 mg, 31%). ¹H NMR (400MHz, CDCl₃): δ=2.20-2.51 (m, 2H), 2.51-2.60 (m, 2H), 2.72 (m, 1H), 3.00 (m, 1H), 3.24 (m, 1H), 3.53 (m, 1H), 6.85-6.99 (m, 2H), 7.14 (m, 1H), 7.31-7.50 (m, 8H).

EXAMPLE 76

2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetamide



A solution of 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetic acid (30 mg, 0.072 mmol), HOBT (18 mg, 0.144 mmol), EDCI (30 mg, 0.144 mmol) and DIEA (0.2 mL) in anhydrous CH₂Cl₂ (3 mL) was stirred at 0 °C under NH₃. Then the solution was stirred at rt overnight. Solvent was removed in vacuo, the

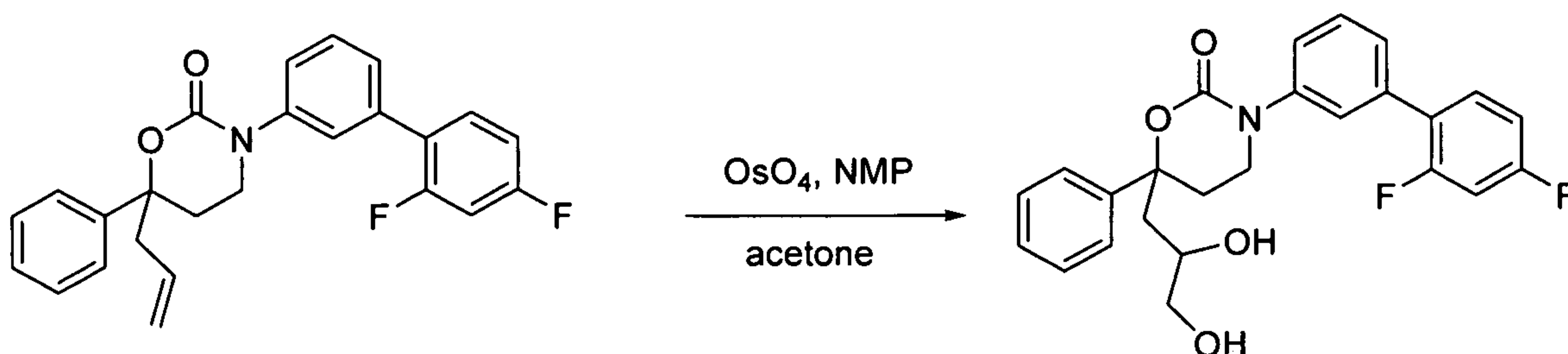
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residue was purified by HPLC to get 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl) acetamide (1.68 mg, 6%). ¹H-NMR (400MHz, CDCl₃): δ=2.58 (m, 2H), 2.80-3.00 (m, 2H), 3.27 (m, 1H), 3.50 (m, 1H), 6.00 (s, 1H), 6.36 (s, 1H), 6.78-6.90 (m, 2H), 7.05 (m, 1H), 7.23-7.55 (m, 9H).

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EXAMPLE 77

3-(2',4'-difluorobiphenyl-3-yl)-6-(2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one



Step 1. 3-(2',4'-difluorobiphenyl-3-yl)-6-(2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

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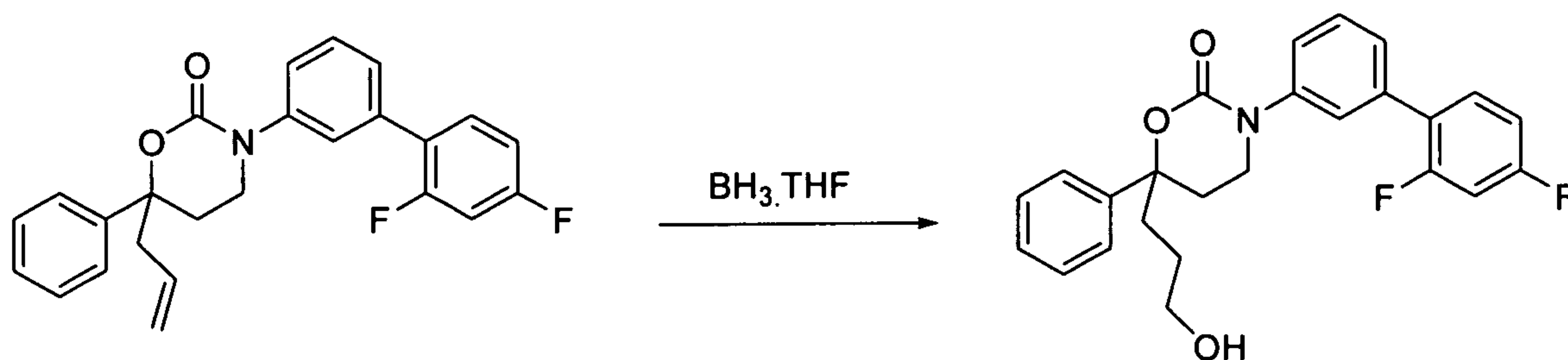
To a solution of 6-allyl-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one (7.1 mg, 0.018 mmol) in acetone (0.5 mL) was added NMO.H₂O (6 mg, .044 mmol), then OsO₄ (10 μL, 2.5 wt % in 2-Me-2-propanol). The reaction was stirred overnight at rt. The solvent was evaporated and the residue was redissolved in EtOAc. The organic layer was washed with 10% aq Na₂S₂O₃ (2 x), 1M aq HCl (2x) and brine (1 x). The organic layer was dried over Na₂SO₄, filtered, evaporated, and purified by prep HPLC to afford 3-(2',4'-difluorobiphenyl-3-yl)-6-(2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one (6.53 mg). LC-MS Method 1, m/z = 440 (M+H)⁺. ¹H NMR (CDCl₃) 7.47-7.33 (m), 7.15-7.12 (m), 6.96-6.86 (m), 3.51 (br m), 3.37-3.26 (m), 2.69 (br m), 2.58-2.48 (m), 2.29-2.23 (m), 2.14 (d), 2.06 (d).

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EXAMPLE 78

3-(2',4'-difluorobiphenyl-3-yl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one



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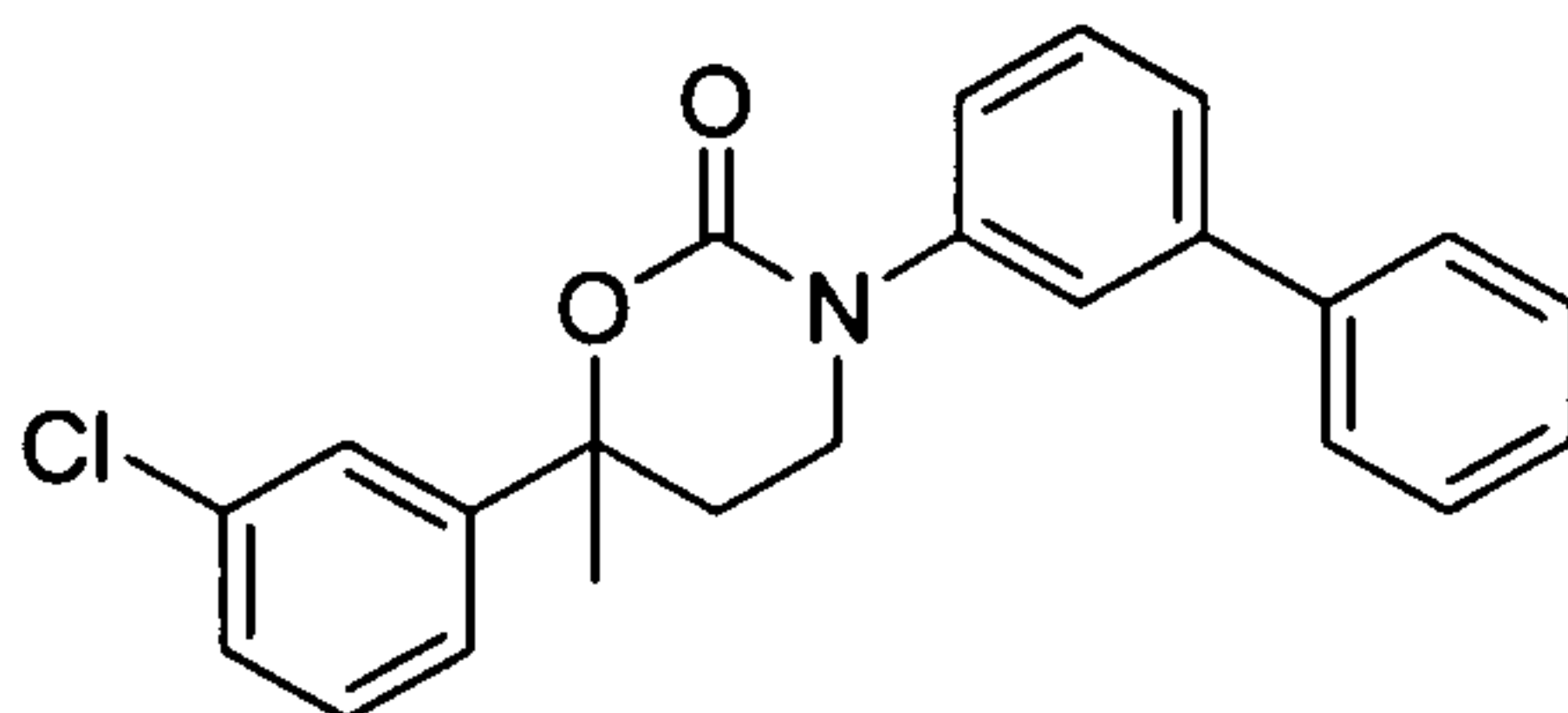
Step 1. 3-(2',4'-difluorobiphenyl-3-yl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

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To a 0 °C solution of 6-allyl-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one (18 mg, 0.045 mmol) in THF (1 mL) was added BH₃.THF (60 µL, 1M THF solution) and the mixture was stirred overnight at rt. The reaction was cooled to 0 °C and NaBO₃.H₂O (19 mg, 0.20 mmol) was added and stirred for 2 h warming to rt. The solvent was removed *in vacuo* and the residue was redissolved in CH₃CN (4 mL). The solution was filtered and purified by prep HPLC to afford 3-(2',4'-difluorobiphenyl-3-yl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one (4.44 mg). LC-MS Method 1, t_R = 1.97 min, m/z = 424 (M+H). ¹H NMR (CDCl₃) 7.47-7.33 (m), 7.32-7.26 (m), 7.16-7.12 (m), 6.96-6.85 (m), 4.28 (t), 3.52-3.13 (m), 3.36-3.27 (m), 2.5-2.47 (m), 2.15-1.99 (m).

EXAMPLE 79

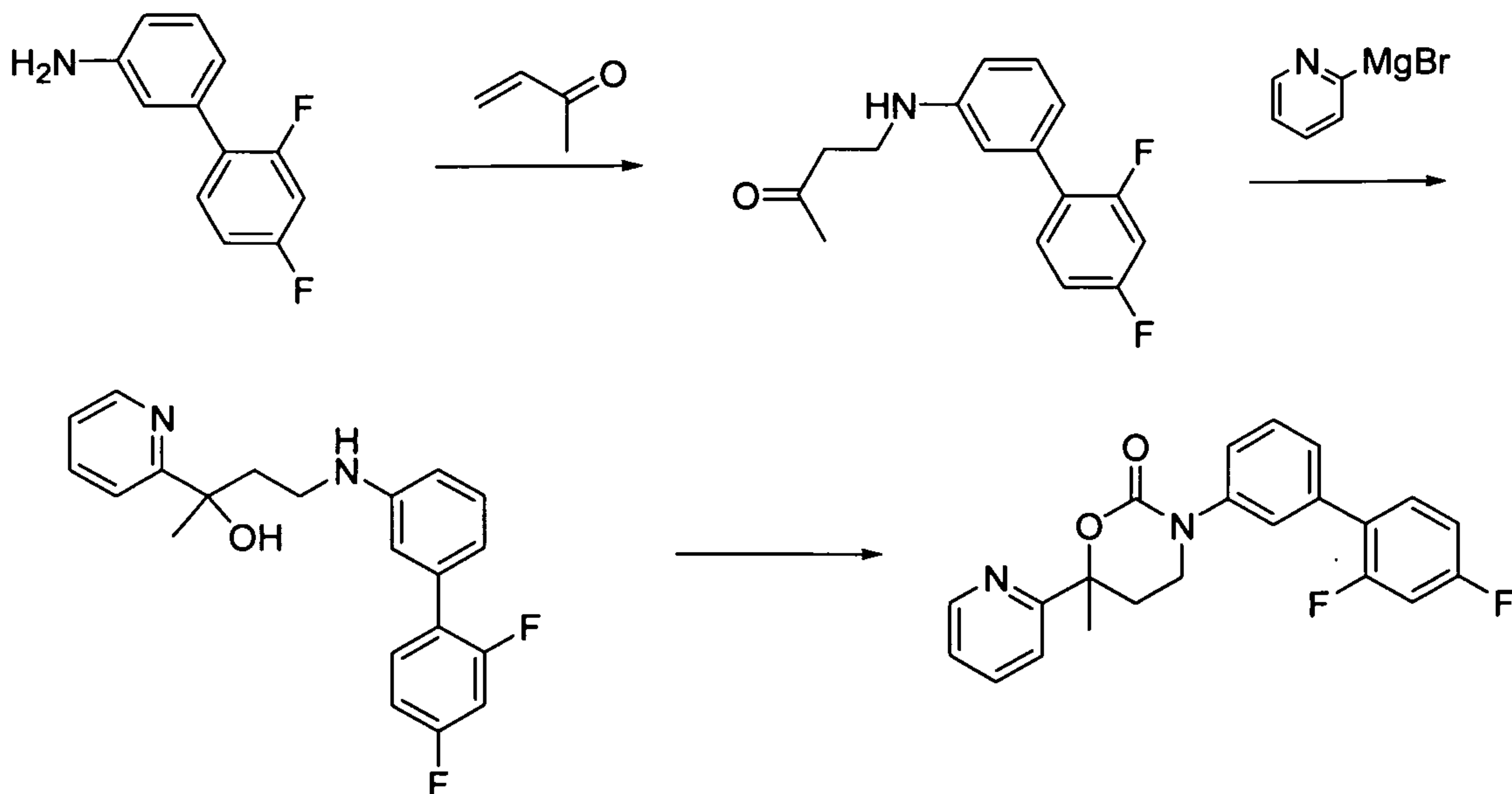
3-(biphenyl-3-yl)-6-(3-chlorophenyl)-6-methyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those described in Example 53 using 3-bromobiphenyl in Step 4. LC-MS Method 1, t_R = 1.99 min, m/z = 378, 380. ¹H NMR (CDCl₃) 1.78 (s, 3H), 2.43 (m, 2H), 3.38 (m, 1H), 3.61 (m, 1H), 7.10-7.60 (13H).

EXAMPLE 80

3-(2',4'-difluorobiphenyl-3-yl)-6-methyl-6-(pyridin-2-yl)-1,3-oxazinan-2-one

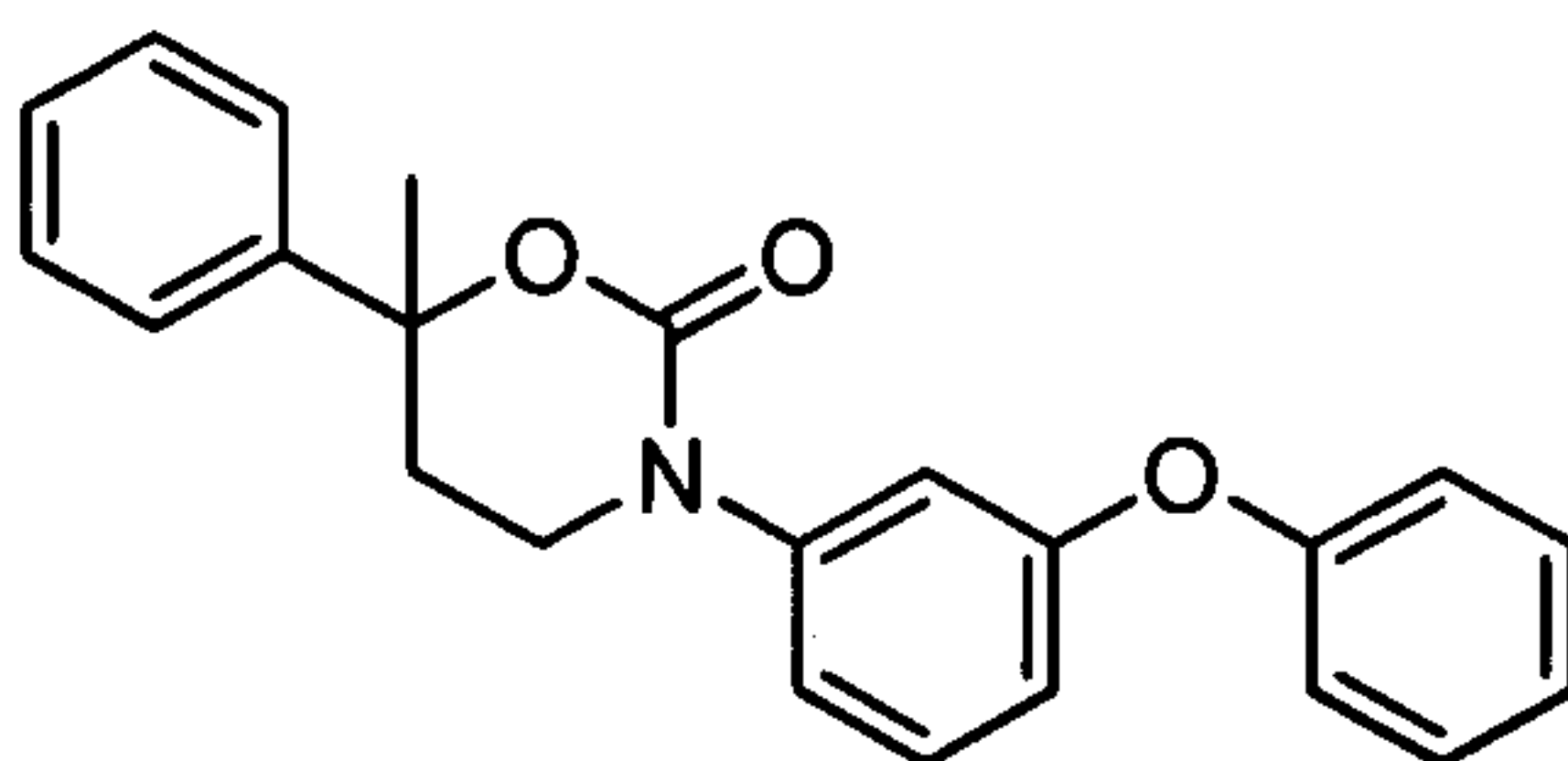


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The title compound was prepared following procedures analogous to those described in Example 82 using 2',4'-difluorobiphenyl-3-amine in Step 1 and 2-pyridylmagnesium bromide in Step 2. LC-MS Method 1, $t_R = 1.72$ min, $m/z = 381$ (M+1). ^1H NMR (CD_3OD) 8.55-8.54 (m, 1H), 7.91-7.87 (m, 1H), 7.62-7.60 (m, 1H), 7.44-7.32 (m, 4H), 7.26-7.25 (m, 1H), 7.14-7.11 (m, 1H), 7.00-6.94 (m, 2H), 3.66-3.60 (m, 1H), 3.25-3.18 (m, 1H), 2.78-2.72 (m, 1H), 2.43-2.35 (m, 1H), 1.69 (s, 3H).

EXAMPLE 81

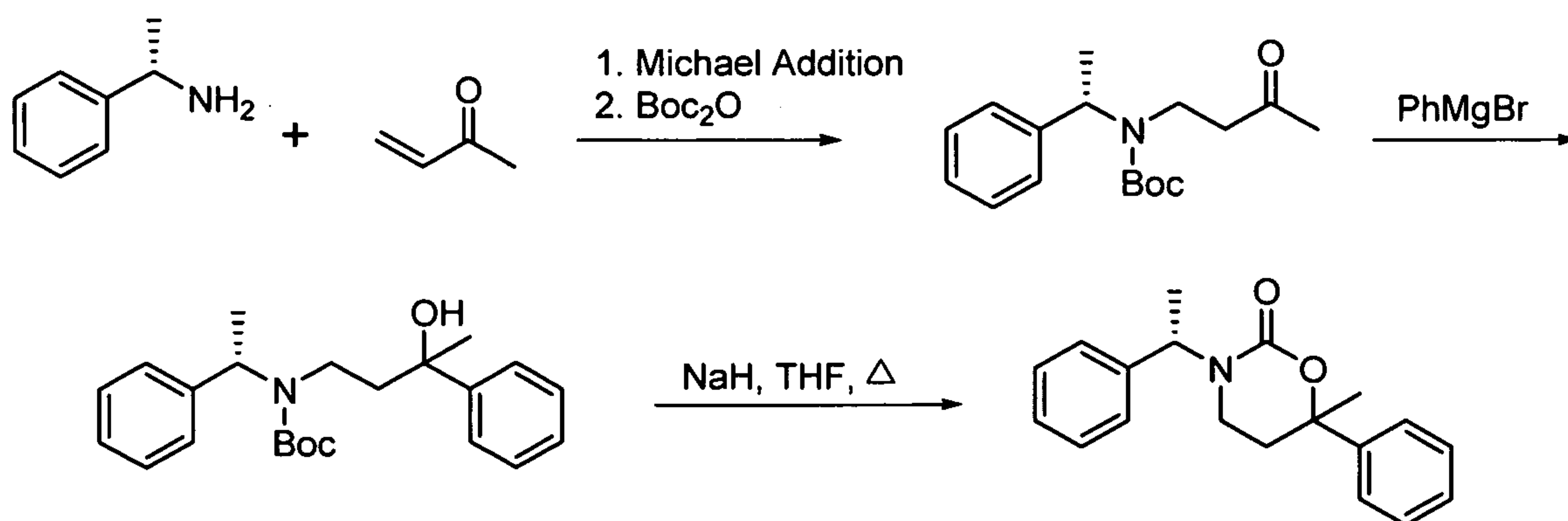
6-methyl-3-(3-phenoxyphenyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared following procedures analogous to those described in Example 82 using 3-phenoxyaniline in Step 1. LC-MS Method 1, $t_R = 1.9$ min, $m/z = 360$ (M+1). ^1H NMR (CD_3OD) 7.37-7.22 (m, 8H), 7.08-7.04 (m, 1H), 6.92-6.90 (m, 2H), 6.81-6.78 (m, 2H), 6.68-6.67 (m, 1H), 3.55-3.50 (m, 1H), 3.18-3.11 (m, 1H), 2.58-2.53 (m, 1H), 2.39-2.31 (m, 1H), 1.63 (s, 3H).

EXAMPLE 82

6-methyl-6-phenyl-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one



Step 1. (S)-*tert*-Butyl 3-oxobutyl(1-phenylethyl)carbamate

A solution of (S)-1-phenylethanamine (0.1901 g, 1.57 mmol, 1.0 equiv) and methyl vinyl ketone (0.1117 g, 1.59 mmol, 1.02 equiv) in THF (5 mL) was allowed to stand in a refrigerator (ca. 3.3 °C) for 2 d. Boc_2O (0.6700 g, 3.07 mmol, 1.95 equiv) was added to the solution at rt. The solution was stirred for 2 h and the solvent was removed under reduced pressure. The residue was purified by chromatography on

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silica gel eluted with hexanes/EtOAc to give (S)-*tert*-butyl 3-oxobutyl(1-phenylethyl)carbamate (0.3235 g, 71% over two steps) as a colorless oil.

Step 2. *tert*-Butyl 3-hydroxy-3-phenylbutyl((S)-1-phenylethyl)carbamate

A solution of phenylmagnesium bromide (1.0 M in THF, 1.0 mL) was added dropwise to a solution of (S)-*tert*-butyl 3-oxobutyl(1-phenylethyl)carbamate (0.0421 g, 0.144 mmol in THF (4 mL) under N₂ at rt. After the solution was stirred for 14 h, the reaction was quenched with 10% aq Na₂CO₃ (0.5 mL) and diluted with CH₂Cl₂. The organic layer was dried over Na₂SO₄. After the solvents were evaporated, the crude product was directly used in the next step without further purification.

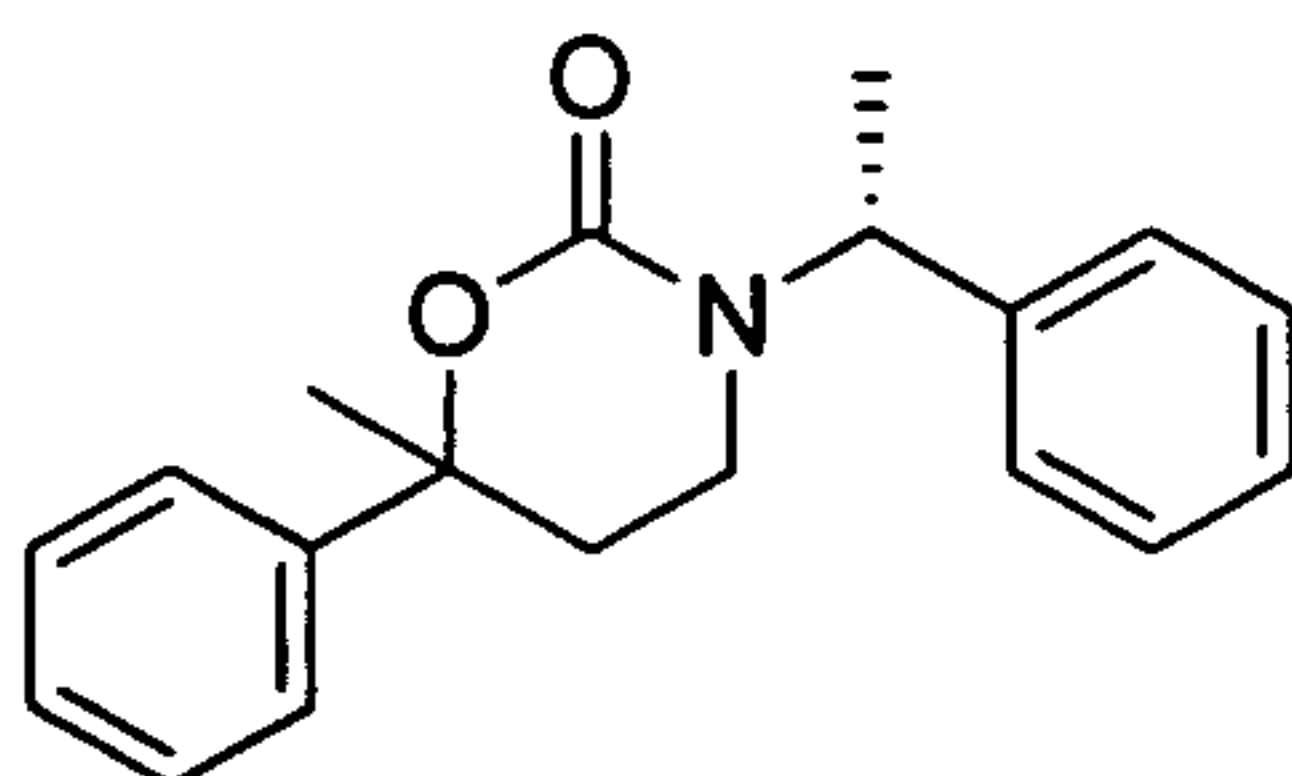
Step 3. 6-Methyl-6-phenyl-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one

A mixture of crude *tert*-butyl 3-hydroxy-3-phenylbutyl((S)-1-phenylethyl)carbamate, obtained as described above, 60% NaH in oil (0.320 g) and THF (5 mL) was heated to reflux for 21 h. The reaction was then quenched with H₂O (1.5 mL) and diluted with CH₂Cl₂. The organic layer was dried over Na₂SO₄. After the solvents were evaporated, the residue was purified by reversed-phase HPLC to afford 6-methyl-6-phenyl-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one. After the solvents were evaporated, the residue was purified by reversed-phase HPLC (phenomenex® Luna 5μ C18(2) 100A, 250 × 21.20 mm, 5 micron, 10% → 90% CH₃CN/H₂O, 0.1% CF₃COOH over 13 min and then 90% CH₃CN/H₂O, 0.1% CF₃COOH over 4 min, flow rate 25 mL/min) to afford 6-methyl-6-phenyl-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one as a mixture of diastereomers. LC-MS Method 1 *t*_R = 1.71, 1.75 min, *m/z* = 296 (MH⁺); ¹H NMR (400 MHz, CD₃OD) δ 7.36-7.18 (m), 7.06-7.02 (m), 6.89-6.85 (m), 5.54 (q, J = 7.1 Hz), 5.47 (q, J = 7.0 Hz), 3.00-2.95 (m), 2.73-2.69 (m), 2.40-2.34 (m), 2.26-2.19 (m), 2.13-2.05 (m), 2.00-1.92 (m), 1.53 (s), 1.52 (s), 1.45 (d, J = 7.0 Hz), 1.23 (d, J = 7.0 Hz). A fraction containing on the less polar diastereomer was also isolated (Isomer 1). LC-MS Method 1 *t*_R = 1.75 min, *m/z* = 296 (MH⁺); ¹H NMR (400 MHz, CD₃OD) δ 7.35-7.18 (m, 10H), 5.54 (q, J = 7.0 Hz, 1H), 2.72-2.69 (m, 2H), 2.39-2.33 (m, 1H), 1.99-1.92 (m, 1H), 1.52 (s, 3H), 1.23 (d, J = 7.0 Hz, 3H).

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EXAMPLE 83

6-methyl-6-phenyl-3-((R)-1-phenylethyl)-1,3-oxazinan-2-one



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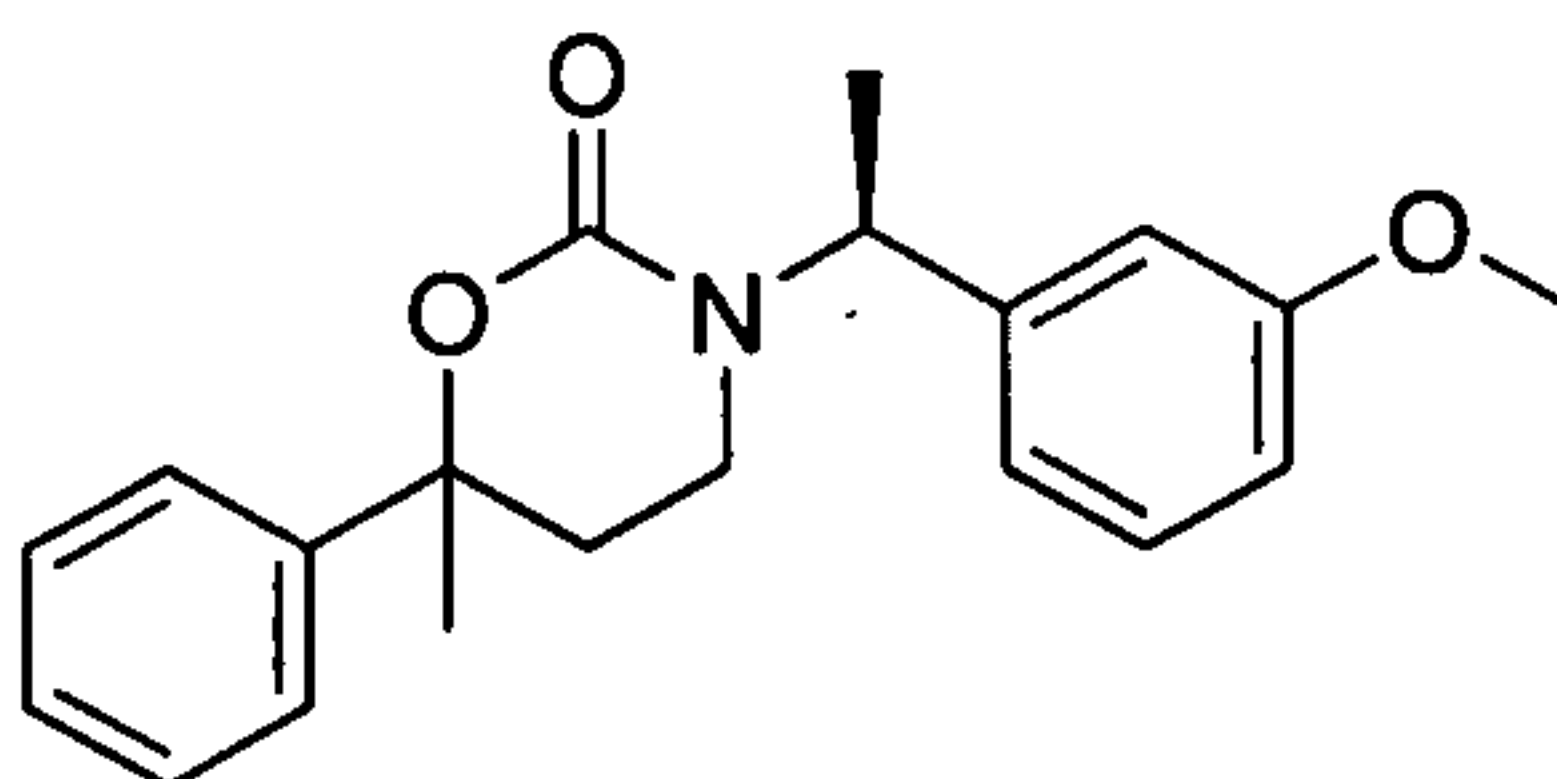
The two diastereomers of the title compound were prepared and separated following procedures analogous to those described in Example 82 using (*R*)-1-phenylethanamine in Step 1.

Isomer 1: LC-MS Method 1, t_R = 1.75 min, m/z = 296 ($M+1$). ^1H NMR (CD₃OD) 7.35-7.18 (m, 10H), 5.54 (q, J = 7.1 Hz, 1H), 2.72-2.69 (m, 2H), 2.39-2.34 (m, 1H), 2.00-1.92 (m, 1H), 1.52 (s, 3H), 1.23 (d, J = 7.0 Hz, 3H).

Isomer 2: LC-MS Method 1, t_R = 1.71 min, m/z = 296 ($M+1$). ^1H NMR (CD₃OD) 7.37-7.18 (m), 7.06-7.01 (m), 6.89-6.85 (m), 5.54 (q, J = 7.2 Hz), 5.47 (q, J = 7.0 Hz), 3.00-2.95 (m), 2.72-2.69 (m), 2.40-2.34 (m), 2.25-2.18 (m), 2.13-2.05 (m), 2.00-1.92 (m), 1.53 (s), 1.52 (s), 1.45 (d, J = 7.0 Hz), 1.23 (d, J = 7.0 Hz).

EXAMPLE 84

3-((*S*)-1-(3-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



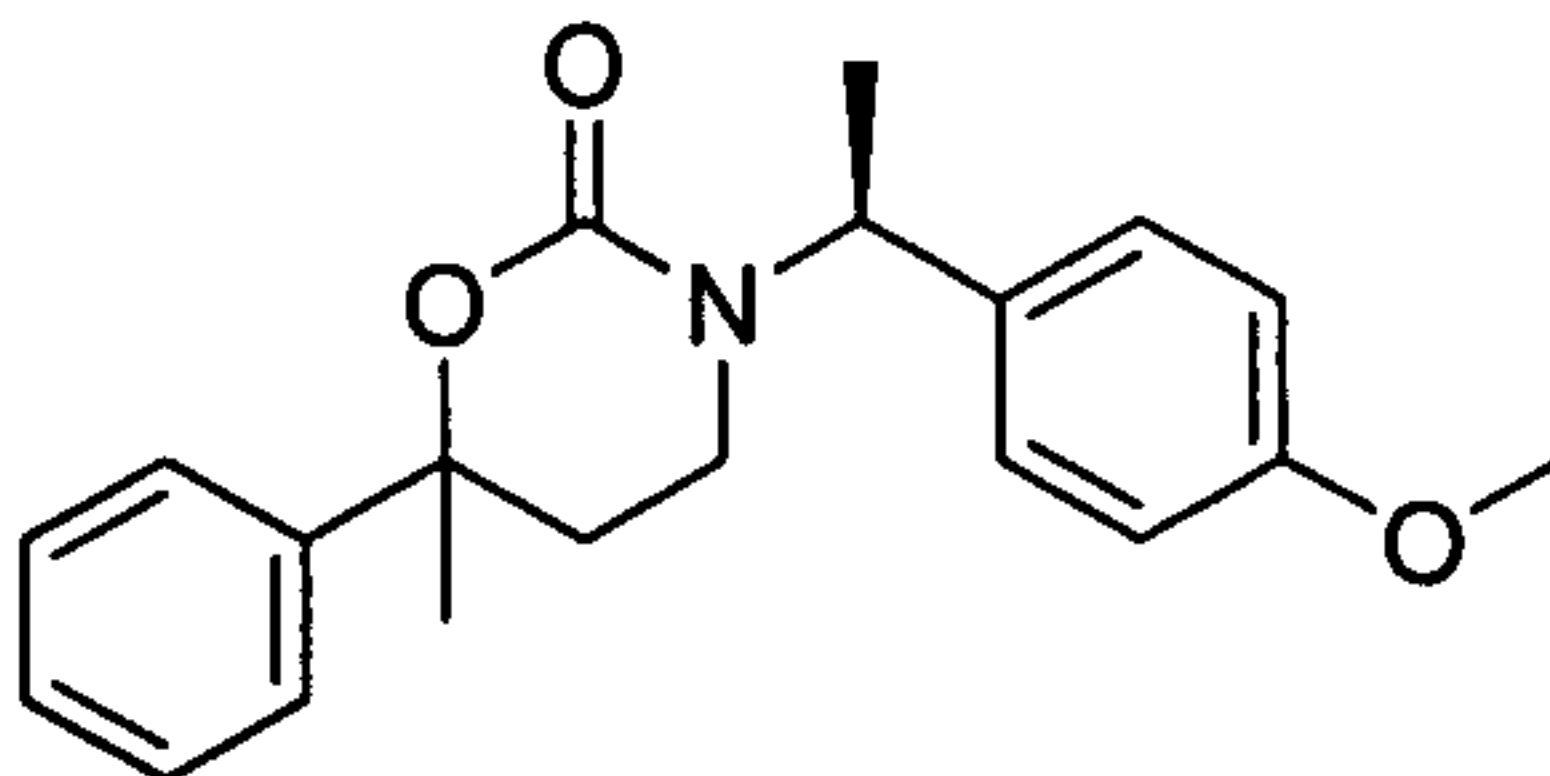
The two diastereomers of the title compound were prepared and separated following procedures analogous to those described in Example 82 using (*S*)-1-(3-methoxyphenyl)ethanamine in Step 1.

Isomer 1: LC-MS Method 1, t_R = 1.72 min, m/z = 326 ($M+1$). ^1H NMR (CDCl₃) 7.40-7.23 (m, 6H), 6.91-6.80 (m, 3H), 5.78 (q, J = 7.0 Hz, 1H), 3.80 (s, 3H), 2.70-2.67 (m, 2H), 2.29-2.23 (m, 1H), 2.06-1.98 (m, 1H), 1.64 (s, 3H), 1.27 (d, J = 7.3 Hz, 3H).

Isomer 2: LC-MS Method 1, t_R = 1.68 min, m/z = 326 ($M+1$). ^1H NMR (CDCl₃) 7.34-7.25 (m, 5H), 7.06-7.02 (m, 1H), 6.70-6.67 (m, 1H), 6.57-6.54 (m, 2H), 5.68 (q, J = 7.0 Hz, 1H), 3.63 (s, 3H), 2.92-2.87 (m, 1H), 2.39-2.26 (m, 2H), 2.17-2.10 (m, 1H), 1.64 (s, 3H), 1.52 (d, J = 7.0 Hz, 3H).

EXAMPLE 85

3-((*S*)-1-(4-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



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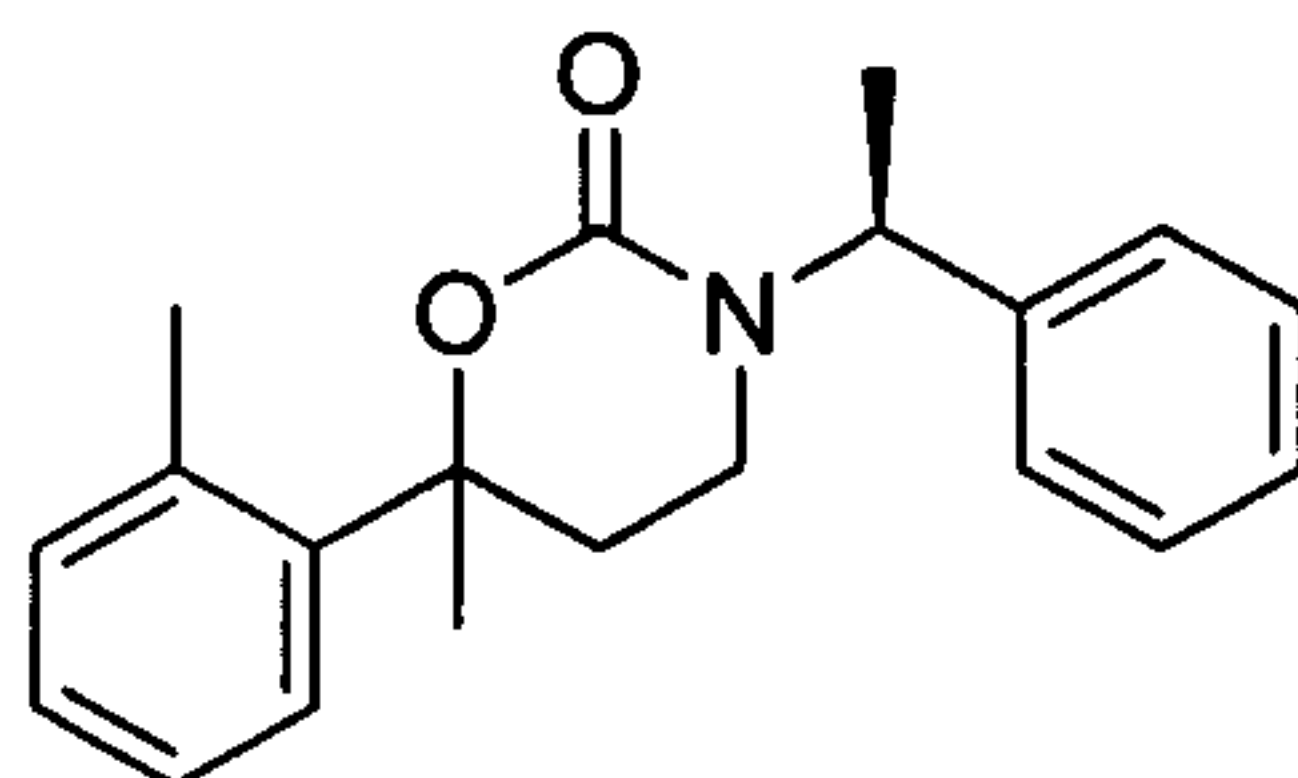
The two diastereomers of the title compound were prepared and separated following procedures analogous to those described in Example 82 (S)-1-(4-methoxyphenyl)ethanamine in Step 1.

Isomer 1: LC-MS Method 1, t_R = 1.72 min, m/z = 326 ($M+1$). ^1H NMR ($CDCl_3$)
 5 7.40-7.21 (m, 7H), 6.88-6.84 (m, 2H), 5.76 (q, J = 7.1 Hz, 1H), 3.80 (s, 3H), 2.68-2.65 (m, 2H), 2.27-2.22 (m, 1H), 2.02-1.95 (m, 1H), 1.62 (s, 3H), 1.26 (d, J = 7.3 Hz, 3H).

Isomer 2: LC-MS Method 1, t_R = 1.68 min, m/z = 326 ($M+1$). ^1H NMR ($CDCl_3$)
 7.37-7.27 (m, 5H), 6.88-6.84 (m, 2H), 6.66-6.62 (m, 2H), 5.65 (q, J = 7.1 Hz, 1H),
 3.73 (s, 3H), 2.90-2.85 (m, 1H), 2.32-2.25 (m, 2H), 2.16-2.09 (m, 1H), 1.64 (s, 3H),
 10 1.50 (d, J = 7.0 Hz, 3H).

EXAMPLE 86

6-methyl-3-((S)-1-phenylethyl)-6-o-tolyl-1,3-oxazinan-2-one



15 The two diastereomers of the title compound were prepared and separated following procedures analogous to those described in Example 82 using o-tolylmagnesium bromide in Step 2.

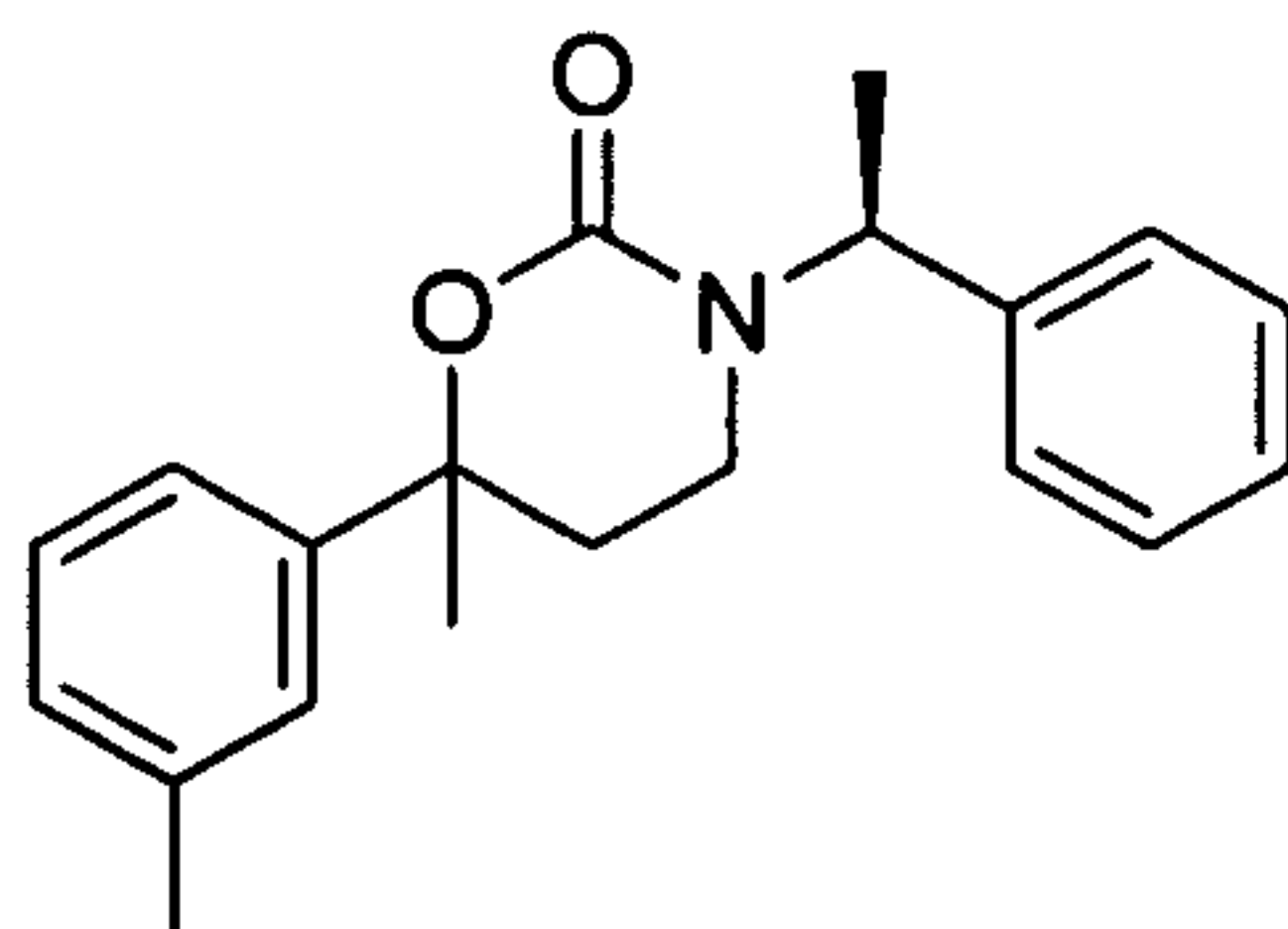
Isomer 1: LC-MS Method 1, t_R = 1.83 min, m/z = 310 ($M+1$). ^1H NMR ($CDCl_3$)
 7.42-7.16 (m, 9H), 5.77 (q, J = 7.1 Hz, 1H), 2.79-2.66 (m, 2H), 2.61-2.55 (m, 1H),
 20 2.47 (s, 3H), 2.03-1.95 (m, 1H), 1.70 (s, 3H), 1.27 (d, J = 7.3 Hz, 3H).

Isomer 2: LC-MS Method 1, t_R = 1.79 min, m/z = 310 ($M+1$). ^1H NMR ($CDCl_3$)
 7.35-7.33 (m, 1H), 7.23-7.06 (m, 6H), 6.86-6.84 (m, 2H), 5.66 (q, J = 7.0 Hz, 1H),
 2.96-2.91 (m, 1H), 2.62-2.56 (m, 1H), 2.48 (s, 3H), 2.43-2.36 (m, 1H), 2.16-2.08 (m,
 1H), 1.71 (s, 3H), 1.53 (d, J = 7.0 Hz, 3H).

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EXAMPLE 87

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



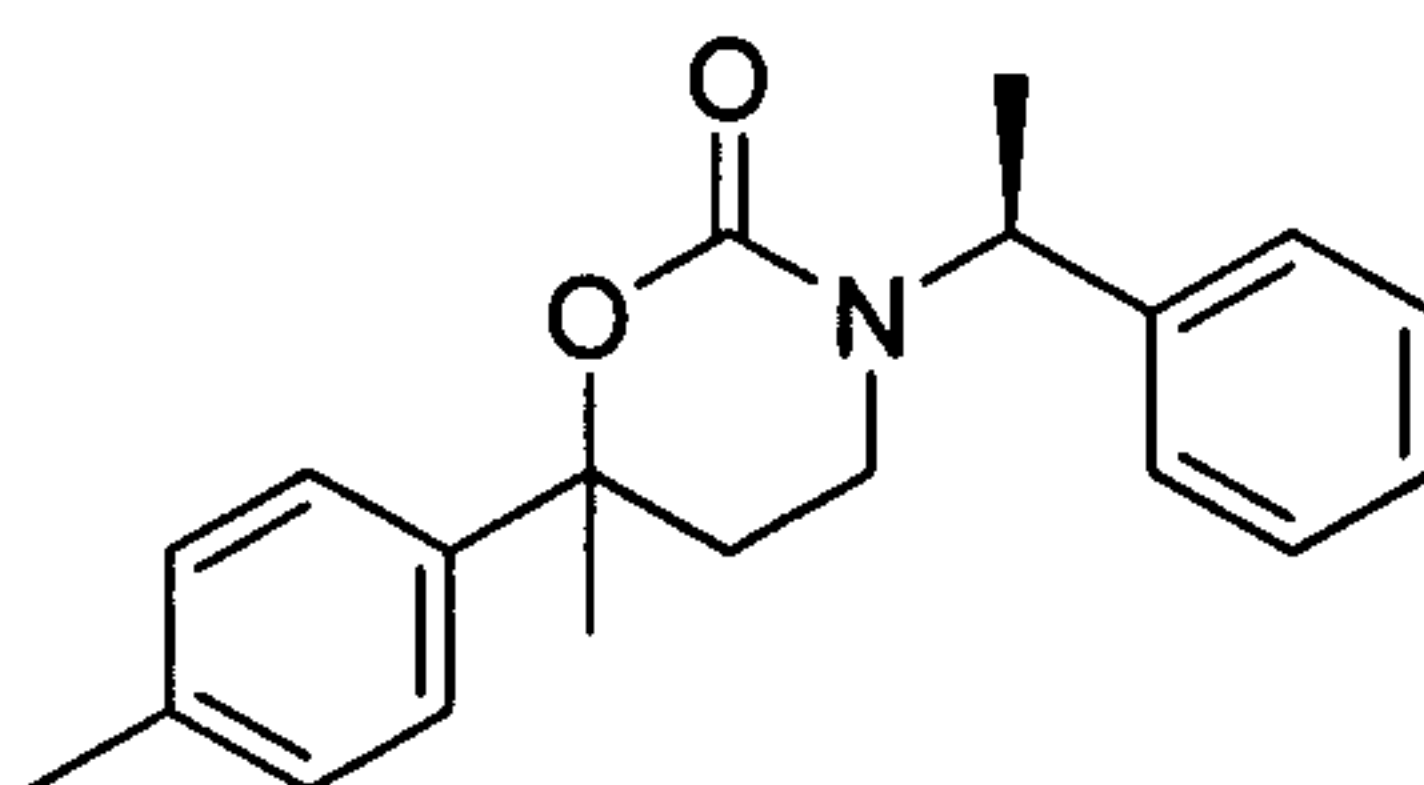
- 163 -

The two diastereomers of the title compound were prepared and separated following procedures analogous to those described in Example 82 using *m*-tolylmagnesium bromide in Step 2.

Isomer 1: LC-MS Method 1, $t_R = 1.84$ min, $m/z = 310$ ($M+1$). ^1H NMR ($CDCl_3$)
 5 7.36-7.24 (m, 6H), 7.16-7.10 (m, 3H), 5.81 (q, $J = 7.1$ Hz, 1H), 2.74-2.63 (m, 2H),
 2.37 (s, 3H), 2.26-2.21 (m, 1H), 2.03-1.95 (m, 1H), 1.62 (s, 3H), 1.31 (d, $J = 7.0$ Hz,
 3H).

Isomer 2: LC-MS Method 1, $t_R = 1.80$ min, $m/z = 310$ ($M+1$). ^1H NMR ($CDCl_3$)
 7.24-7.20 (m, 1H), 7.14-7.09 (m, 6H), 6.98-6.95 (m, 2H), 5.73 (q, $J = 7.0$ Hz, 1H),
 10 2.93-2.87 (m, 1H), 2.35 (s, 3H), 2.34-2.23 (m, 2H), 2.17-2.09 (m, 1H), 1.64 (s, 3H),
 1.53 (d, $J = 7.0$ Hz, 3H).

EXAMPLE 88

6-methyl-3-((*S*)-1-phenylethyl)-6-*p*-tolyl-1,3-oxazinan-2-one

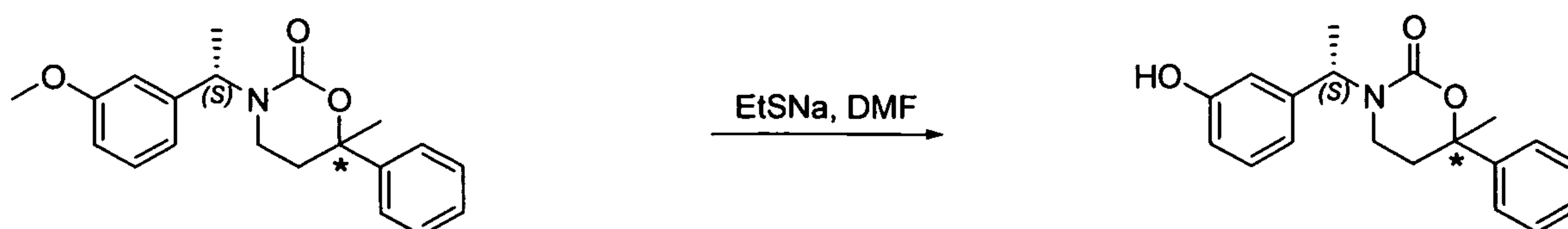
15

The two diastereomers of the title compound were prepared and separated following procedures analogous to those described in Example 82 using *p*-tolylmagnesium bromide in Step 2.

Isomer 1: LC-MS Method 1, $t_R = 1.86$ min, $m/z = 310$ ($M+1$). ^1H NMR ($CDCl_3$)
 20 7.36-7.17 (m, 9H), 5.81 (q, $J = 7.2$ Hz, 1H), 2.74-2.63 (m, 2H), 2.35 (s, 3H), 2.25-2.20
 (m, 1H), 2.03-1.95 (m, 1H), 1.61 (s, 3H), 1.31 (d, $J = 7.3$ Hz, 3H).

Isomer 2: LC-MS Method 1, $t_R = 1.80$ min, $m/z = 310$ ($M+1$). ^1H NMR ($CDCl_3$)
 7.22-7.19 (m, 2H), 7.16-7.08 (m, 5H), 6.96-6.93 (m, 2H), 5.71 (q, $J = 7.0$ Hz, 1H),
 2.92-2.87 (m, 1H), 2.36 (s, 3H), 2.35-2.23 (m, 2H), 2.16-2.08 (m, 1H), 1.62 (s, 3H),
 25 1.53 (d, $J = 7.0$ Hz, 3H).

EXAMPLE 89

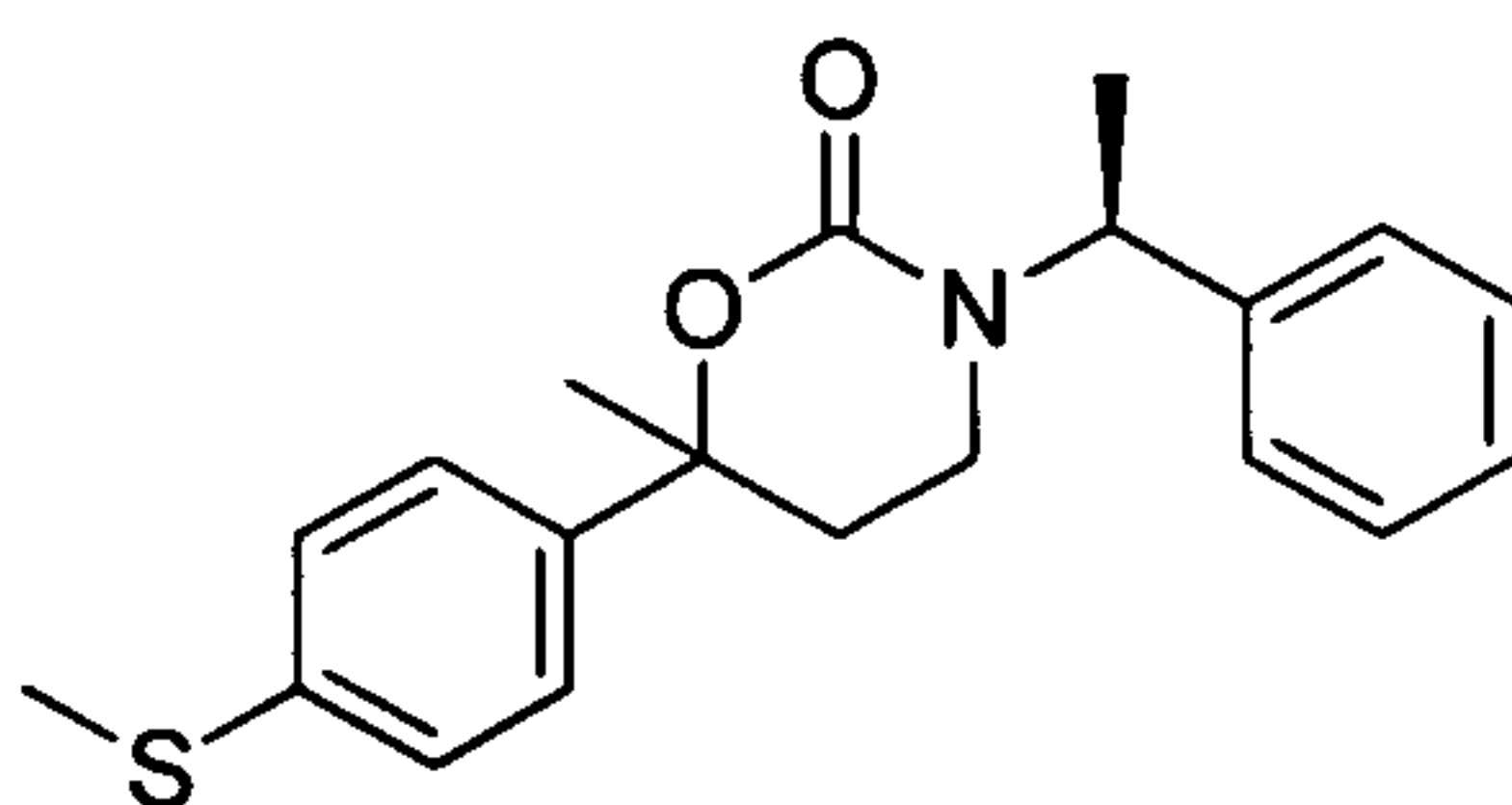
3-((*S*)-1-(3-hydroxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one

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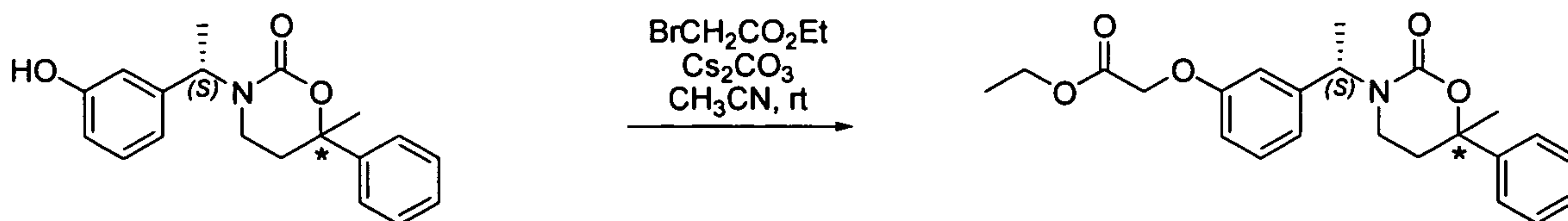
A mixture of 3-((*S*)-1-(3-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one Isomer 1 (0.1240 g, 0.381 mmol) and EtSNa (0.2115 g, 2.51 mmol) in DMF (2 mL) was heated at 170 °C for 2.5 h under nitrogen. The mixture was diluted with EtOAc, washed with 1 *N* aq HCl. The aqueous phase was extracted with EtOAc (2 ×). The combined organic phase was dried over Na₂SO₄. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/EtOAc to afford of 3-((*S*)-1-(3-hydroxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (0.1036 g, 87%). LC-MS Method 1 *t_R* = 1.49 min, *m/z* 312 (MH⁺); ¹H NMR (400 MHz, CDCl₃) δ 7.59-7.53 (m, 1H), 7.40-7.28 (m, 5H), 7.19-7.15 (m, 1H), 6.98 (m, 1H), 6.83-6.75 (m, 2H), 5.74 (q, *J* = 7.1 Hz, 1H), 2.80-2.67 (m, 2H), 2.30-2.25 (m, 1H), 2.09-2.01 (m, 1H), 1.62 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H).

EXAMPLE 90

6-methyl-6-(4-(methylthio)phenyl)-3-((*S*)-1-phenylethyl)-1,3-oxazinan-2-one

The title compound was prepared following procedures analogous to those described in Example 82 using *p*-(methylthio)phenylmagnesium bromide in Step 2. LC-MS Method 1, *t_R* = 1.84 min, *m/z* = 342 (M+1). ¹H NMR (CDCl₃) 7.37-7.24 (m, 9H), 5.81 (q, *J* = 7.2 Hz, 1H), 2.75-2.65 (m, 2H), 2.50 (s, 3H), 2.25-2.19 (m, 1H), 2.04-1.96 (m, 1H), 1.61 (s, 3H), 1.33 (d, *J* = 7.0 Hz, 3H).

EXAMPLE 91

ethyl 2-(3-((1*S*)-1-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)ethyl)phenoxy)acetate

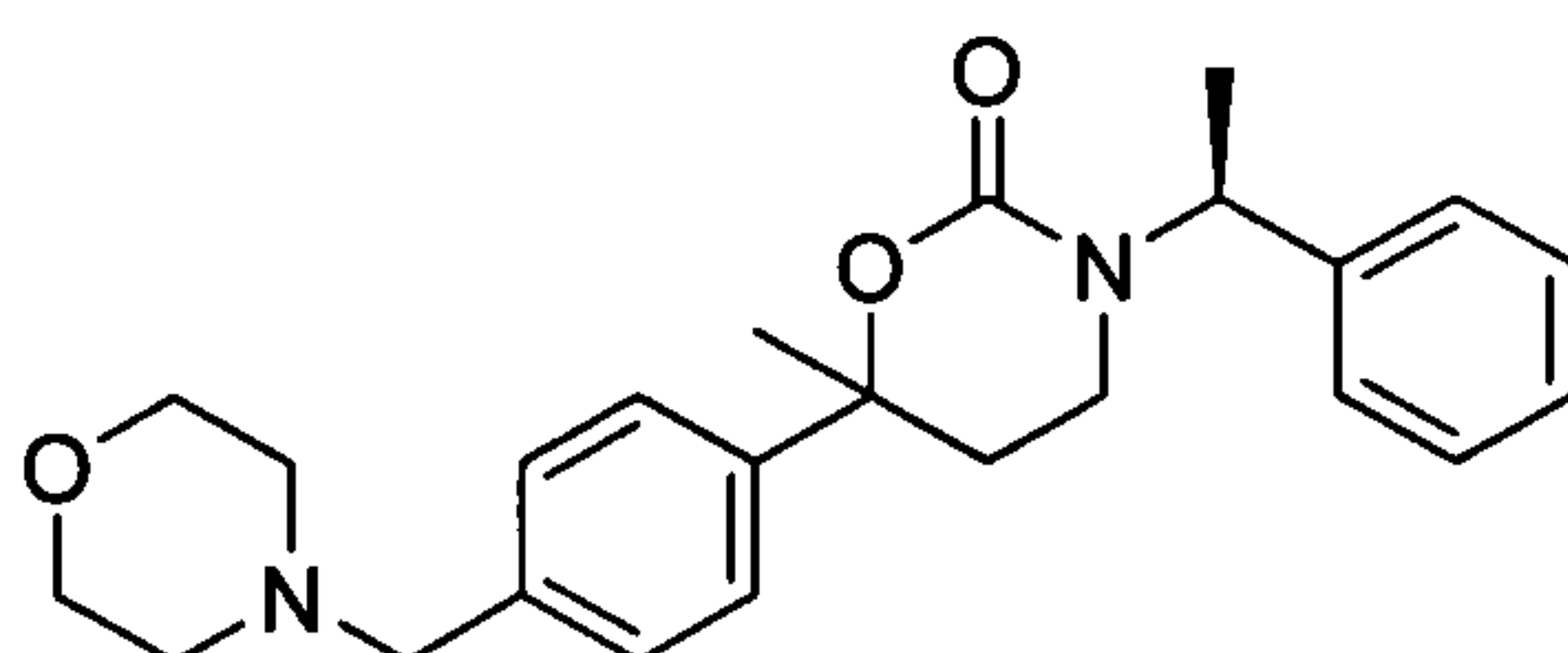
A mixture of (*R/S*)-3-((*S*)-1-(3-hydroxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one (0.0955 g, 0.31 mmol, 1.0 equiv), Cs₂CO₃ (0.3307 g, 1.01 mmol, 3.3 equiv), and ethyl bromoacetate (0.1468 g, 0.88 mmol, 2.8 equiv) in CH₃CN (1.5 mL) was stirred at rt for 3 d. The mixture was diluted with CH₂Cl₂, treated with H₂O (2 mL), dried over Na₂SO₄. After the solvents were evaporated, the residue was purified

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by chromatography on silica gel eluted with hexanes/EtOAc to afford 0.1025 g (84%) of ethyl 2-(3-((*S*)-1-((*R/S*)-6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)ethyl)phenoxy)acetate. LC-MS Method 1, $t_R = 1.75$ min, $m/z = 398$ ($M+1$). ^1H NMR ($CDCl_3$) 7.40-7.23 (m, 6H), 6.95-6.93 (m, 1H), 6.88 (m, 1H), 6.81-6.78 (m, 1H), 5.76 (q, $J = 7.1$ Hz, 1H), 4.61 (s, 2H), 4.27 (q, $J = 7.1$ Hz, 2H), 2.68-2.65 (m, 2H), 2.28-2.23 (m, 1H), 2.06-1.98 (m, 1H), 1.63 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.26 (d, $J = 7.3$ Hz, 3H).

EXAMPLE 92

10 6-methyl-6-(4-(morpholinomethyl)phenyl)-3-((*S*)-1-phenylethyl)-1,3-oxazinan-2-one

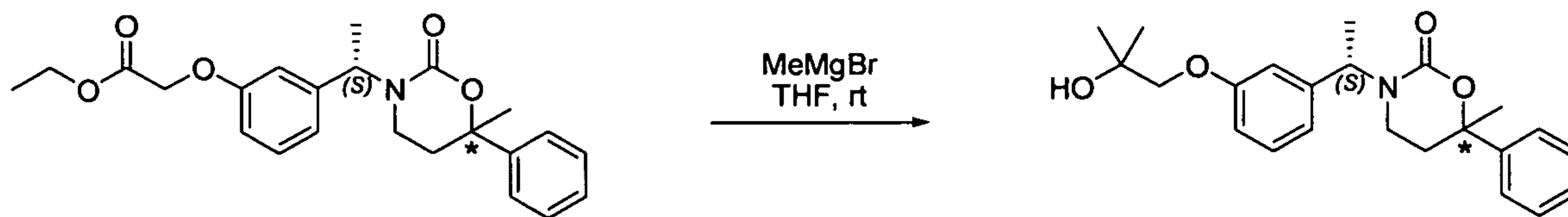


The title compound was prepared following procedures analogous to those described in Example 82 using (4-(morpholinomethyl)phenyl)magnesium bromide in Step 2. LC-MS Method 1, $t_R = 1.12$ min, $m/z = 395$ ($M+1$). ^1H NMR (CD_3OD) 7.48 (d, $J = 8.5$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.27-7.16 (m, 5H), 5.51 (q, $J = 7.2$ Hz, 1H), 4.28 (s, 2H), 3.95-3.92 (m, 2H), 3.66-3.60 (m, 2H), 3.28-3.25 (m, 2H), 3.13-3.08 (m, 2H), 2.72-2.69 (m, 2H), 2.36-2.30 (m, 1H), 2.02-1.94 (m, 1H), 1.49 (s, 3H), 1.22 (d, $J = 7.0$ Hz, 3H).

20

EXAMPLE 93

(*R/S*)-3-((*S*)-1-(3-(2-hydroxy-2-methylpropoxy)phenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one



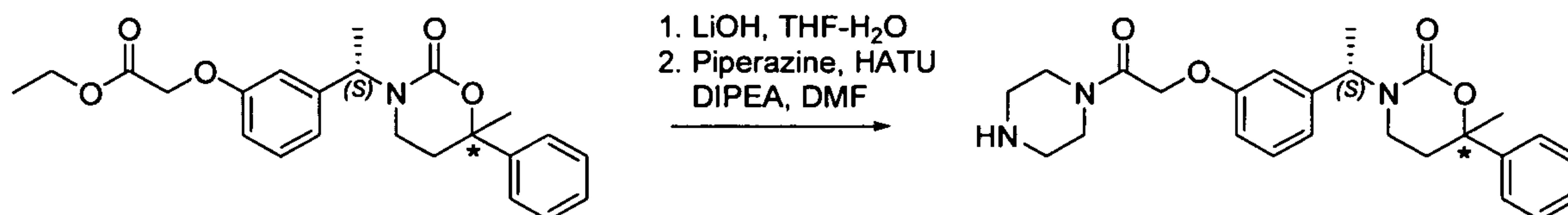
To a solution of ethyl 2-(3-((*S*)-1-((*R/S*)-6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)ethyl)phenoxy)acetate (0.0369 g, 0.0928 mmol) in THF (5 mL) was added methylmagnesium bromide (1.4 *M* in toluene/THF, 1.0 mL, 1.4 mmol) at rt under nitrogen. After stirring for 1 h, the mixture was quenched with saturated NH_4Cl (1 mL), diluted with CH_2Cl_2 , and dried over Na_2SO_4 . After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/EtOAc to afford 0.0268 g (75%) of (*R/S*)-3-((*S*)-1-(3-(2-hydroxy-2-

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methylpropoxy)phenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one. LC-MS Method 1, $t_R = 1.64$ min, $m/z = 384$ ($M+1$). ^1H NMR ($CDCl_3$) 7.41-7.23 (m, 6H), 6.92-6.88 (m, 2H), 6.84-6.81 (m, 1H), 5.77 (q, $J = 7.0$ Hz, 1H), 3.78 (s, 2H), 2.70-2.67 (m, 2H), 2.29-2.24 (m, 1H), 2.23 (s, 1H), 2.06-1.98 (m, 1H), 1.64 (s, 3H), 1.35 (s, 6H), 1.27 (d, $J = 7.0$ Hz, 3H).

EXAMPLE 94

(*R/S*)-6-methyl-3-((*S*)-1-(3-(2-oxo-2-(piperazin-1-yl)ethoxy)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



Step 1. 2-(3-((*S*)-1-((*R/S*)-6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)ethyl)phenoxy)-acetic acid

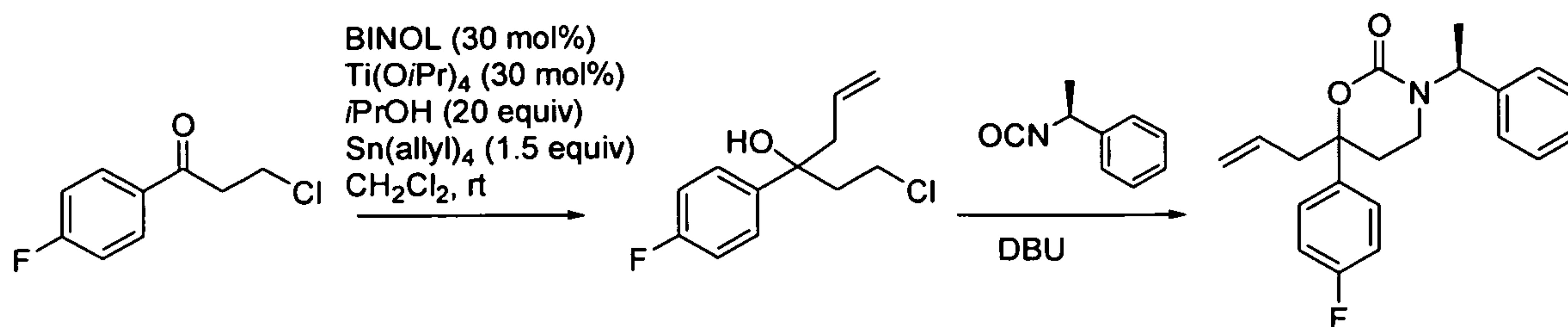
A mixture of ethyl 2-(3-((*S*)-1-((*R/S*)-6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)ethyl)phenoxy)acetate (0.0587 g, 0.148 mmol) and lithium hydroxide monohydrate (0.4275 g, 10.2 mmol) in THF (10 mL) and H_2O (10 mL) was vigorously stirred at rt for 2 d. The mixture was treated with 1 *N* HCl (30 mL), extracted with EtOAc (3 $\times$), dried over Na_2SO_4 . After the solvents were evaporated, the crude product was directly used in the next step without further purification. LC-MS $t_R = 1.48$ min in 3 min chromatography, m/z 370 (MH^+).

Step 2. (*R/S*)-6-methyl-3-((*S*)-1-(3-(2-oxo-2-(piperazin-1-yl)ethoxy)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

A mixture of 2-(3-((*S*)-1-((*R/S*)-6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)ethyl)phenoxy)acetic acid (0.0178 g, 0.0481 mmol), piperazine (0.0575 g, 0.67 mmol), HATU (0.1136 g, 0.30 mmol), and $i-Pr_2NEt$ (0.5 mL, 2.87 mmol) in DMF (1 mL) was stirred overnight at rt. After the solvents were removed in vacuo, the residue was purified by reversed-phase HPLC (Phenomenex® Luna 5 μ C18(2) 100A, 250 $\times$ 21.20 mm, 5 micron, 10% $\rightarrow$ 90% CH_3CN/H_2O , 0.1% CF_3COOH over 13 min, flow rate 25 mL/min) to give 0.0207 g of TFA salt of (*R/S*)-6-methyl-3-((*S*)-1-(3-(2-oxo-2-(piperazin-1-yl)ethoxy)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one. LC-MS Method 1, $t_R = 1.17$ min, $m/z = 438$ ($M+1$). ^1H NMR (CD_3OD) 7.34-7.17 (m, 6H), 6.84-6.80 (m, 3H), 5.47 (q, $J = 7.1$ Hz, 1H), 4.78 (m, 2H), 3.78-3.75 (m, 4H), 3.18 (m, 4H), 2.72-2.69 (m, 2H), 2.40-2.34 (m, 1H), 2.01-1.93 (m, 1H), 1.52 (s, 3H), 1.20 (d, $J = 7.3$ Hz, 3H).

EXAMPLE 95

6-allyl-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one



5 Step 1. 1-Chloro-3-(4-fluorophenyl)hex-5-en-3-ol.

To a solution of 1,1'-bi-2-naphthol (0.2280 g, 0.80 mmol, 0.26 equiv), CH_2Cl_2 (5 mL) and titanium(IV) isopropoxide (0.2243 g, 0.79 mmol, 0.26 equiv) were added 2-propanol (3.1620 g, 52.6 mmol, 17 equiv), tetraallylstannane (1.2538 g, 4.43 mmol, 1.43 equiv), and 3-chloro-1-(4-fluorophenyl)propan-1-one (0.5760 g, 3.09 mmol, 1.0 equiv) successively. The reaction mixture was stirred at rt under nitrogen for 22 h. The reaction was quenched with satd aq NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 . After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/EtOAc to afford 1-chloro-3-(4-fluorophenyl)hex-5-en-3-ol as an oil.

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Step 2. 6-Allyl-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one.

A mixture of 1-chloro-3-(4-fluorophenyl)hex-5-en-3-ol (0.0889 g, 0.39 mmol, 1.0 equiv), (S)-(-)- α -methylbenzyl isocyanate (0.0823 g, 0.56 mmol, 1.44 equiv), and DBU (0.1397 g, 0.92 mmol, 2.36 equiv) in THF (2 mL) was heated to reflux for 17 h. After the solvent was removed, the residue was purified by chromatography on silica gel eluted with hexanes/EtOAc to give 0.0990 g (75%) of the product as a mixture of diastereomers. Selected fractions contained the individual diastereomers.

Isomer 1: (R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one. LC-MS Method 1, $t_R = 1.89$ min, $m/z = 340$ ($M+1$). ^1H NMR (CDCl_3) 7.36-7.27 (m, 7H), 7.10-7.05 (m, 2H), 5.79-5.67 (m, 2H), 5.09-4.98 (m, 2H), 2.72-2.68 (m, 2H), 2.64-2.53 (m, 2H), 2.22-2.16 (m, 1H), 2.09-2.01 (m, 1H), 1.26 (d, $J = 7.3$ Hz, 3H).

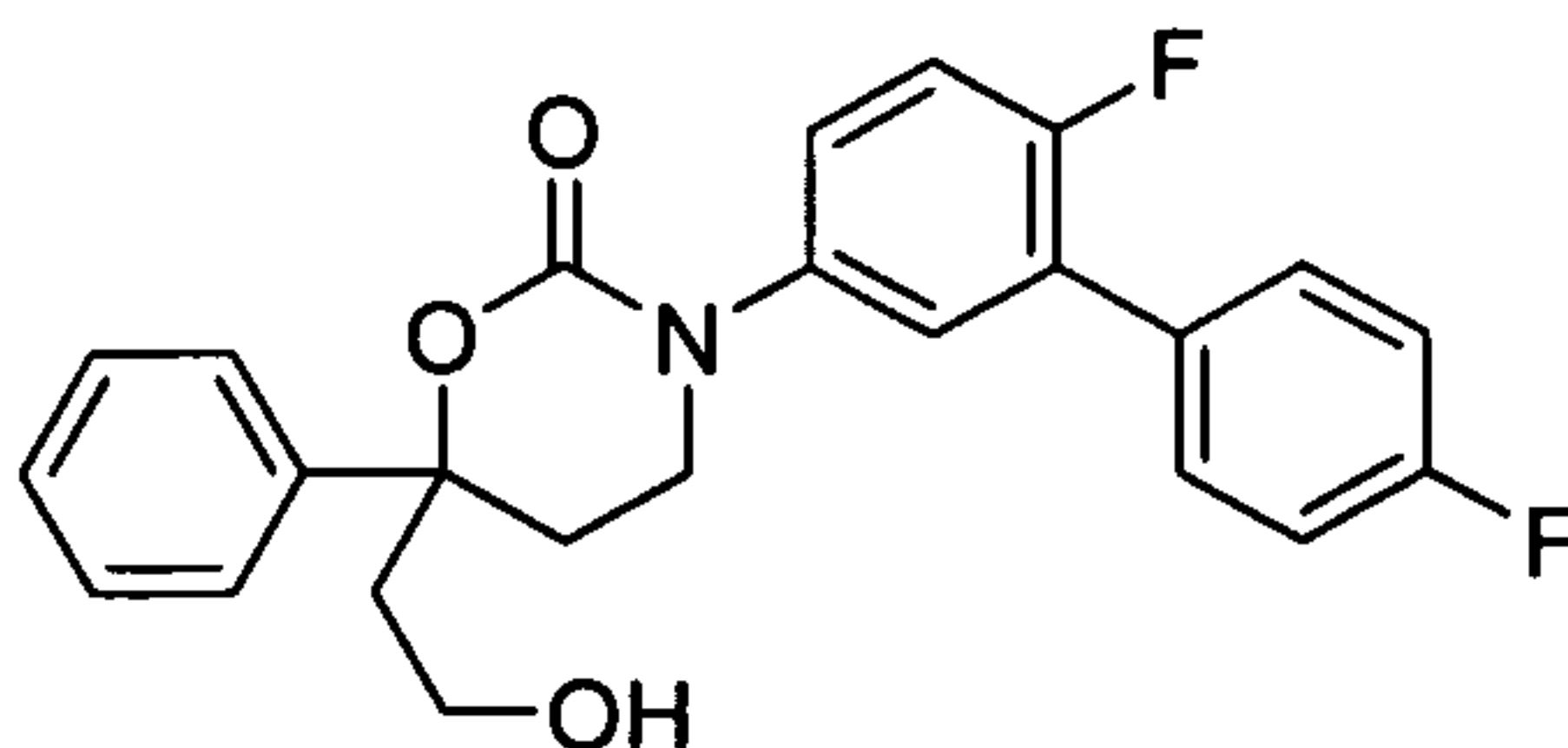
Isomer 2: (S)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one. LC-MS Method 1, $t_R = 1.86$ min, $m/z = 340$ ($M+1$). ^1H NMR (CDCl_3) 7.29-7.24 (m, 2H), 7.14-7.08 (m, 3H), 7.05-7.00 (m, 2H), 6.88-6.85 (m, 2H), 5.77-5.63 (m, 2H), 5.10-5.00 (m, 2H), 2.93-2.88 (m, 1H), 2.65-2.52 (m, 2H), 2.32-2.17 (m, 3H), 1.51 (d, $J = 7.0$ Hz, 3H).

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EXAMPLE 96

3-(4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared by application of procedures analogous to those described in Example 63 using 4',6-difluorobiphenyl-3-amine in Step 2 followed by Example 65. LC-MS Method 3, $t_R = 1.215$ min, $m/z = 410$. ^1H NMR ($CDCl_3$) 2.12-2.30 (m, 2H), 2.47(m, 2H), 3.21 (m, 1H), 3.42 (m, 1H), 3.54 (m, 1H), 3.75 (m, 2H), 7.06-7.11 (m, 5H), 7.26-7.40 (m, 7H).

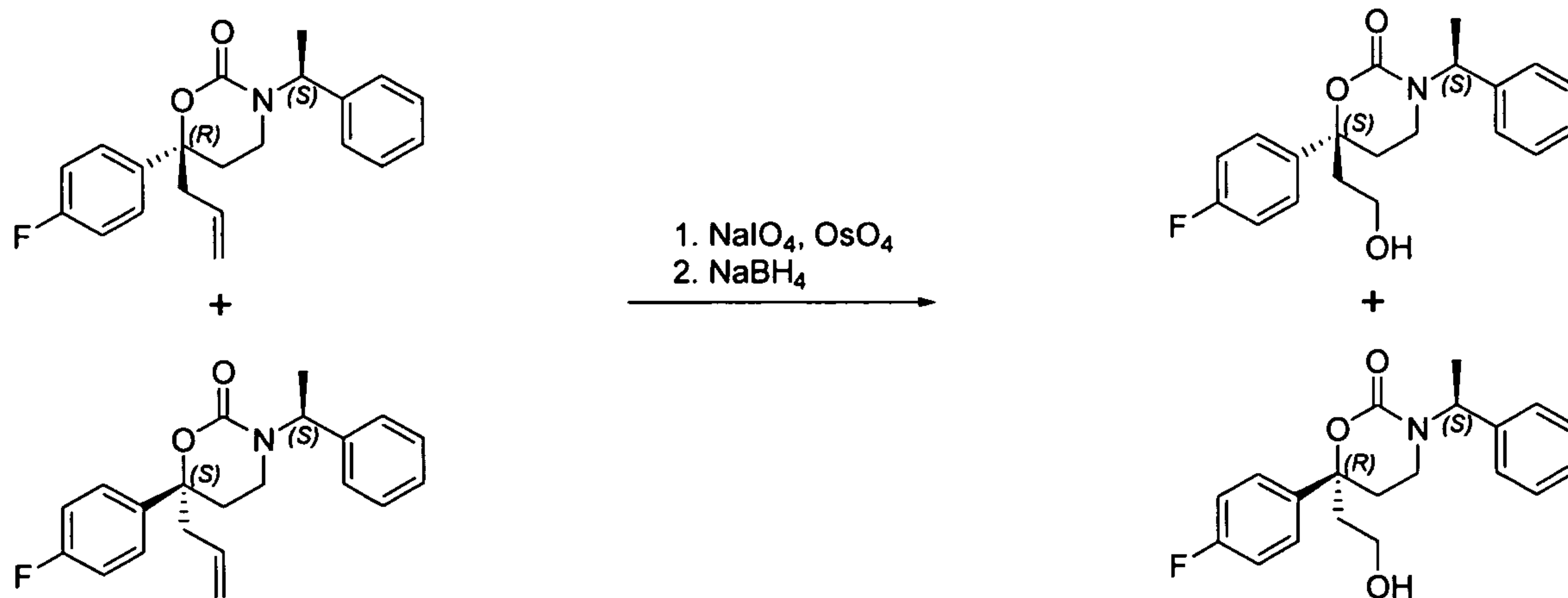
Chiral preparative SFC using a ChiralCel-AS, 400×25 mm I.D, $20 \mu m$ (Daicel Chemical Industries, Ltd) column maintained at $35^\circ C$ eluted with 70:30 supercritical CO_2 /0.1% diethylamine in MeOH at a flow rate of $70 mL min^{-1}$ and a nozzle pressure of 100 bar afforded the two enantiomers.

Isomer 1: (S)-3-(4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one. LC-MS Method 3, $t_R = 1.214$ min, $m/z = 410$. ^1H NMR ($CDCl_3$) $\delta=2.12$ -2.30 (m, 2H), 2.47(m, 2H), 3.21 (m, 1H), 3.42 (m, 1H), 3.54 (m, 1H), 3.75 (m, 2H), 7.06-7.11 (m, 5H), 7.26-7.40 (m, 7H).

Isomer 2: (R)-3-(4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one. LC-MS Method 3, $t_R = 1.207$ min, $m/z = 410$. ^1H NMR ($CDCl_3$) $\delta=2.20$ -2.40 (m, 2H), 2.57 (m, 2H), 3.30 (m, 1H), 3.53 (m, 2H), 3.64 (m, 1H), 3.84 (m, 1H), 7.06-7.20 (m, 5H), 7.39 (m, 1H), 7.45 (m, 6H).

EXAMPLE 97

6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one



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To a solution of 6-allyl-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one (0.1016 g, 0.30 mmol, 1.0 equiv) in THF-H₂O (1:1, 6 mL) were added NaIO₄ (0.3240 g, 1.5 mmol, 5 equiv) and OsO₄ (2.5 wt.% solution in *t*-BuOH, 0.0507 g, 0.0049 mmol, 0.016 equiv), and the mixture was stirred at rt for 2 h. The mixture was diluted with EtOAc, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was dissolved in MeOH (3 mL) and NaBH₄ (0.100 g) was added. After the mixture was stirred for 1.5 h at rt, acetone was added. The solvents were removed in vacuo, the residue was treated with saturated brine, extracted with CH₂Cl₂, and dried over Na₂SO₄. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/EtOAc to afford the two diastereomers of 6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one.

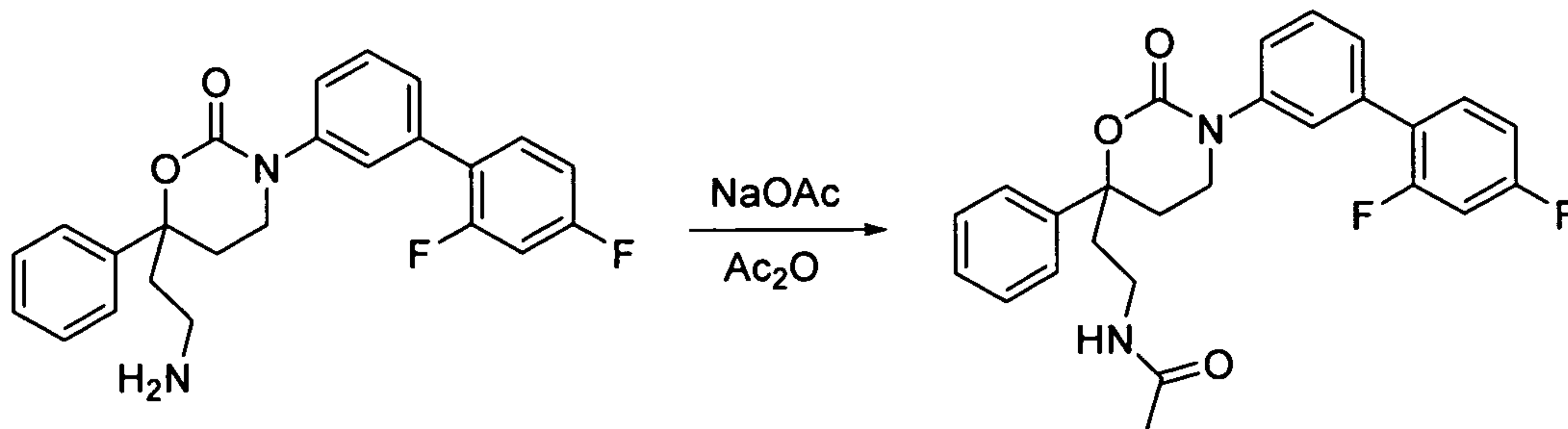
Isomer 1: (R)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one. LC-MS Method 1 *t_R* = 1.51 min, *m/z* = 344 (MH⁺); ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.27 (m, 7H), 7.12-7.07 (m, 2H), 5.76 (q, *J* = 7.1 Hz, 1H), 3.78-3.74 (m, 1H), 3.58-3.51 (m, 1H), 2.72-2.62 (m, 2H), 2.28-2.08 (m, 4H), 1.80 (br s, 1H), 1.28 (d, *J* = 7.3 Hz, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -114.84 (m).

Isomer 2: (S)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one. LC-MS Method 1 *t_R* = 1.48 min, *m/z* = 344 (MH⁺); ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.25 (m, 2H), 7.16-7.10 (m, 3H), 7.07-7.02 (m, 2H), 6.93-6.90 (m, 2H), 5.66 (q, *J* = 7.0 Hz, 1H), 3.80-3.74 (m, 1H), 3.58-3.53 (m, 1H), 2.94-2.88 (m, 1H), 2.32-2.07 (m, 5H), 1.79 (br s, 1H), 1.52 (d, *J* = 7.0 Hz, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -115.03 (m).

25

EXAMPLE 98

N-(2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl)acetamide



In a 5 dram vial, sodium acetate (3 mg, 0.04 mmol) was added to 6-(2-aminoethyl)-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one (5.13 mg, 0.013 mmol) in acetic anhydride (0.5 mL). The reaction was stirred for 2 h. The solvent was evaporated and the crude residue purified via prep HPLC to afford 1.88

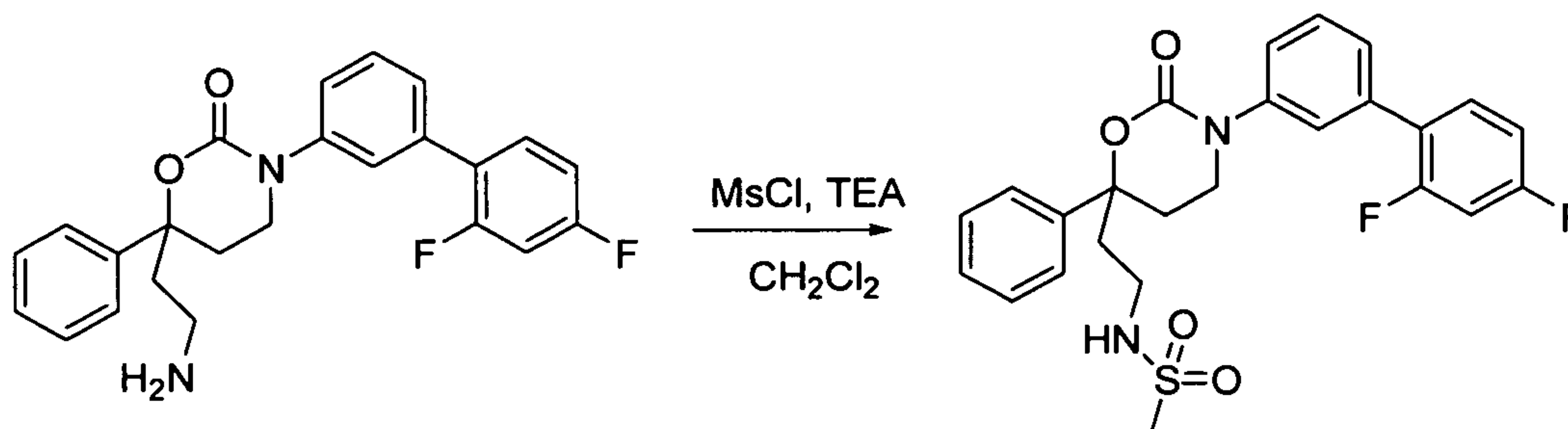
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mg of *N*-(2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl)acetamide. LC-MS Method 1 m/z = 451 ($M+H$)⁺.

EXAMPLE 99

5 *N*-(2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl)methanesulfonamide

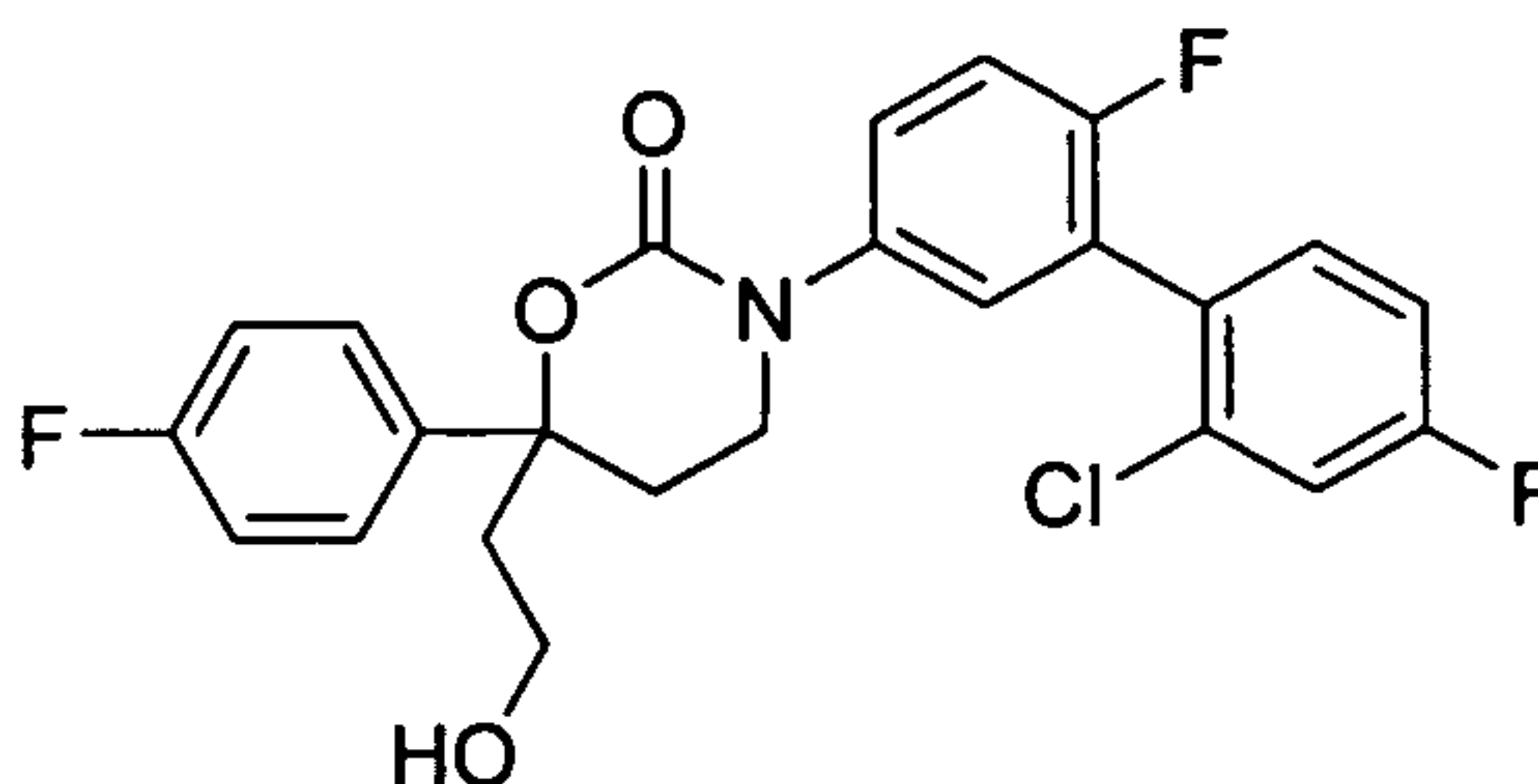


10 In a 5 dram vial, methanesulfonyl chloride (5 drops) was added to 6-(2-aminoethyl)-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one (5 mg, 0.012 mmol) and TEA (5 drops) dissolved in methylene chloride (0.5 mL). The reaction was stirred for 2 h. The solvent was evaporated and the crude residue purified via prep HPLC to afford 3.56 mg of *N*-(2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl)methanesulfonamide. LC-MS Method 1 m/z = 487 ($M+H$)⁺.

15

EXAMPLE 100

3-(2'-chloro-4',6-difluorobiphenyl-3-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one



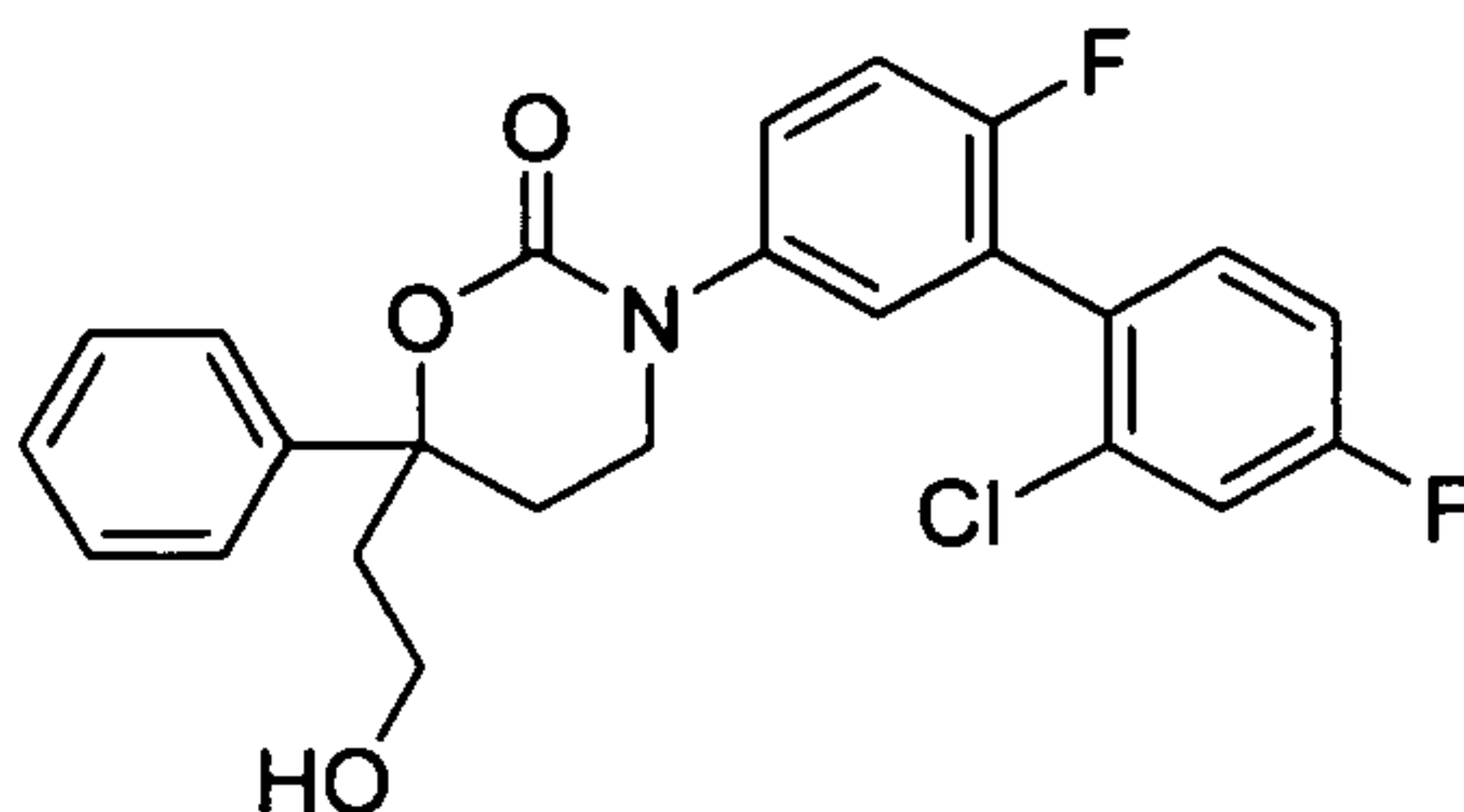
20 The title compound was prepared by sequential application of procedures analogous to those described in Example 63 using *p*-fluoroacetophenone in Step 1 and 3-bromo-4-fluoroaniline in Step 2, Example 74 and Example 75 Step 1 using 2-chloro-4-fluorophenylboronic acid. LC-MS Method 3, t_R = 1.265 min, m/z = 462. ¹H NMR (CDCl₃) 2.10-2.30 (m, 2H), 2.45-2.51 (m, 2H), 3.20-3.31 (m, 1H), 3.55-3.60 (m, 2H), 3.70-3.80 (m, 1H), 6.90-7.16 (m, 6H), 7.20-7.40 (m, 4H).

25

EXAMPLE 101

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3-(2'-chloro-4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one

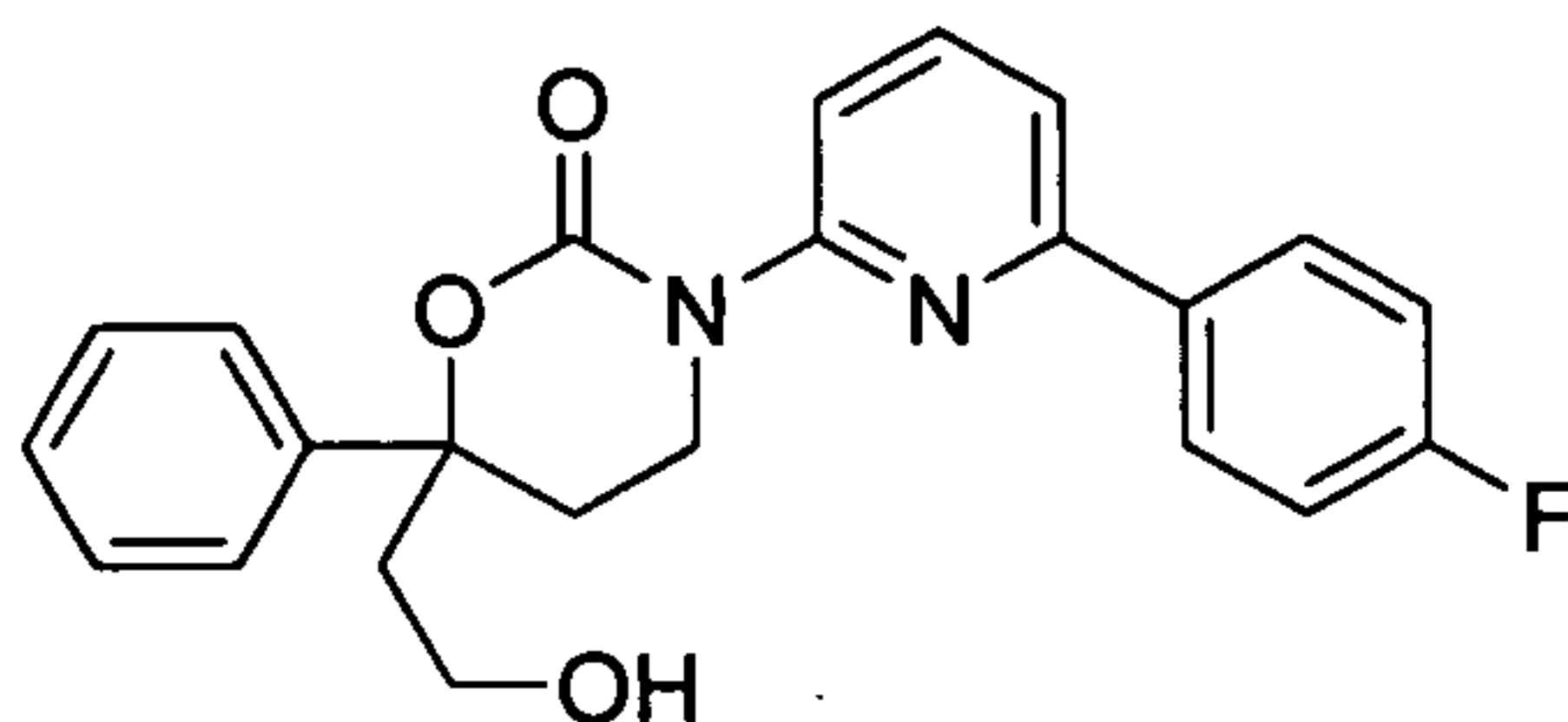


The title compound was prepared by sequential application of procedures analogous to those described in Example 63 using 3-bromo-4-fluoroaniline in Step 2, Example 74 and Example 75 Step 1 using 2-chloro-4-fluorophenylboronic acid. LC-MS Method 3, t_R = 1.367 min, m/z = 466.1. ^1H NMR (CD_3OD) δ =2.17 (m, 2H), 2.47(m, 1H), 2.58 (m,1H), 3.16 (m, 1H), 3.25 (m, 1H), 3.54 (m, 1H), 3.63 (m, 1H), 6.98 (m, 1H), 7.08 (m, 3H), 7.26 (m, 3H), 7.37 (m, 4H).

10

EXAMPLE 102

3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared by application of procedures analogous to those described in Example 63 using 2-amino-6-bromopyridine in Step 2, followed by Example 74 and Example 75 Step 1 using 4-fluorophenylboronic acid. LC-MS Method 3, t_R = 1.217 min, m/z = 393. ^1H NMR (CD_3OD) δ =2.29 (m, 2H), 2.51(m, 1H), 2.73 (m, 1H), 3.47 (m, 2H), 3.75 (m, 1H), 4.21 (m, 1H), 7.14 (m, 2H), 7.35 (m, 1H), 7.46 (m, 4H), 7.63 (m, 1H), 7.68 (m, 1H), 7.72 (m, 1H), 8.00 (m, 2H).

20

Chiral preparative SFC using a ChiralCel-AS, 400 × 25 mm I.D, 20 μ m (Daicel Chemical Industries, Ltd) column maintained at 35 °C eluted with 65:35 supercritical CO_2 /0.1% diethylamine in MeOH at a flow rate of 70 mL min⁻¹ and a nozzle pressure of 100 bar afforded the two enantiomers.

Isomer 1: (R)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one. LC-MS Method 3, t_R = 1.2 min, m/z = 393. ^1H NMR (CD_3OD) δ =2.29 (m, 2H), 2.51(m, 1H), 2.68 (m, 1H), 3.42 (m, 2H), 3.75 (m, 1H), 4.16 (m, 1H), 7.11 (m, 2H), 7.33 (m, 1H), 7.46 (m, 4H), 7.53 (m, 1H), 7.72 (m, 2H), 7.98 (m, 2H).

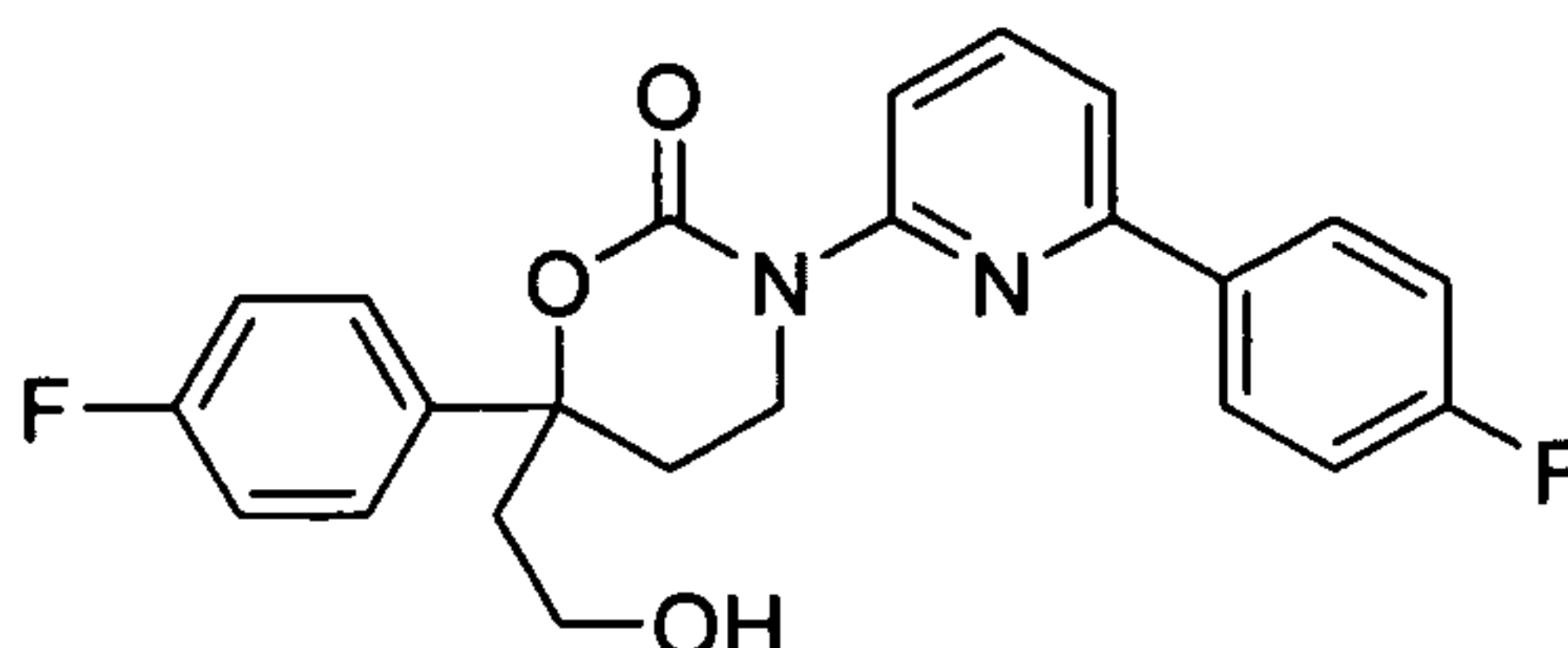
Isomer 2: (S)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one. LC-MS Method 3, t_R = 1.183 min, m/z = 393. ^1H NMR (CD_3OD)

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δ =2.27 (m, 2H), 2.48 (m, 1H), 2.63 (m, 1H), 3.45 (m, 2H), 3.75 (m, 1H), 4.18 (m, 1H), 7.08 (m, 2H), 7.31 (m, 1H), 7.44 (m, 4H), 7.50 (m, 1H), 7.68 (m, 2H), 7.91 (m, 2H).

EXAMPLE 103

5 6-(4-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one

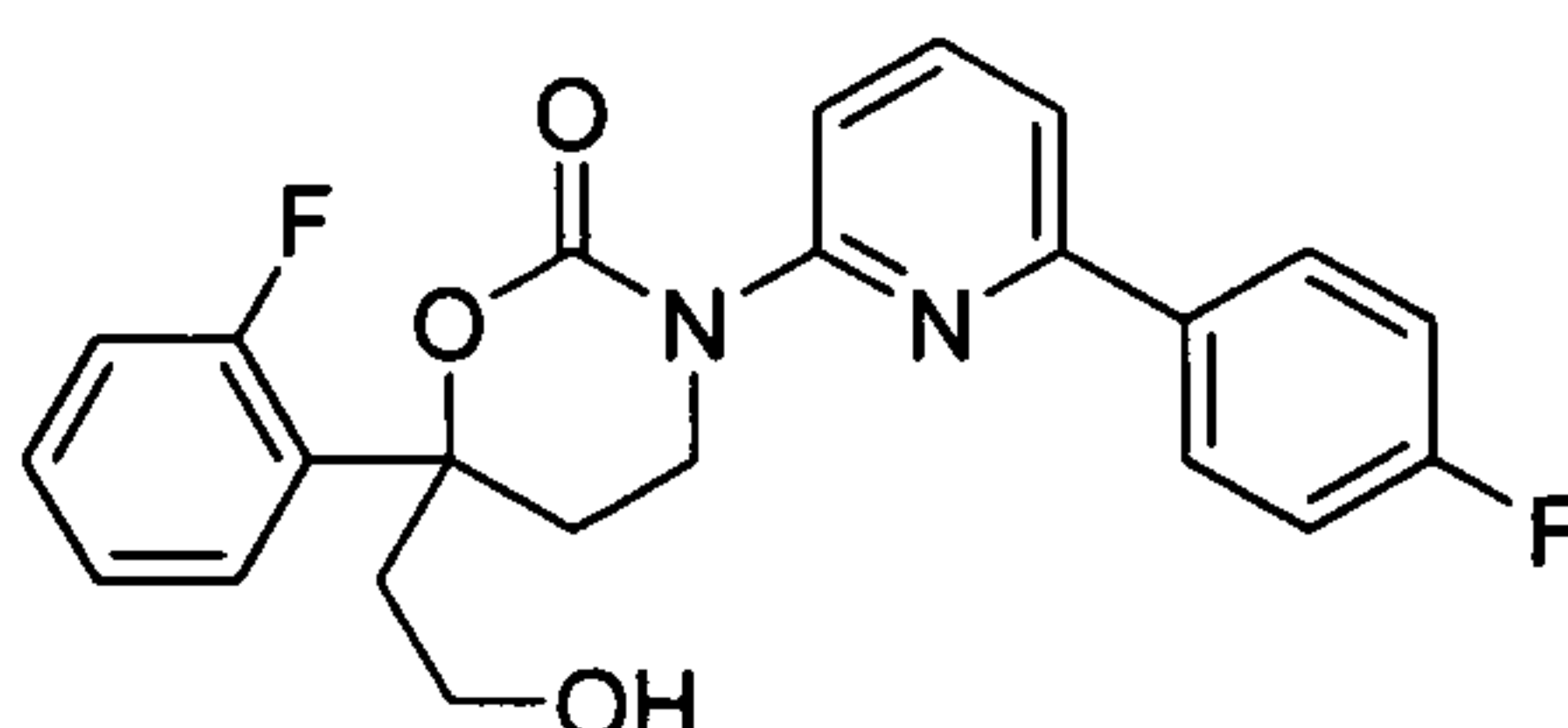


The title compound was prepared by application of procedures analogous to those described in Example 63 using *p*-fluoroacetophenone in Step 1 and 2-amino-6-bromopyridine in Step 2, followed by Example 74 and Example 75 Step 1 using 4-fluorophenylboronic acid. LC-MS Method 2, t_R = 2.25 min, m/z = 411. ^1H NMR (CD₃OD) δ =2.25 (m, 2H), 2.55 (m, 1H), 2.60 (m, 1H), 3.40 (m, 1H), 3.50 (m, 1H), 3.75 (m, 1H), 4.20 (m, 1H), 7.15 (m, 4H), 7.50 (m, 2H), 7.65 (m, 2H), 7.80 (m, 1H), 8.00 (m, 2H).

15

EXAMPLE 104

6-(2-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one



20 The title compound was prepared by application of procedures analogous to those described in Example 63 using *o*-fluoroacetophenone in Step 1 and 2-amino-6-bromopyridine in Step 2, followed by Example 74 and Example 75 Step 1 using 4-fluorophenylboronic acid. LC-MS Method 3, t_R = 1.26 min, m/z = 410.14. ^1H NMR (CD₃OD) δ =2.20-2.40 (m, 2H), 2.45 (m, 1H), 2.75 (m, 1H), 3.42 (m, 2H), 3.72 (m, 1H), 4.15 (m, 1H), 7.03-7.20 (m, 4H), 7.35 (m, 2H), 7.55 (m, 1H), 7.65 (m, 1H), 7.75 (m, 1H), 7.95 (m, 2H).

25

Chiral preparative SFC using a ChiralCel-AS, 400 × 25 mm I.D, 20 μ m (Daicel Chemical Industries, Ltd) column maintained at 35 °C eluted with 75:25 supercritical CO₂/0.1% diethylamine in MeOH at a flow rate of 70 mL min⁻¹ and a

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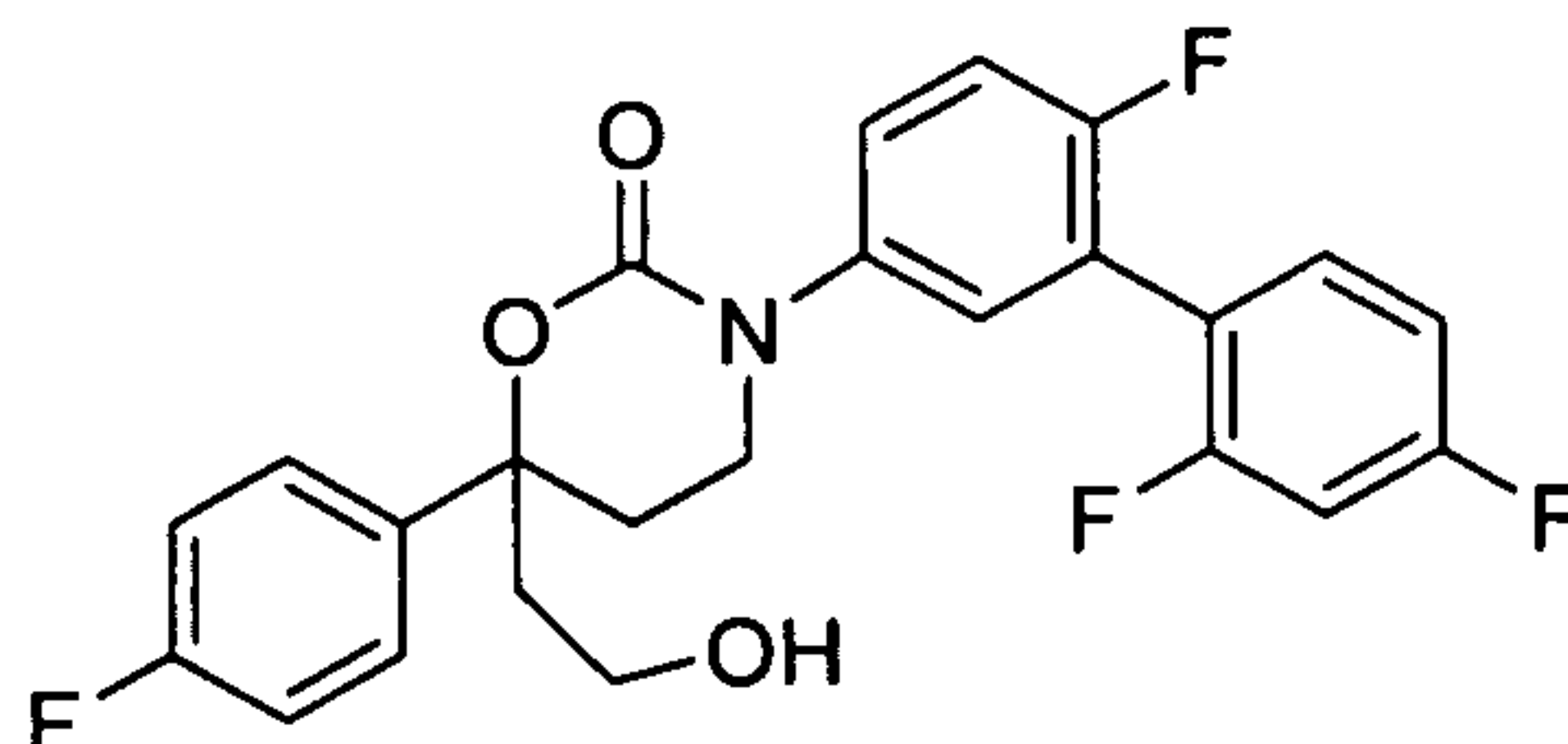
nozzle pressure of 100 bar afforded the two enantiomers.

Isomer 1: (R)-6-(2-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one. LC-MS Method 3, t_R = 1.255 min, m/z = 410.14. ^1H NMR (CD_3OD) δ =2.20-2.40 (m, 2H), 2.45 (m, 1H), 2.75 (m, 1H), 3.35 (m, 2H), 3.72 (m, 1H), 4.15 (m, 1H), 7.03-7.20 (m, 4H), 7.35 (m, 2H), 7.55 (m, 1H), 7.65 (m, 1H), 7.75 (m, 1H), 7.95 (m, 2H).

Isomer 2: (S)-6-(2-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one. LC-MS Method 3, t_R = 1.262 min, m/z = 410.14. ^1H NMR (CD_3OD) δ =2.20-2.40 (m, 2H), 2.45 (m, 1H), 2.75 (m, 1H), 3.42 (m, 2H), 3.72 (m, 1H), 4.15 (m, 1H), 7.03-7.20 (m, 4H), 7.45 (m, 2H), 7.55 (m, 1H), 7.65 (m, 1H), 7.75 (m, 1H), 7.95 (m, 2H).

EXAMPLE 105

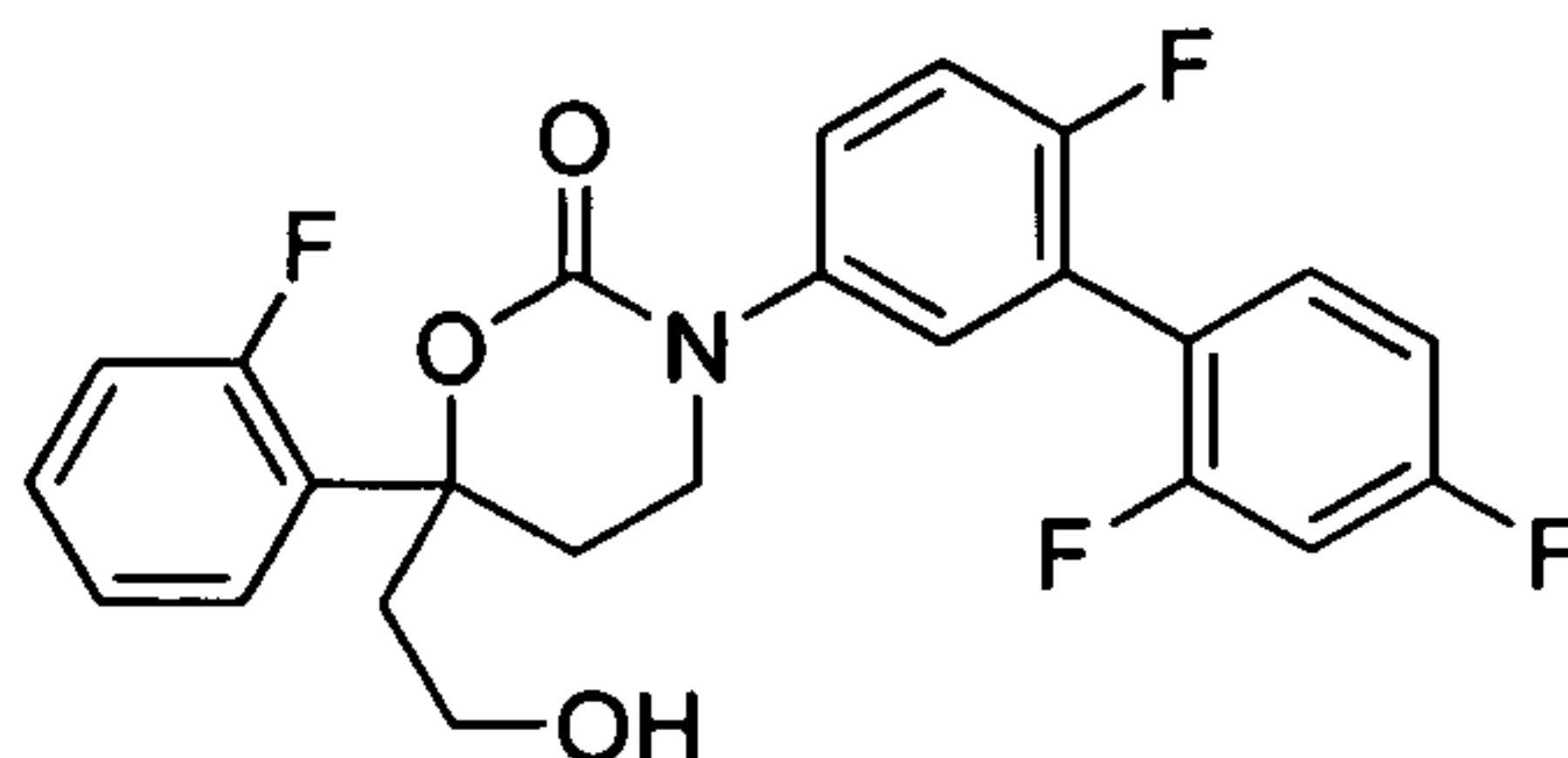
6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-(2',4',6-trifluorobiphenyl-3-yl)-1,3-oxazinan-2-one



The title compound was prepared by sequential application of procedures analogous to those described in Example 63 using *p*-fluoroacetophenone in Step 1 and 3-bromo-4-fluoroaniline in Step 2, Example 74 and Example 75 Step 1 using 2,4-difluorophenylboronic acid. LC-MS Method 3, t_R = 1.225 min, m/z = 446. ^1H NMR (CDCl_3) δ =2.15-2.30 (m, 2H), 2.50-2.60 (m, 2H), 3.22-3.37 (m, 1H), 3.50-3.65 (m, 2H), 3.75-3.85 (m, 1H), 6.89-6.92 (m, 2H), 7.10-7.20 (m, 5H), 7.30-7.40 (m, 3H).

EXAMPLE 106

6-(2-fluorophenyl)-6-(2-hydroxyethyl)-3-(2',4',6-trifluorobiphenyl-3-yl)-1,3-oxazinan-2-one



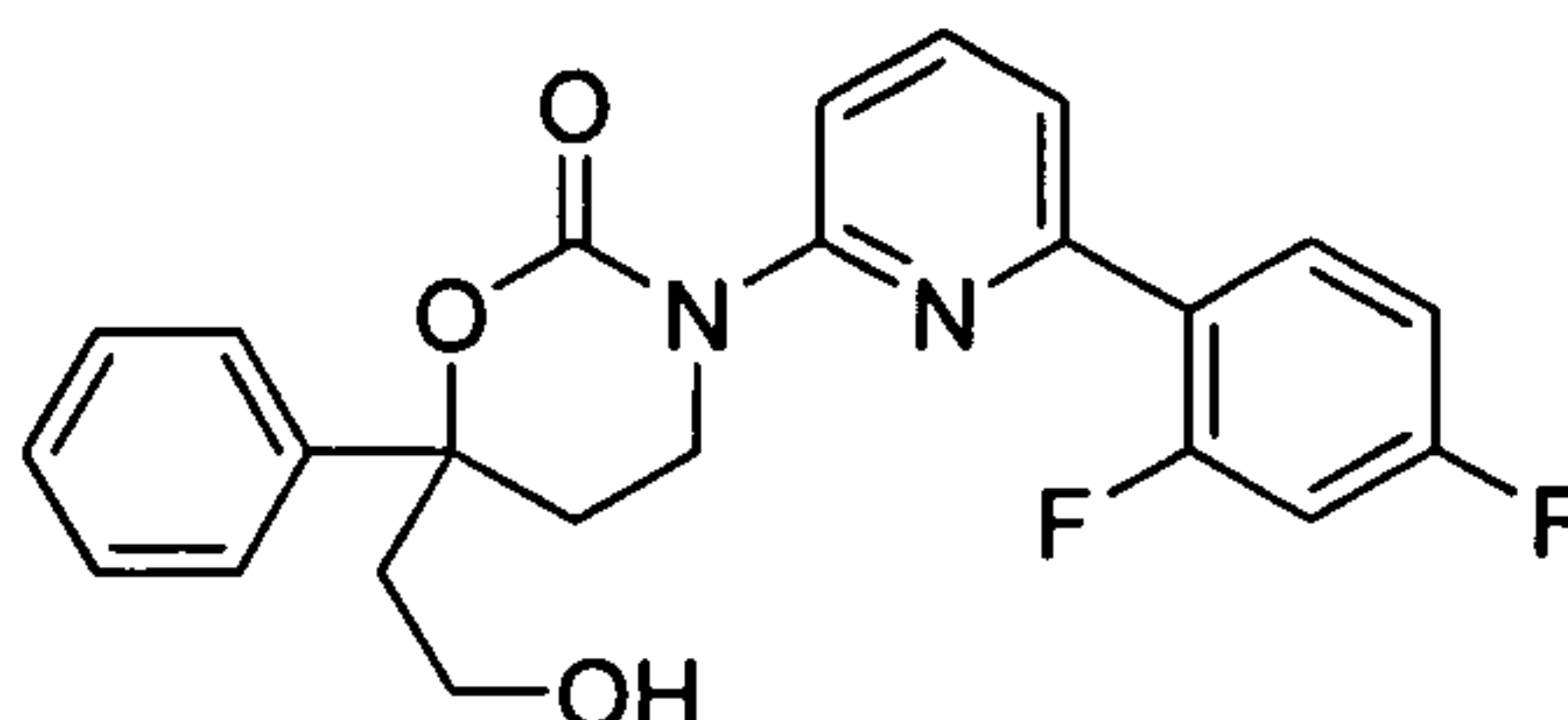
The title compound was prepared by sequential application of procedures analogous to those described in Example 63 using *o*-fluoroacetophenone in Step 1

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and 3-bromo-4-fluoroaniline in Step 2, Example 74 and Example 75 Step 1 using 2,4-difluorophenylboronic acid. LC-MS Method 3, $t_R = 1.237$ min, $m/z = 446$. ^1H NMR (CDCl_3) $\delta=2.30$ - 2.50 (m, 3H), 2.70 - 2.80 (m, 1H), 3.20 - 3.30 (m, 1H), 3.40 - 3.50 (m, 1H), 3.55 - 3.65 (m, 1H), 3.70 - 3.80 (m, 1H), 6.85 - 6.90 (m, 2H), 7.00 - 7.10 (m, 4H),
 5 7.20 - 7.38 (m, 3H), 7.45 - 7.52 (m, 1H).

EXAMPLE 107

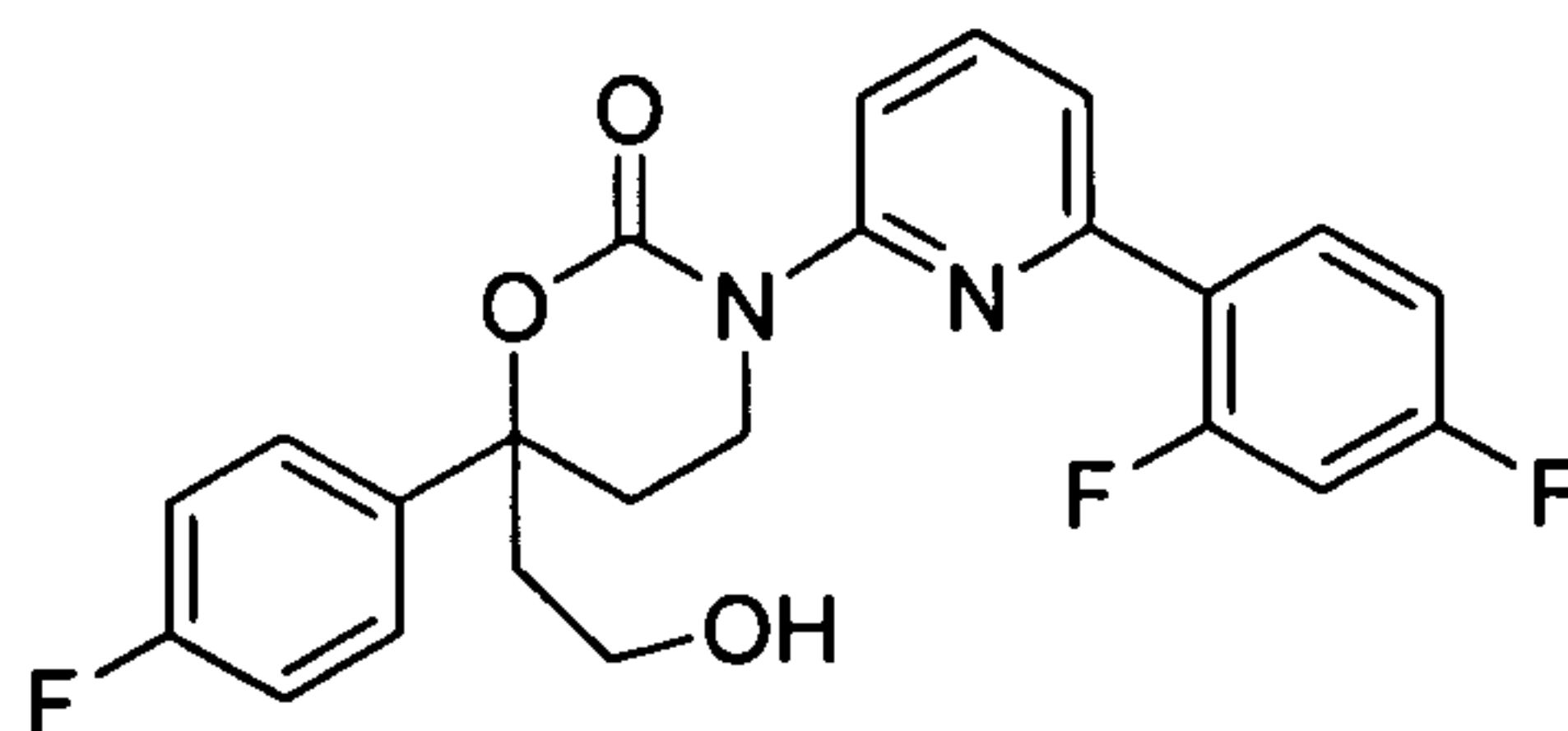
3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one



10 The title compound was prepared by application of procedures analogous to those described in Example 63 using 2-amino-6-bromopyridine in Step 2, followed by Example 74 and Example 75 Step 1 using 2,4-difluorophenylboronic acid. LC-MS Method 3, $t_R = 1.25$ min, $m/z = 411$. ^1H NMR (CD_3OD) $\delta=2.27$ (m, 2H), 2.53 (m, 1H), 2.72 (m, 1H), 3.38 (m, 2H), 3.74 (m, 1H), 4.15 (m, 1H), 7.02 (m, 2H), 7.32 (m, 1H),
 15 7.42 (m, 4H), 7.55 (m, 1H), 7.71 (m, 1H), 7.78 (m, 1H), 7.91 (m, 1H).

EXAMPLE 108

3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one

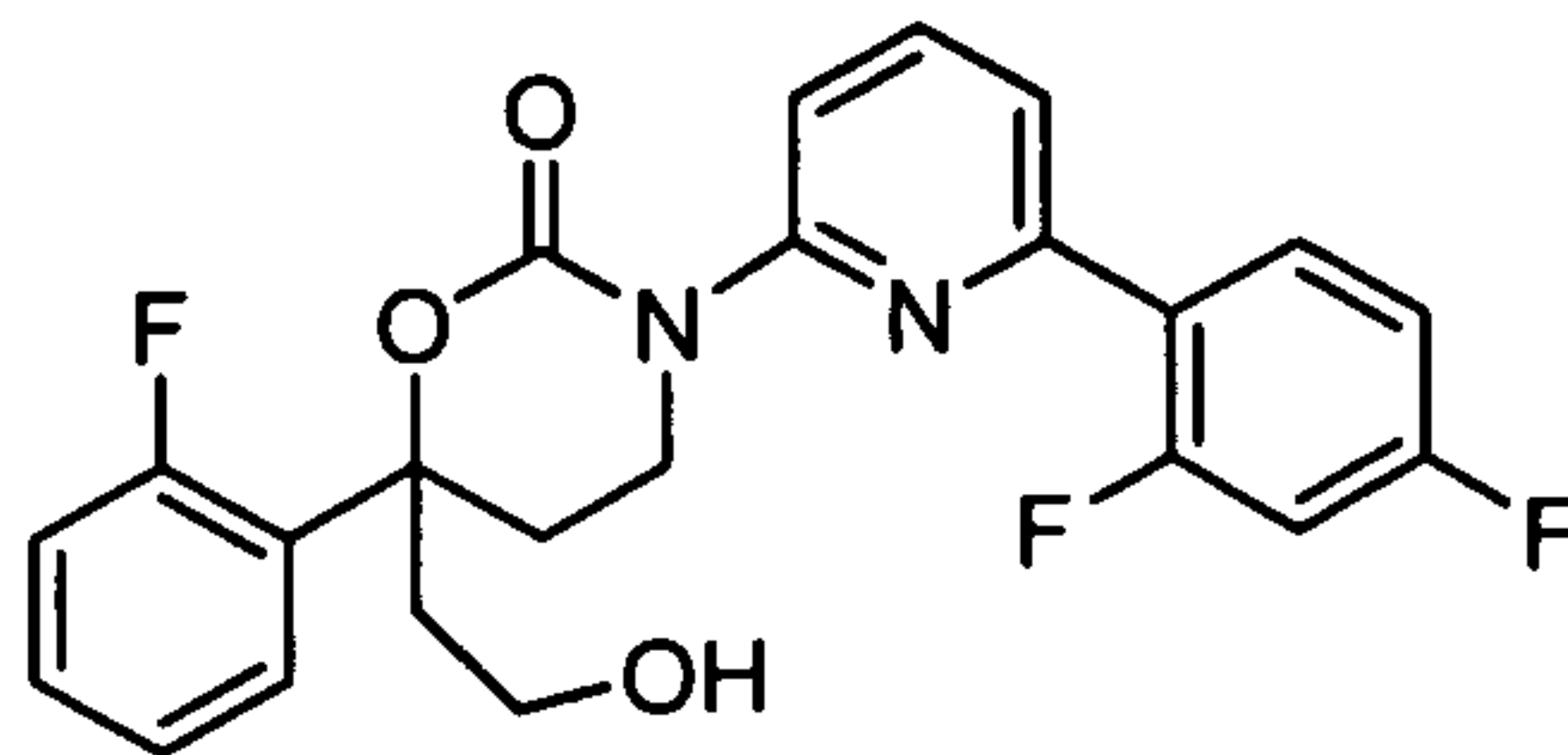


20 The title compound was prepared by application of procedures analogous to those described in Example 63 using *p*-fluoroacetophenone in Step 1 and 2-amino-6-bromopyridine in Step 2, followed by Example 74 and Example 75 Step 1 using 2,4-difluorophenylboronic acid. LC-MS Method 2, $t_R = 2.311$ min, $m/z = 429.4$. ^1H NMR (CD_3OD) 2.25 (m, 2H), 2.55 (m, 1H), 2.60 (m, 1H), 3.40 (m, 2H), 3.50 (m, 1H), 3.75
 25 (m, 1H), 7.15 (m, 3H), 7.30 (m, 1H), 7.45 (m, 3H), 7.75 (m, 1H), 7.80 (m, 1H).

EXAMPLE 109

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3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one



The title compound was prepared by application of procedures analogous to those described in Example 63 using *o*-fluoroacetophenone in Step 1 and 2-amino-6-bromopyridine in Step 2, followed by Example 74 and Example 75 Step 1 using 2,4-difluorophenylboronic acid. LC-MS Method 2, $t_R = 2.311$ min, $m/z = 429$. ^1H NMR (CD₃OD) 2.35 (m, 2H), 2.55 (m, 1H), 2.80 (m, 1H), 3.45 (m, 2H), 3.75 (m, 1H), 4.20 (m, 1H), 7.05 (m, 2H), 7.20 (m, 2H), 7.40 (m, 2H), 7.60 (m, 1H), 7.80 (m, 2H), 7.90 (m, 1H).

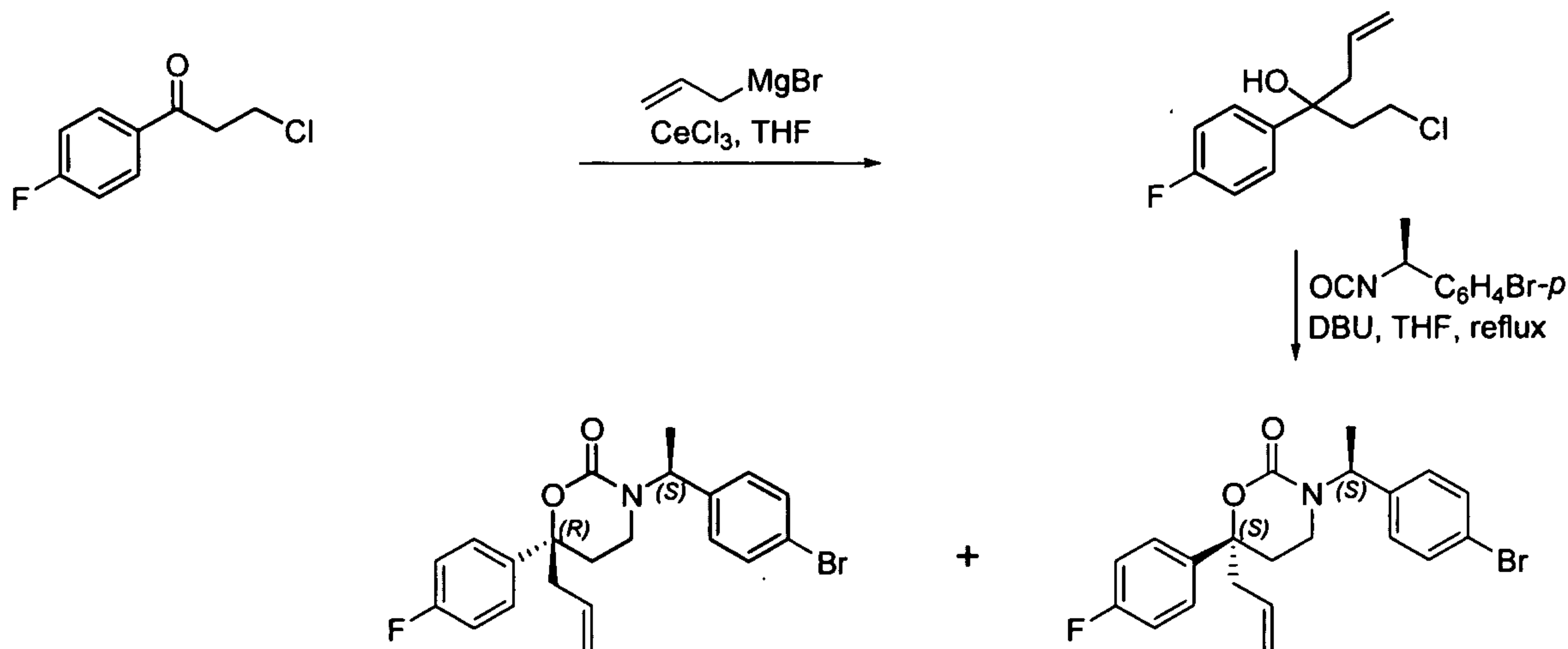
The isomers were separated by

Isomer 1: (R)-3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one.

Isomer 2: (S)-3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one.

EXAMPLE 110

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



Step 1. 1-chloro-3-(4-fluorophenyl)hex-5-en-3-ol

A 250-mL flask was charged with anhydrous CeCl₃ (5.58 g, 22.6 mmol) and THF (40 mL). The mixture was vigorously stirred for 3.5 h at rt. The suspension was then cooled to -78 °C and a solution of allylmagnesium bromide (1.0 M in THF, 21

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mL, 21.0 mmol) was added. After stirring for 2 h at -78 °C, a solution of 3-chloro-1-(4-fluorophenyl)propan-1-one (2.522 g, 13.5 mmol) in THF (30 mL) was added via cannula. The reaction mixture was allowed to slowly warm to 8 °C while stirring overnight (18 h). The reaction was then quenched with satd aq NaHCO₃, extracted with EtOAc, and dried over Na₂SO₄. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/EtOAc to afford of 1-chloro-3-(4-fluorophenyl)hex-5-en-3-ol (3.0049 g, 97%) as an oil. LC-MS Method 1 t_R = 1.79 min, m/z 213, 211 (M-OH)⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.32 (m, 2H), 7.07-7.02 (m, 2H), 5.57-5.47 (m, 1H), 5.20-5.19 (m, 1H), 5.16 (m, 1H), 3.59-3.52 (m, 1H), 3.24-3.18 (m, 1H), 2.70 (dd, J = 13.8, 5.9 Hz, 1H), 2.50 (dd, J = 13.8, 8.5 Hz, 1H), 2.29 (t, J = 7.9 Hz, 2H), 2.22 (s, 1H); ¹⁹F NMR (376 MHz, CDCl₃) δ -116.52 (m). Step 2. (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one and (S)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one.

A mixture of 1-chloro-3-(4-fluorophenyl)hex-5-en-3-ol (0.4129 g, 1.8 mmol, 1.0 equiv), (S)-(-)-1-(4-bromophenyl)ethyl isocyanate (0.5005 g, 2.2 mmol, 1.2 equiv), and DBU (0.7375 g, 4.8 mmol, 2.7 equiv) in THF (10 mL) was heated to reflux for 25 h. The mixture was diluted with EtOAc and washed with 1 N aq HCl. The aqueous phase was extracted with EtOAc (2 x). The combined organic phase was dried over Na₂SO₄. After the solvents were evaporated, the crude product was directly used in the next step without further purification.

An analytical sample was purified by chromatography on silica gel eluted with hexanes/EtOAc to afford the two diastereomers of 6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one.

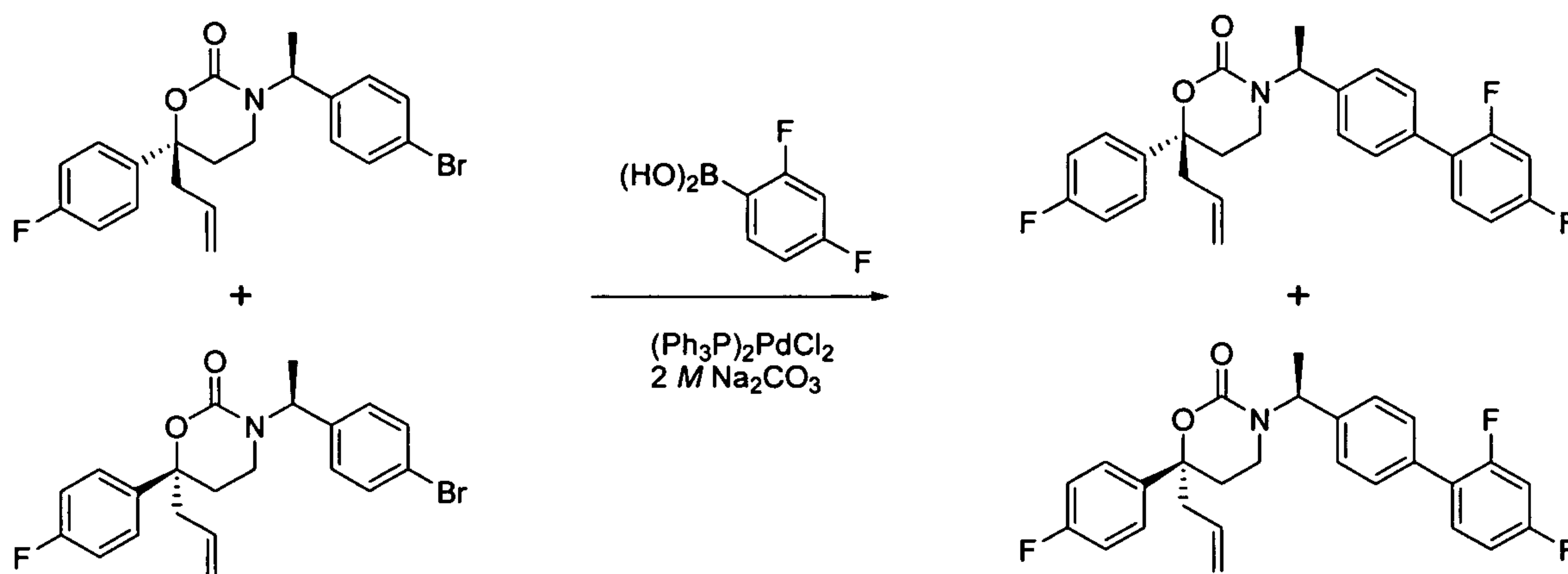
Isomer 1: (S)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 1 t_R = 2.03 min, m/z 420, 418 (MH⁺); ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, J = 8.2 Hz, 2H), 7.31-7.28 (m, 2H), 7.17 (d, J = 8.2 Hz, 2H), 7.07 (t, J = 8.5 Hz, 2H), 5.76-5.66 (m, 2H), 5.10-4.99 (m, 2H), 2.75-2.52 (m, 4H), 2.23-2.19 (m, 1H), 2.08-2.00 (m, 1H), 1.24 (d, J = 7.0 Hz, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -115.07 (m).

Isomer 2: (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 1 t_R = 1.98 min, m/z 420, 418 (MH⁺); ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.20 (m, 4H), 7.05-7.01 (m, 2H), 6.71 (d, J = 8.5 Hz, 2H), 5.74-5.64 (m, 1H), 5.58 (q, J = 7.0 Hz, 1H), 5.09-4.99 (m, 2H), 2.92-2.87 (m, 1H), 2.63-2.50 (m, 2H), 2.33-2.16 (m, 3H), 1.47 (d, J = 7.0 Hz, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -114.91 (m).

(R)-6-allyl-3-((S)-1-(4-chlorophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one was prepared following procedures analogous to those described above using 3-chloro-1-phenylpropan-1-one in Step 1 and (S)-1-chloro-4-(1-isocyanatoethyl)benzene in Step 2.

EXAMPLE 111

6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one



Step 1. 6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

To a solution of 6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (0.3860 g, 0.92 mmol, 1.0 equiv) in THF (10 mL) were added, under a nitrogen atmosphere, 2,4-difluorophenylboronic acid (0.2708 g, 1.71 mmol, 1.86 equiv), 2 M aq Na_2CO_3 (8 mL), and $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (0.0308 g, 0.0438 mmol, 0.047 equiv). The mixture was stirred for 2 d at 100 °C. Brine was then added, the mixture was extracted with Et_2O (3 ×), and the combined ether extracts were dried over Na_2SO_4 . After the solvents were evaporated, the crude product was directly used in the next step without further purification. LC-MS t_R = 2.13, 2.17 min in 3 min chromatography, m/z 452 (MH^+).

Analytical samples were separated by silica gel chromatography.

Isomer 1: (S)-6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 1, t_R = 2.17 min, m/z = 452. ^1H NMR (CDCl_3) 7.47 (d, J = 8.2 Hz, 2H), 7.42-7.30 (m, 5H), 7.08 (t, J = 8.2 Hz, 2H), 6.98-6.88 (m, 2H), 5.82-5.68 (m, 2H), 5.08 (d, J = 10.2 Hz, 1H), 5.02 (d, J = 17.0 Hz,

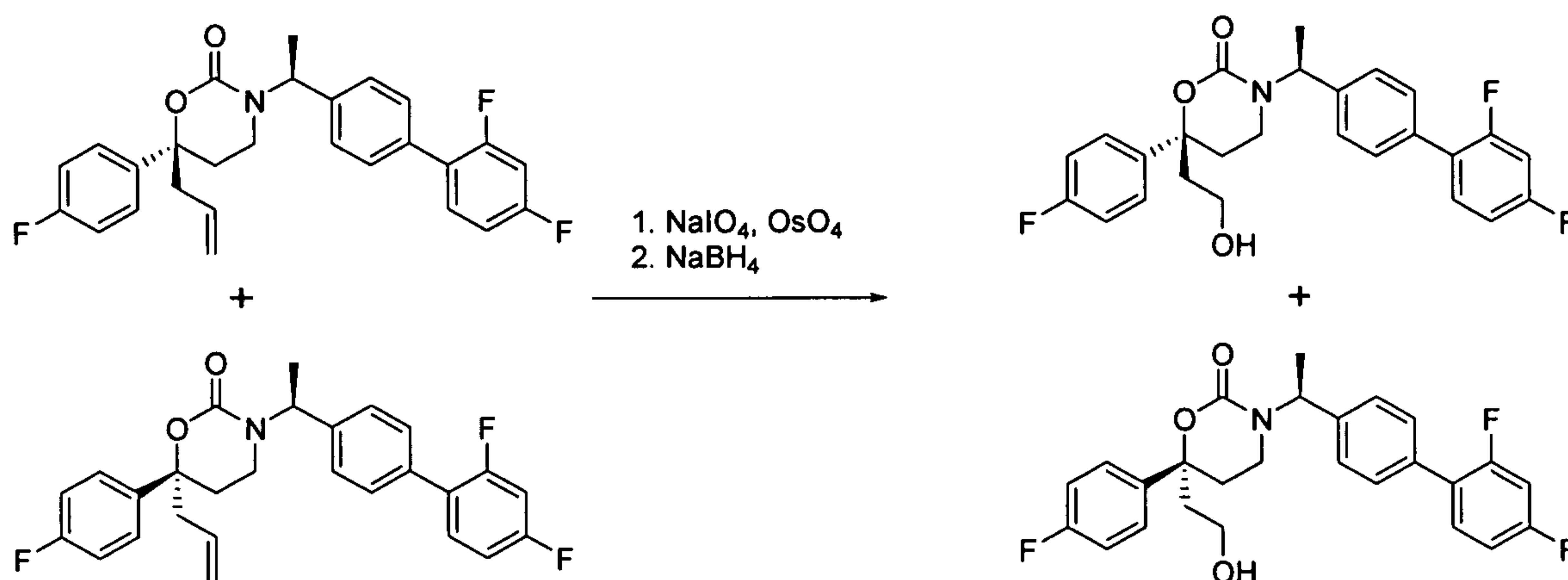
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1H), 2.78-2.71 (m, 2H), 2.66-2.54 (m, 2H), 2.25-2.20 (m, 1H), 2.13-2.05 (m, 1H), 1.30 (d, J = 7.0 Hz, 3H).

Isomer 2: (R)-6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 1, t_R = 2.13 min, m/z = 452. ^1H NMR ($CDCl_3$) 7.33-7.23 (m, 5H), 7.03 (t, J = 8.2 Hz, 2H), 6.96-6.86 (m, 4H), 5.77-5.67 (m, 2H), 5.10 (d, J = 10.3 Hz, 1H), 5.04 (d, J = 17.3 Hz, 1H), 2.99-2.94 (m, 1H), 2.66-2.54 (m, 2H), 2.41-2.34 (m, 1H), 2.30-2.17 (m, 2H), 1.55 (d, J = 7.0 Hz, 3H).

EXAMPLE 112

10 3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one



Step 1. (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one and (R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one

To a solution of 6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (obtained as described in Example 111) in THF-H₂O (1:1, 20 mL) were added NaIO₄ (1.0148 g, 4.74 mmol, 5 equiv) and OsO₄ (2.5 wt.% solution in *t*-BuOH, 0.1708 g, 0.0167 mmol, 0.018 equiv), and the mixture was stirred at rt for 2 h. The mixture was diluted with EtOAc, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL) and NaBH₄ (0.200 g) was added. After the mixture was stirred for 1 h at rt, acetone was added. The solvents were removed in vacuo, the residue was treated with saturated brine, extracted with CH₂Cl₂, and dried over Na₂SO₄. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/EtOAc to afford the two diastereomers of 3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one.

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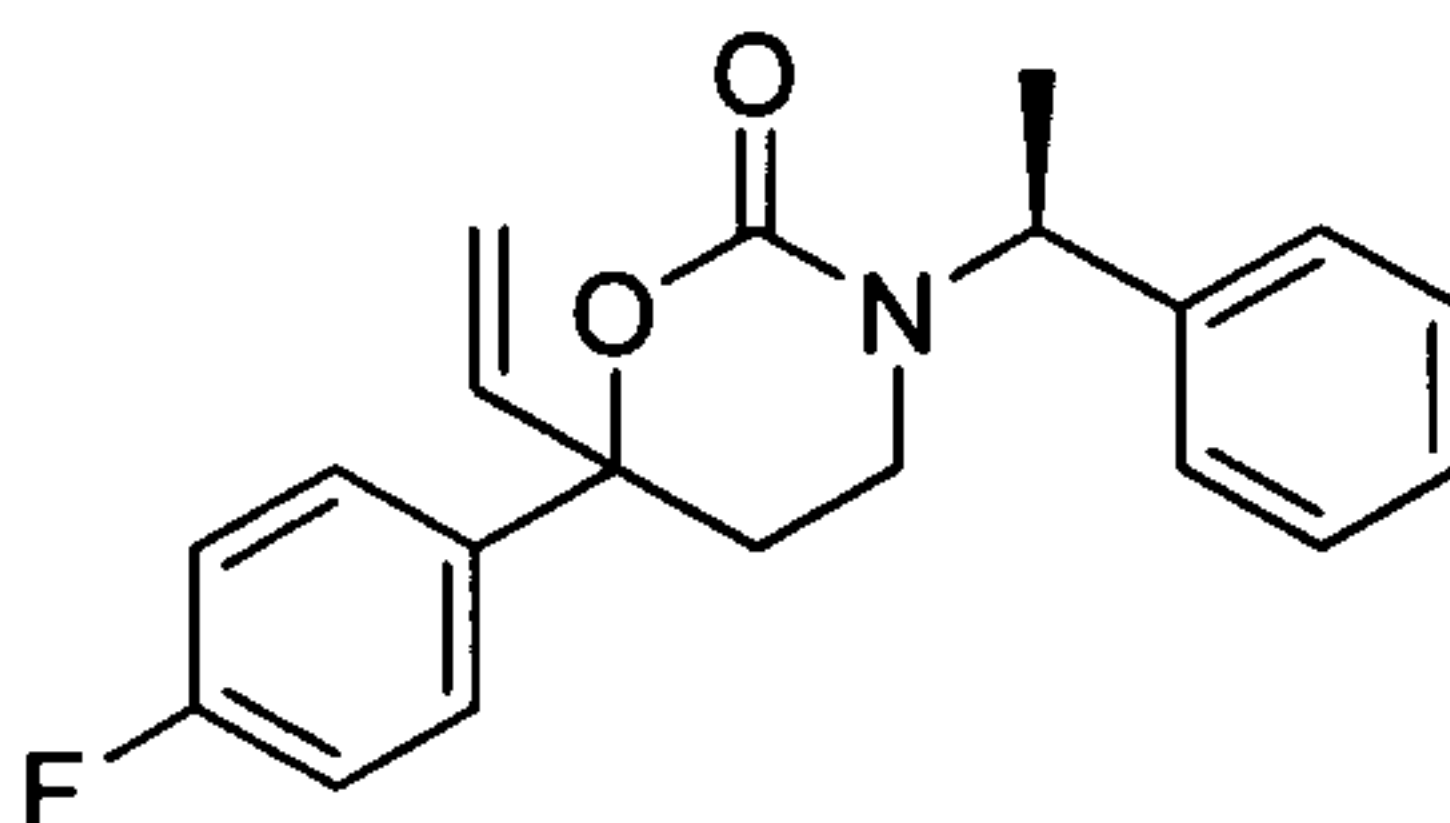
Isomer 1: (R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one, less polar isomer, LC-MS Method 1 t_R = 1.86 min, m/z 456 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.30 (m, 7H), 7.13-6.88 (m, 4H), 5.78 (q, J = 7.0 Hz, 1H), 3.78-3.74 (m, 1H), 3.57-3.50 (m, 1H), 2.79-2.67 (m, 2H), 2.31-2.11 (m, 4H), 1.81 (br s, 1H), 1.31 (d, J = 7.3 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.48 (m), -113.88 (m), -114.67 (m).

Isomer 2: (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one, more polar isomer, LC-MS Method 1 t_R = 1.80 min, m/z 456 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.17 (m, 5H), 7.00-6.79 (m, 6H), 5.62 (q, J = 7.0 Hz, 1H), 3.74-3.68 (m, 1H), 3.51-3.45 (m, 1H), 2.91-2.88 (m, 1H), 2.30-2.01 (m, 5H), 1.96 (br s, 1H), 1.48 (d, J = 7.0 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.61 (m), -114.05 (m), -114.90 (m). The absolute configuration was determined by X-ray crystallography.

15

EXAMPLE 113

6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-6-vinyl-1,3-oxazinan-2-one



The title compound was prepared by application of procedures analogous to those described in Example 110 using vinylmagnesium bromide in Step 1 and (S)-(1-isocyanatoethyl)benzene in Step 2. The isomers were separated by chromatography on silica gel.

Isomer 1: LC-MS Method 1, t_R = 1.8 min, m/z = 348 ($M+23$), 326 ($M+1$). ^1H NMR ($CDCl_3$) 7.39-7.28 (m, 7H), 7.06 (t, J = 8.6 Hz, 2H), 5.96 (dd, J = 17.3, 10.8 Hz, 1H), 5.80 (q, J = 7.0 Hz, 1H), 5.32 (d, J = 17.3 Hz, 1H), 5.21 (d, J = 10.8 Hz, 1H), 2.87-2.81 (m, 1H), 2.74-2.68 (m, 1H), 2.31-2.24 (m, 1H), 2.18-2.11 (m, 1H), 1.41 (d, J = 7.3 Hz, 3H).

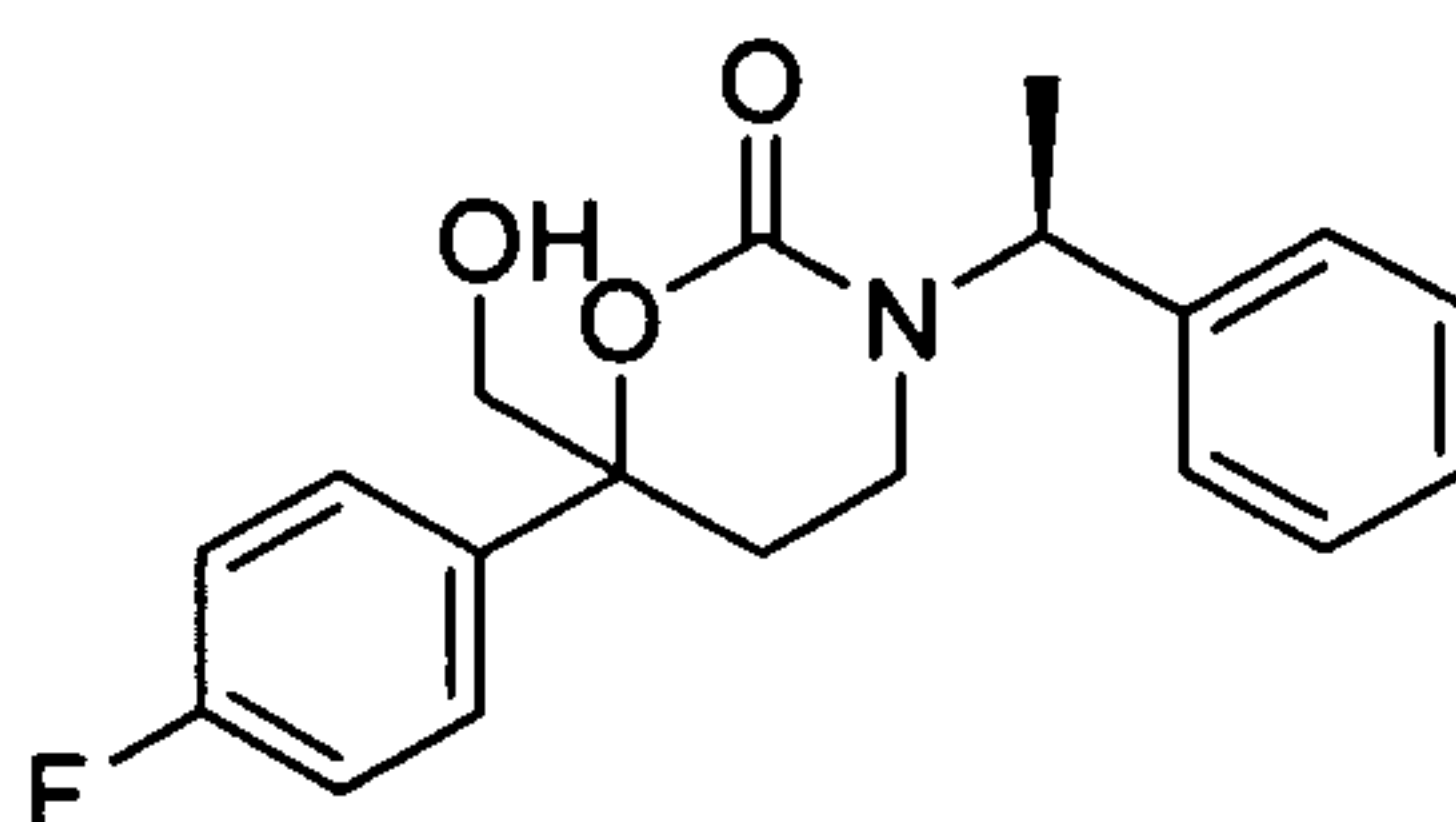
Isomer 2: LC-MS Method 1, t_R = 1.79 min, m/z = 348 ($M+23$), 326 ($M+1$). ^1H NMR ($CDCl_3$) 7.39-7.35 (m, 2H), 7.25-7.22 (m, 3H), 7.12-7.10 (m, 2H), 7.03 (t, J = 8.6 Hz, 2H), 6.00 (dd, J = 17.3, 10.8 Hz, 1H), 5.78 (q, J = 7.0 Hz, 1H), 5.34 (d, J = 17.3 Hz, 1H), 5.27 (d, J = 10.5 Hz, 1H), 3.10-3.04 (m, 1H), 2.59-2.53 (m, 1H), 2.24-2.20 (m, 2H), 1.53 (d, J = 7.3 Hz, 3H).

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EXAMPLE 114

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6-(4-fluorophenyl)-6-(hydroxymethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one



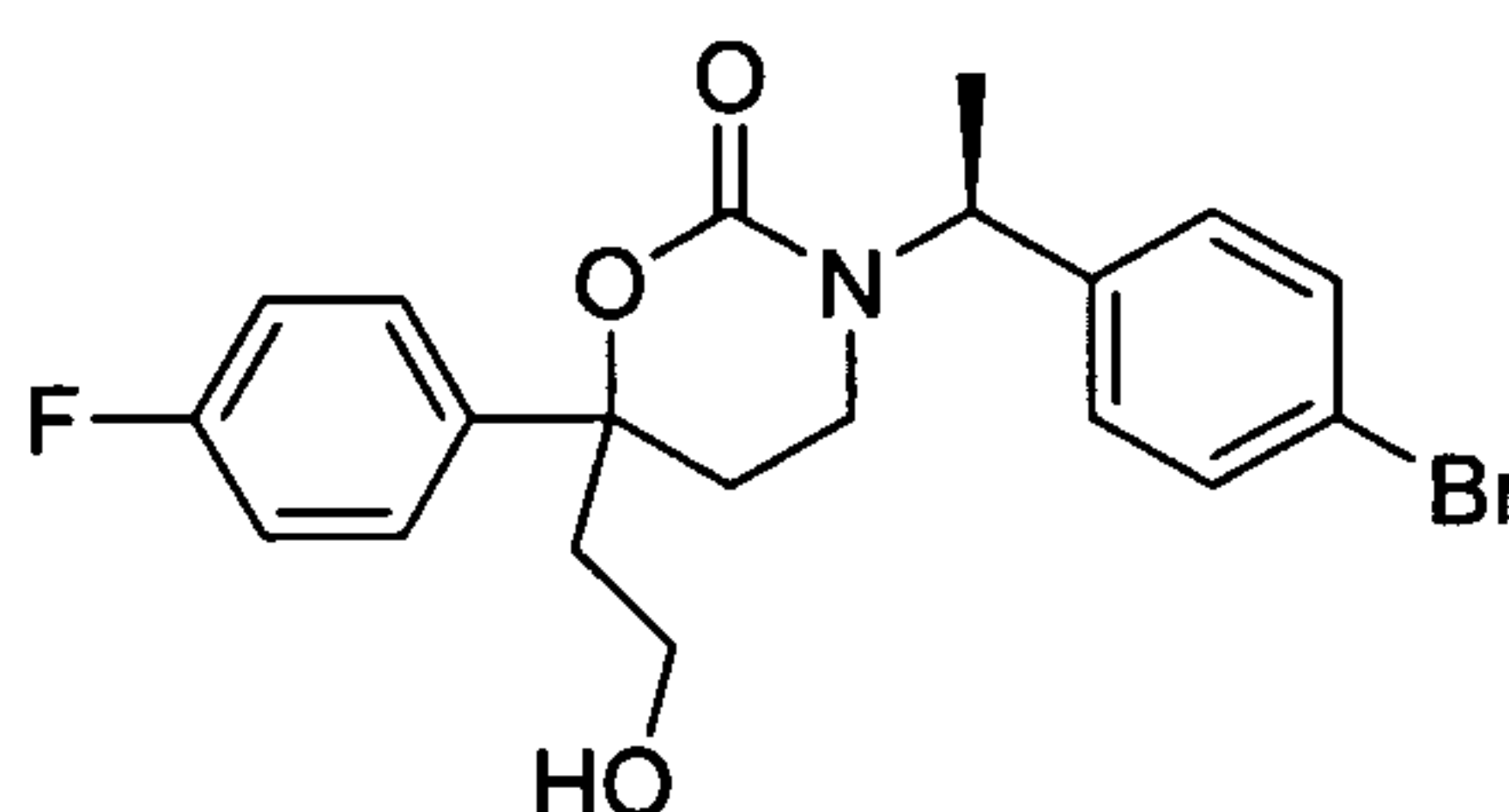
The title compound was prepared from 6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-6-vinyl-1,3-oxazinan-2-one by application of procedures analogous to those described in Example 112. The isomers were separated by chromatography on silica gel.

Isomer 1 of 6-(4-fluorophenyl)-6-(hydroxymethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one: LC-MS Method 1, $t_R = 1.5$ min, $m/z = 330$. ^1H NMR ($CDCl_3$) 7.34-7.25(m, 7H), 7.07(t, 2H), 7.73(q, 1H), 3.76(d, 1H), 3.62(d, 1H), 2.75(m, 2H), 2.39(m, 1H), 2.13(dt, 1H), 1.30(d, 3H).

Isomer 2 of 6-(4-fluorophenyl)-6-(hydroxymethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one: LC-MS Method 1, $t_R = 1.48$ min, $m/z = 330$. ^1H NMR ($CDCl_3$) 7.27(m, 2H), 7.12(m, 3H), 7.02(t, 2H), 7.90(m, 2H), 5.63(q, 1H), 3.78(d, 1H), 3.61(d, 1H), 2.96(m, 1H), 2.54(m, 1H), 2.29(m, 1H), 2.18(m, 1H), 1.51(d, 3H).

EXAMPLE 115

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



The title compound was prepared from 6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one by application of procedures analogous to those described in Example 112. The isomers were separated by chromatography on silica gel.

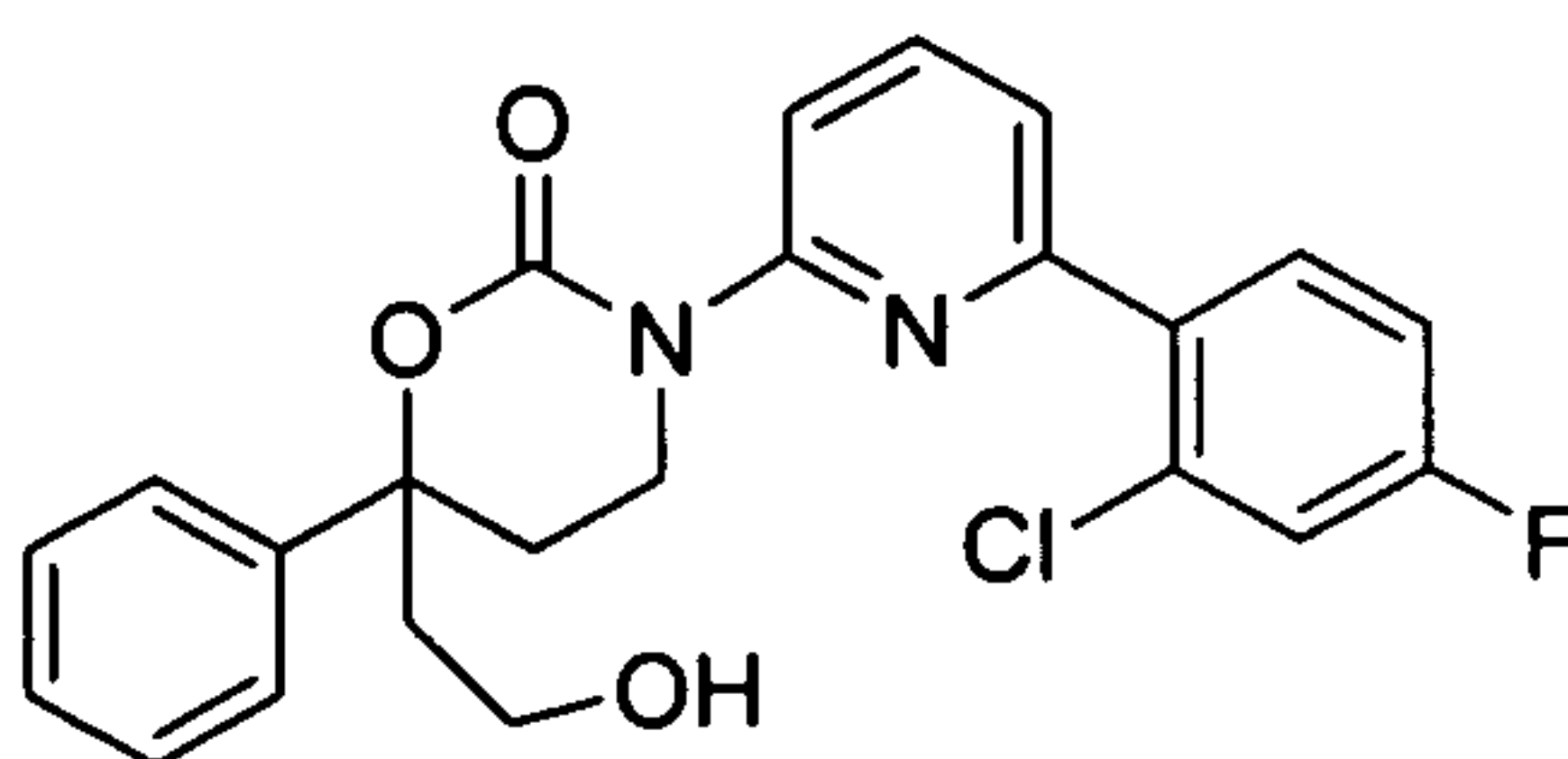
Isomer 1: (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one: LC-MS Method 1, $t_R = 1.67$ min, $m/z = 423$. ^1H NMR ($CDCl_3$) 7.44-7.48 (ad, 2H), 7.28-7.32 (m, 2H), 7.16-7.19 (ad, 7.09 (at, 2H), 5.69 (q, 1H), 3.73-3.79 (m, 1H), 3.51-3.57 (m, 1H), 2.67 (dd, 2H), 2.28 (dt, 1H), 2.22-2.07 (m, 3H), 1.25 (d, 3H).

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Isomer 2: (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one: LC-MS Method 1, $t_R = 1.63$ min, $m/z = 423$. ^1H NMR ($CDCl_3$) 7.23-7.29 (m, 4H), 7.02-7.08 (m, 2H), 6.77 9d, 2H), 5.58 (q, 1H), 3.73-3.79 (m, 1H), 3.51-3.57 (m, 1H), 2.86-2.94 (m, 1H), 2.25-2.34 (m, 3H), 2.06-2.21 (m, 2H), 1.49 (d, 3H).

EXAMPLE 116

3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one



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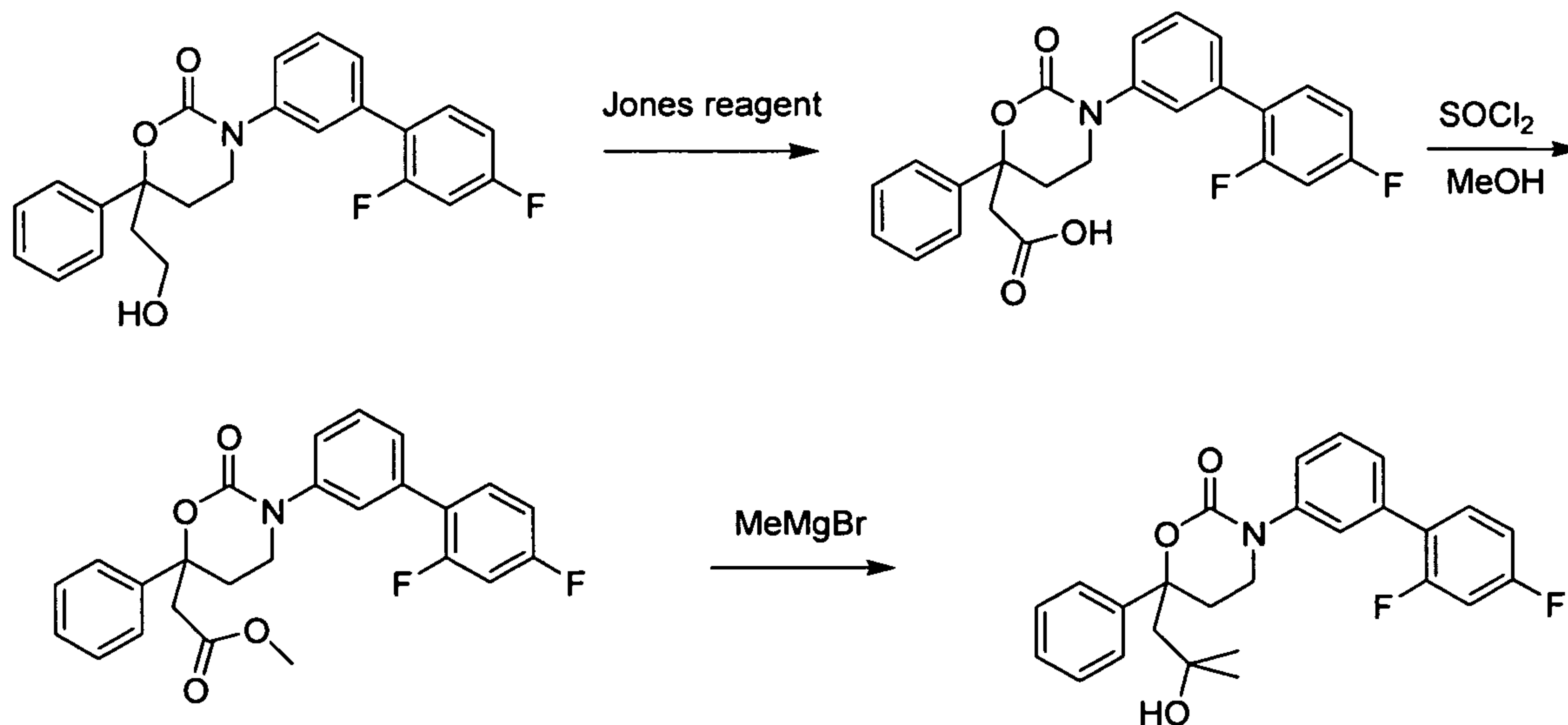
The title compound was prepared by application of procedures analogous to those described in Example 63 using acetophenone in Step 1 and 2-amino-6-bromopyridine in Step 2, followed by Example 74 and Example 75 Step 1 using 2-chloro-4-fluorophenylboronic acid. LC-MS Method 3, $t_R = 1.267$ min, $m/z = 427$. ^1H NMR (CD_3OD) δ =2.28 (m, 2H), 2.53 (m, 1H), 2.72 (m, 1H), 3.41 (m, 2H), 3.76 (m, 1H), 4.13 (m, 1H), 7.15 (m, 1H), 7.32 (m, 2H), 7.44 (m, 5H), 7.55 (m, 1H), 7.76 (m, 1H), 7.85 (m, 1H).

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EXAMPLE 117

3-(2', 4'-difluorobiphenyl-3-yl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

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Step 1. 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetic acid

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A 100-mL of flask was charged with 3-(2', 4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl) -6-phenyl-1,3-oxazinan-2-one (1 g, 2.4 mmol) dissolved in acetone (10 mL). Jones reagent (CrO₃: 1 g; H₂SO₄: 1 mL, H₂O: 4 mL) was added at 0 °C under N₂ protection. The mixture was stirred overnight at rt. Aqueous K₂CO₃ (5 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue (1.03 g) was used directly for the next step.

Step 2. methyl 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetate

A 100-mL of flask was charged with 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl -1,3-oxazinan-6-yl)acetic acid (1.02 g, 2.4 mmol) dissolved in MeOH (15 mL). Then thionyl chloride (418 mg, 3.5 mmol) was added dropwise slowly at 0 °C under N₂ protection. The mixture was stirred overnight under reflux. The mixture was concentrated to give the crude product, which was purified by chromatography to give the pure product (230 mg, 23%).

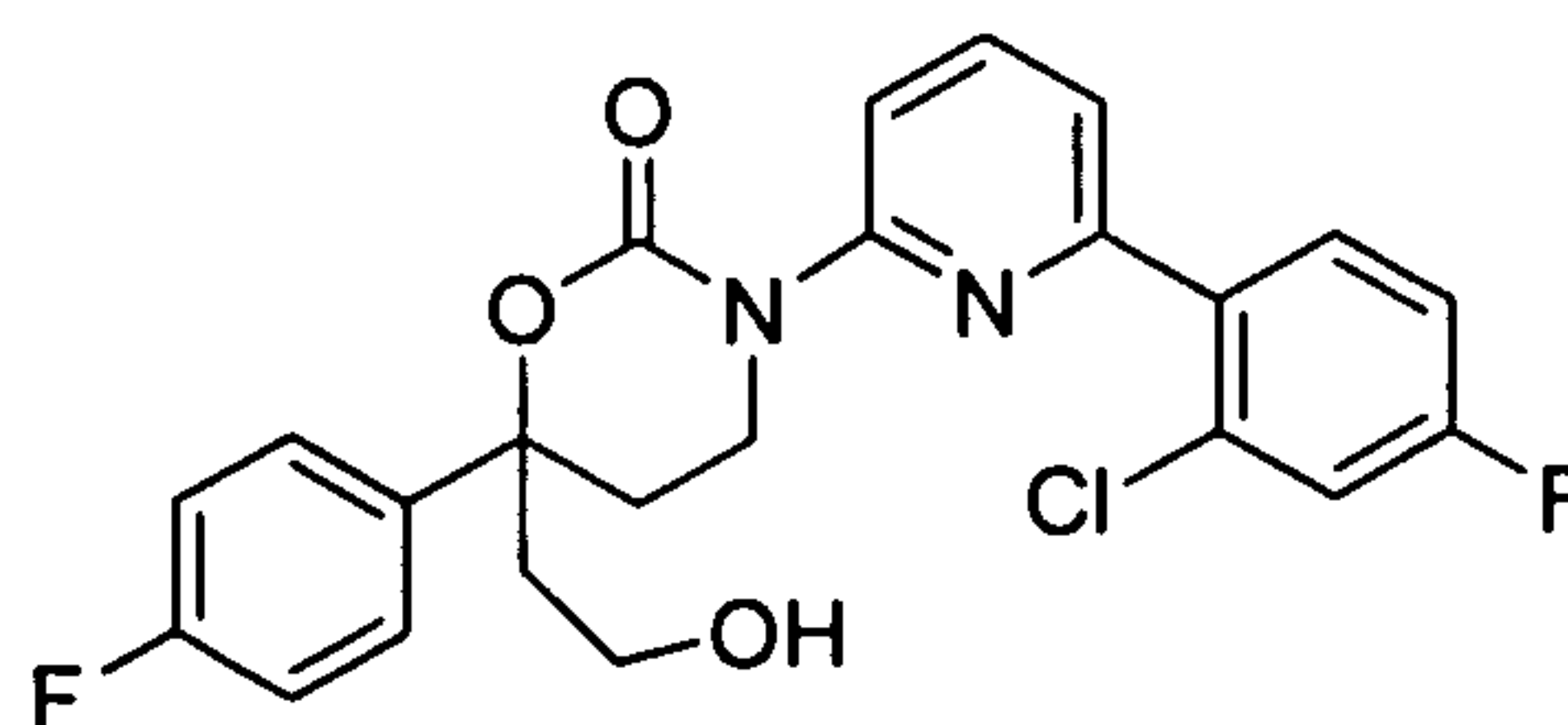
Step 3. 3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

A 25-mL of flask was charged with methyl 2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetate (100 mg, 0.23 mmol) dissolved in dry THF (3 mL) under N₂ protection at -78 °C. Then methylmagnesium bromide (3.0 M, 1 mL, 3 mmol) was added dropwise slowly at -78 °C and stirred overnight. The mixture was quenched with water and extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC to give the pure product (2.38 mg, 2%).

LC-MS Method 3, t_R = 1.267 min, m/z = 897.3. ¹H NMR (CD₃OD): 1.0 (s, 3H), 1.30 (s, 3H), 2.30 (s, 2H), 2.60 (m, 1H), 2.80 (m, 1H), 3.17 (m, 1H), 3.60 (m, 1H), 7.02 (m, 2H), 7.10 (m, 1H), 7.23 (s, 1H), 7.30-7.50 (m, 6H).

EXAMPLE 118

3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one

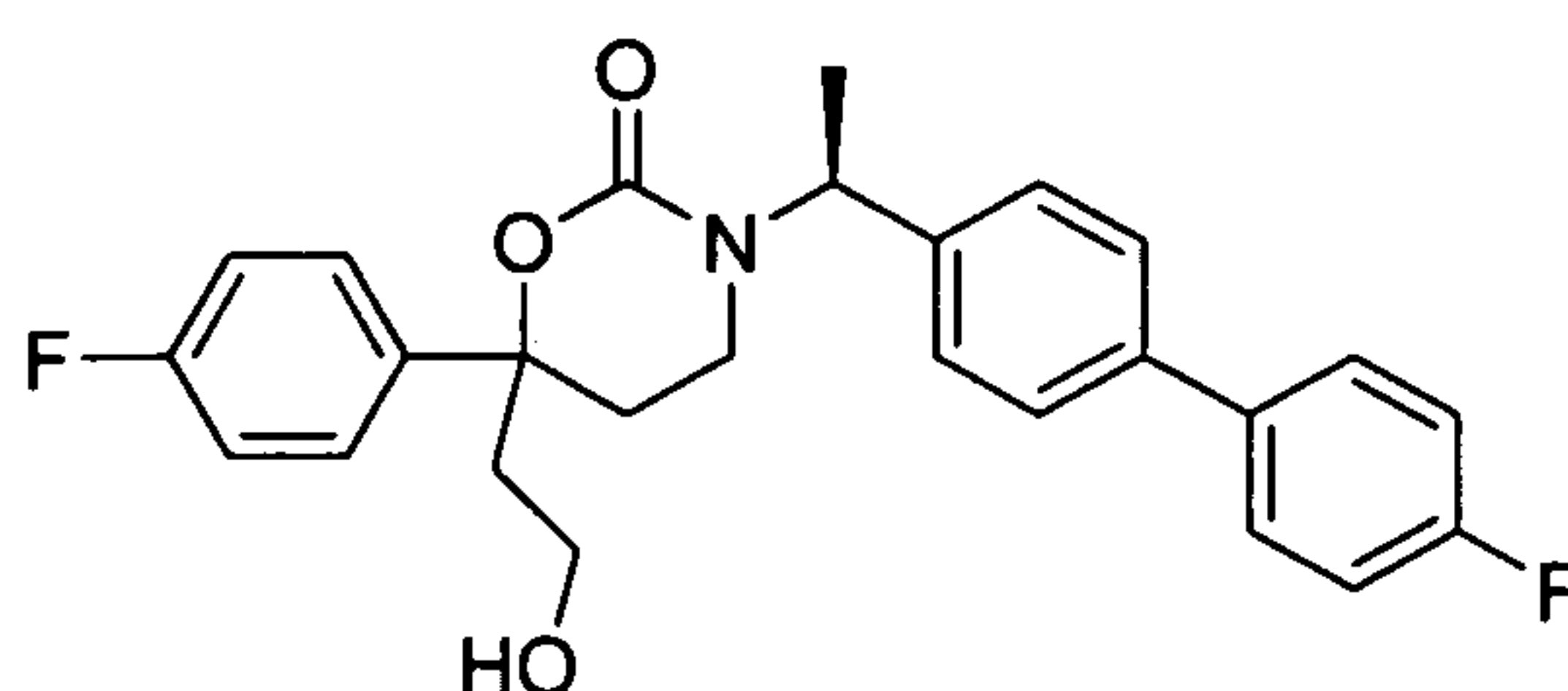


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The title compound was prepared by application of procedures analogous to those described in Example 63 using *p*-fluoroacetophenone in Step 1 and 2-amino-6-bromopyridine in Step 2, followed by Example 74 and Example 75 Step 1 using 2-chloro-4-fluorophenylboronic acid. LC-MS Method 3, $t_R = 1.347$ min, $m/z = 445.1$. ^1H NMR (CD_3OD) 2.25 (m, 2H), 2.55 (m, 1H), 2.60 (m, 1H), 3.40 (m, 2H), 3.50 (m, 1H), 3.75 (m, 1H), 7.15 (m, 3H), 7.30 (m, 1H), 7.45 (m, 3H), 7.75 (m, 1H), 7.80 (m, 1H).

EXAMPLE 119

3-((*S*)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one



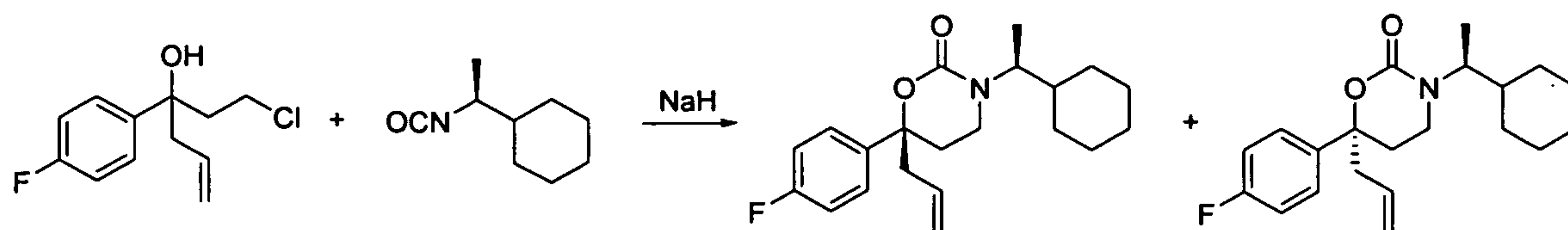
The title compound was prepared from 3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one by application of procedures analogous to those described in Example 75 Step 1 using 4-fluorophenylboronic acid. The isomers were separated by chromatography on silica gel.

Isomer 1: (*S*)-3-((*S*)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one. LC-MS Method 1, $t_R = 1.79$ min, $m/z = 438$. ^1H NMR (CDCl_3) 7.47-7.44 (m, 2H), 7.32-7.27 (m, 4H), 7.13-7.04 (m, 4H), 6.98 (d, $J = 7.9$ Hz, 2H), 5.69 (q, $J = 7.0$ Hz, 1H), 3.80-3.74 (m, 1H), 3.60-3.54 (m, 1H), 2.99-2.95 (m, 1H), 2.38-2.28 (m, 3H), 2.24-2.19 (m, 1H), 2.18-2.08 (m, 1H), 1.56 (d, $J = 7.0$ Hz, 3H).

Isomer 2: (*R*)-3-((*S*)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one. LC-MS Method 1, $t_R = 1.84$ min, $m/z = 438$.

EXAMPLE 120

6-allyl-3-((*S*)-1-cyclohexylethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one



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1-chloro-3-(4-fluorophenyl)hex-5-en-3-ol (126 mg, 0.55 mmol), (S)-(+)-1-cyclohexylethyl isocyanate (160mg, 1.44 equiv.) and proton sponge (271mg, 2.3equiv.) were dissolved in dry THF (5mL) and heated to reflux for 3 h. The mixture was then cooled to 0°C and NaH (22 mg, 1.0 equiv.) was added slowly. After 5 min, the mixture was heated to reflux overnight. LC-MS showed the reaction was complete. The mixture was diluted with EtOAc (50 mL) and washed with 1% aq HCl (2 x 15 mL), satd aq NaHCO₃ (10 mL) and brine (10 mL), and dried over Na₂SO₄. After filtration and concentration, the residue was purified by chromatography on a 12-g silica cartridge eluted with a 10-45% EtOAc in hexanes gradient to afford two isomeric products.

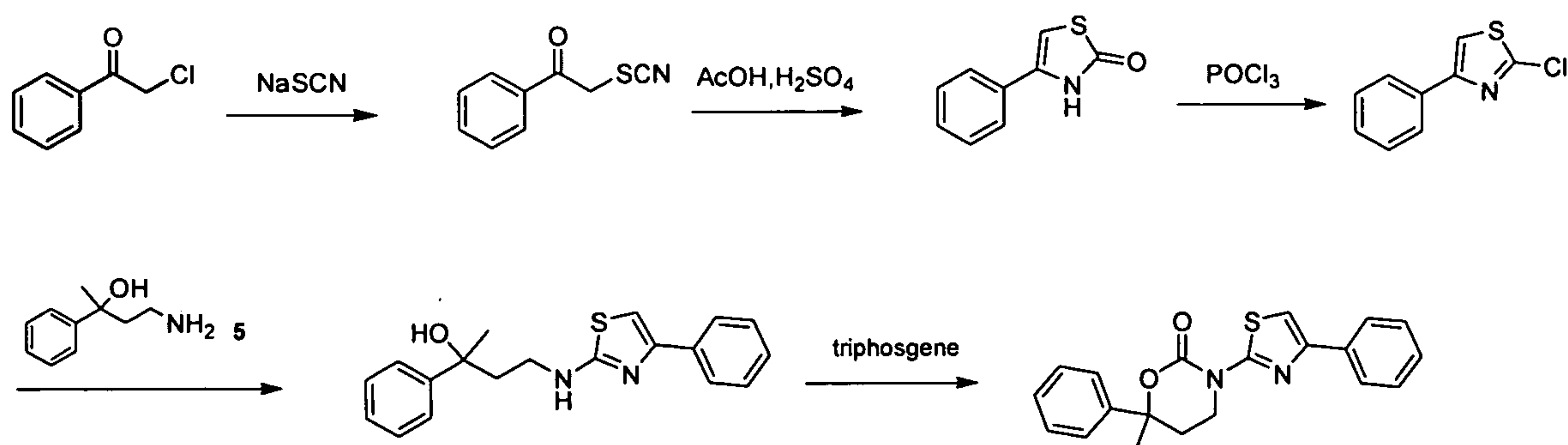
Isomer 1: (R)-6-allyl-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (57.5mg, 30%). LC-MS Method 1, t_R = 2.05 min, m/z = 346. ¹H NMR (CDCl₃) 7.29(m, 2H), 7.02(m, 2H), 5.70(m, 1H), 5.05(dd, 2H), 3.94(m, 1H), 3.06(m, 1H), 2.68-2.49(m, 3H), 2.33(m, 1H), 2.14(m, 1H), 1.17(d, 3H), 0.78(m, 2H).

Isomer 2: (S)-6-allyl-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (56mg, 29%). LC-MS Method 1, t_R = 2.06 min, m/z = 346. ¹H NMR (CDCl₃) 7.27(m, 2H), 7.03(t, 2H), 5.71(m, 1H), 5.05(dd, 2H), 3.95(m, 1H), 2.92(m, 1H), 2.72(m, 1H), 2.57 (m, 2H), 2.22 (m, 2H), 1.49(d, 1H), 1.32(m, 1H), 0.86(d, 3H).

20

EXAMPLE 121

6-methyl-6-phenyl-3-(4-phenylthiazol-2-yl)-1,3-oxazinan-2-one



25 Step 1. 1-Phenyl-2-thiocyanatoethanone

To a solution of 2-bromo-1-phenylethanone (20 g, 0.1 mol) in acetone (170 mL) was added NaSCN (8.1 g, 0.1 mol). The mixture was stirred till the reaction was complete. The mixture was filtered, and the filtrate was concentrated to give the

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crude 1-phenyl-2-thiocyanato-ethanone (20 g), which was used for the next step without further purification.

Step 2. 4-Phenylthiazol-2(3H)-one

5

To a solution of 1-phenyl-2-thiocyanato-ethanone (20 g, 113 mmol) in HOAc (100 mL) was added 50% aqueous H₂SO₄ (20 mL). The mixture was refluxed for 10 min. The mixture was poured into water. The solid formed was collected by filtration to give crude 4-phenyl-3H-thiazol-2-one (20 g) which was used for the next step without further purification.

10

Step 3. 2-Chloro-4-phenylthiazole

4-Phenyl-3H-thiazol-2-one (5 g, 28.2 mmol) was dissolved in POCl₃ (30 mL), and the mixture was refluxed overnight. The mixture was concentrated in vacuum, and the residue was purified by column chromatography to give 2-chloro-4-phenylthiazole (3.1 g, 57%).

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Step 4. 2-Phenyl-4-(4-phenylthiazol-2-ylamino)butan-2-ol

A mixture of 2-chloro-4-phenylthiazole (300 mg, 1.5 mmol), 4-amino-2-phenylbutan-2-ol (294 mg, 1.5 mmol) and DBU (1.5 mL) was heated to 100 °C under N₂ in a microwave for 2 h. After the material was consumed, the mixture was neutralized with 1 N HCl solution (5 mL), extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated to leave a residue, which was purified by column chromatography (1:2 petroleum ether/EtOAc) to afford 2-phenyl-4-(4-phenylthiazol-2-ylamino)butan-2-ol (100 mg, 20%).

20

Step 5. 6-methyl-6-phenyl-3-(4-phenylthiazol-2-yl)-1,3-oxazinan-2-one

To a solution of 2-phenyl-4-(4-phenylthiazol-2-ylamino)butan-2-ol (50 mg, 0.15 mmol) and Et₃N (80 mg, 0.75 mmol) in CH₂CH₂ (5 mL) was added triphosgene (15 mg, 0.05 mmol) at 0 °C. Then, the mixture was stirred at rt overnight. The reaction solution was concentrated to give an oil, which was purified by column chromatography (1:2 petroleum ether/EtOAc) to afford 6-methyl-6-phenyl-3-(4-phenylthiazol-2-yl)-1,3-oxazinan-2-one (20 mg, 37%). LC-MS Method 3, t_R = 1.446 min, m/z = 351. ¹H NMR (CDCl₃, 400 Hz): 1.80 (s, 3H), 2.45 (m, 1H), 2.65b (m, 1H), 3.70 (m, 1H), 4.42 (m, 1H), 7.18 (s, 1H), 7.20-7.40 (m, 8H), 7.80 (d, 2H).

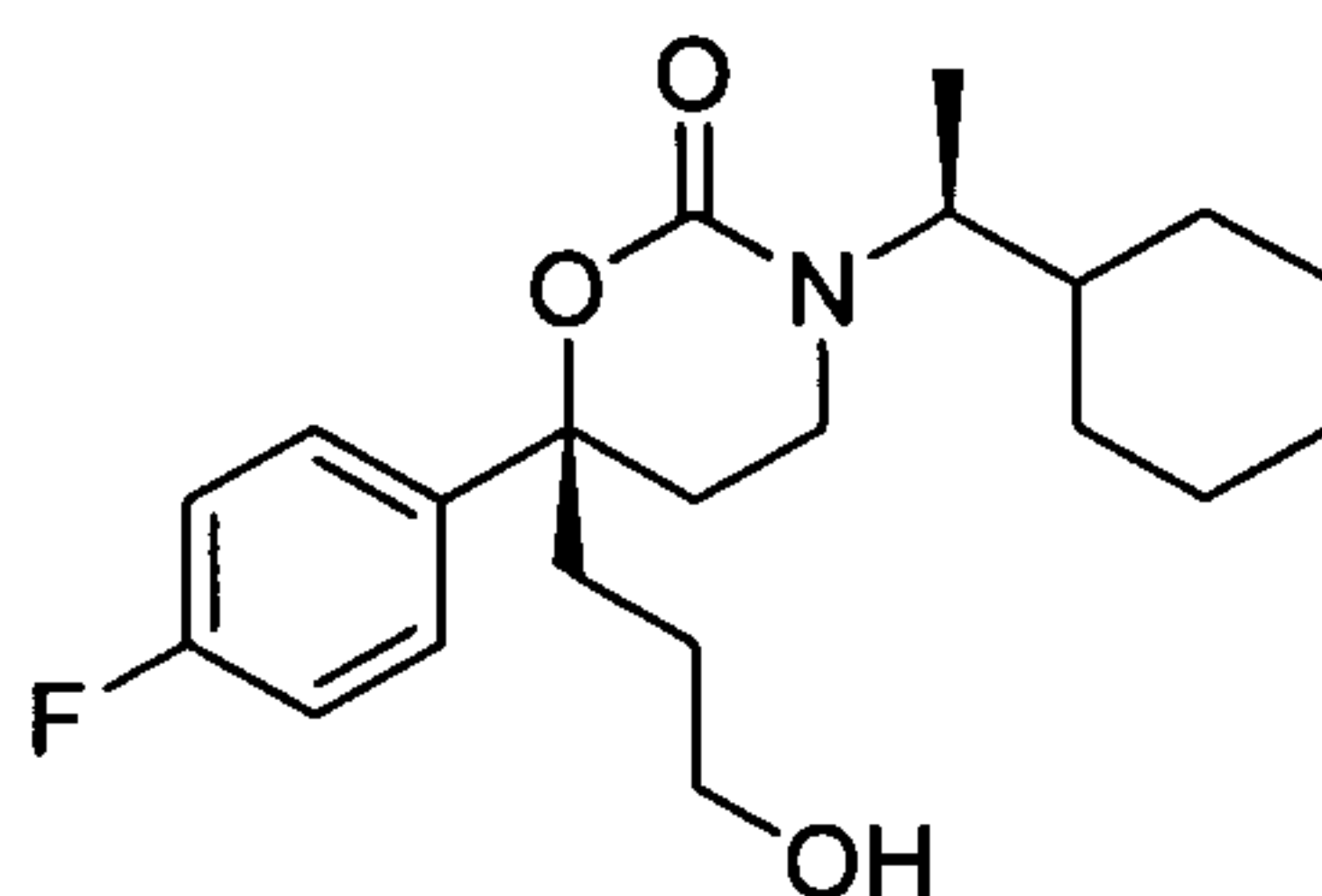
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EXAMPLE 122

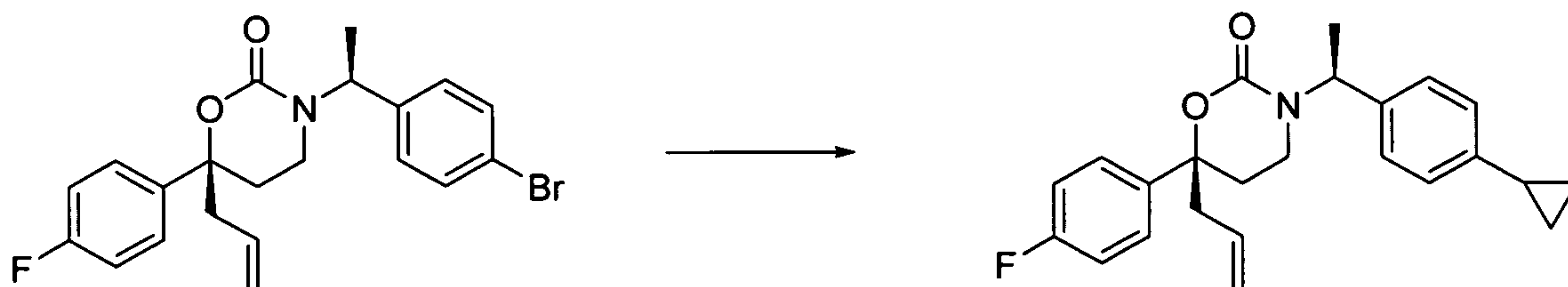
(R)-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one



The title compound was prepared from (R)-6-allyl-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one using a procedure analogous to that described in Example 78. LC-MS Method 1, $t_R = 1.72$ min, $m/z = 364$. ^1H NMR ($CDCl_3$) 7.29(m, 2H), 7.06(m, 2H), 3.98(m, 1H), 3.57(t, 2H), 3.07(m, 1H), 2.64(m, 1H), 2.16(m, 1H), 1.95(m, 2H), 1.09(d, 3H), 0.66(m, 1H).

EXAMPLE 123

(R)-6-allyl-3-((S)-1-(4-cyclopropylphenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

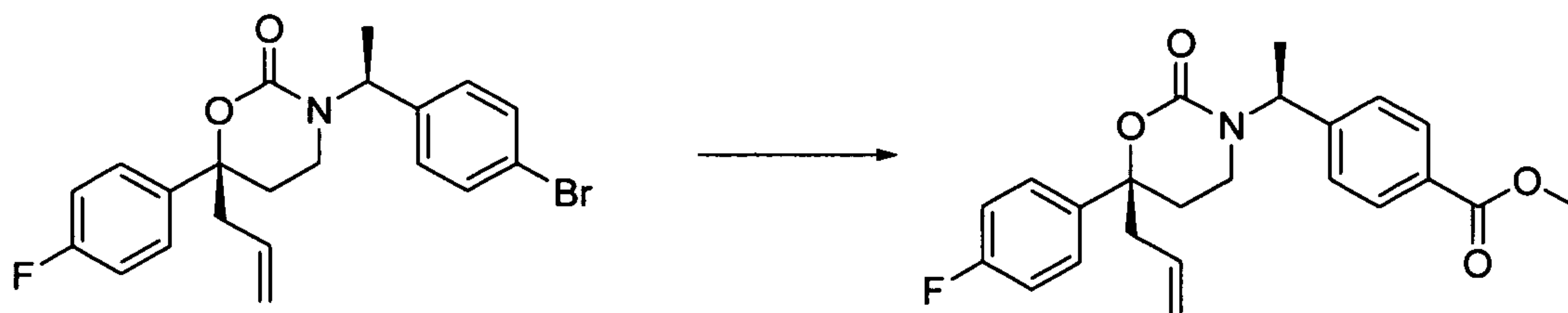


A mixture of (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (15mg, 0.036mmol), cyclopropylboronic acid (5.5mg, 1.78 equiv.), $Pd(OAc)_2$ (2mg, 25%mol), tricyclohexylphosphine (5mg, 50%mol), K_3PO_4 (20mg, excess), water (1mL) and DMF(1mL) were heated in a microwave oven for 45 min at 100 °C. The mixture was diluted with EtOAc (10 mL), washed with water (4mL) and brine (5mL), and dried over Na_2SO_4 . After filtration and concentration, the residue was purified by preparative HPLC to afford (R)-6-allyl-3-((S)-1-(4-cyclopropylphenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (6.2mg, 45%). LC-MS Method 1, $t_R = 2.02$ min, $m/z = 380$. ^1H NMR ($CDCl_3$) 7.24(m, 2H), 7.02(t, 2H), 6.76(q, 4H), 5.75-5.56(m, 2H), 5.10-4.98(dd, 2H), 2.57(m, 2H), 1.48(d, 3H), 0.92(m, 2H), 0.60(m, 2H).

EXAMPLE 124

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Methyl 4-((S)-1-((R)-6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoate



5 To a 16mm culture tube with a Teflon-coated stirring bar, a solution of (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (87 mg, 0.209 mmol) in dry DMSO (4 mL) and dry methanol (1.5 mL), triethylamine (60 μ L, 2 equiv), Pd(OAc)₂ (10 mg, 0.2 equiv) and 1,3-bis(diphenylphosphino)propane (35mg, 0.4 equiv) were added. The tube was sealed with a septum and Parafilm tape. The

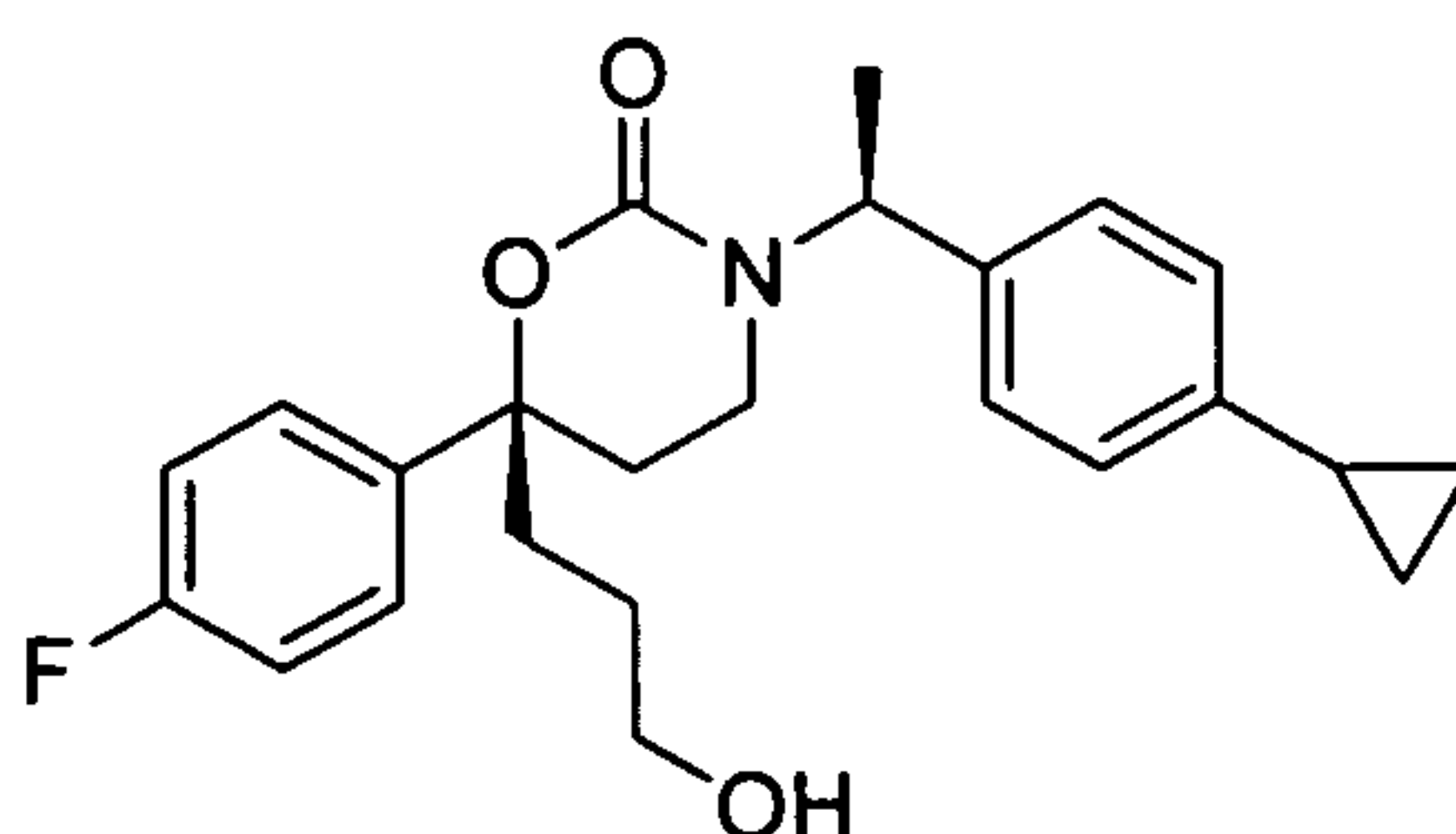
10 reaction mixture was purged with CO gas through a long needle for 1 min. A balloon filled with CO gas was attached to maintain a CO atmosphere. The reaction mixture was submerged in an oil bath preheated to 85 °C and stirred vigorously. After 12 h, LC-MS showed the reaction was complete. The mixture was filtered through a thin pad of Celite. The Celite was washed with EtOAc (35 mL). The filtrate was washed

15 with 3% aq HCl (10 mL), water (2 x 8mL) and brine (2 x 7 mL), and dried over Na₂SO₄. After filtration and concentration, the residue was purified by chromatography on a 12-g silica gel cartridge eluted with a 10-60% EtOAc in hexanes gradient to afford methyl 4-((S)-1-((R)-6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoate (68.4 mg, 83%). LC-MS Method 1, t_R = 1.79 min, m/z =

20 398. ¹H NMR (CDCl₃) 7.79(d, 2H), 7.26(m, 2H), 7.04(t, 2H), 6.94(d, 2H), 5.69(m, m, 2H), 5.07(dd, 2H), 3.89(s, 3H), 2.94(m, 1H), 2.58(m, 2H), 1.54(d, 3H).

EXAMPLE 125

(R)-3-((S)-1-(4-cyclopropylphenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one



The title compound was prepared from (R)-6-allyl-3-((S)-1-(4-cyclopropylphenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one using a procedure analogous to

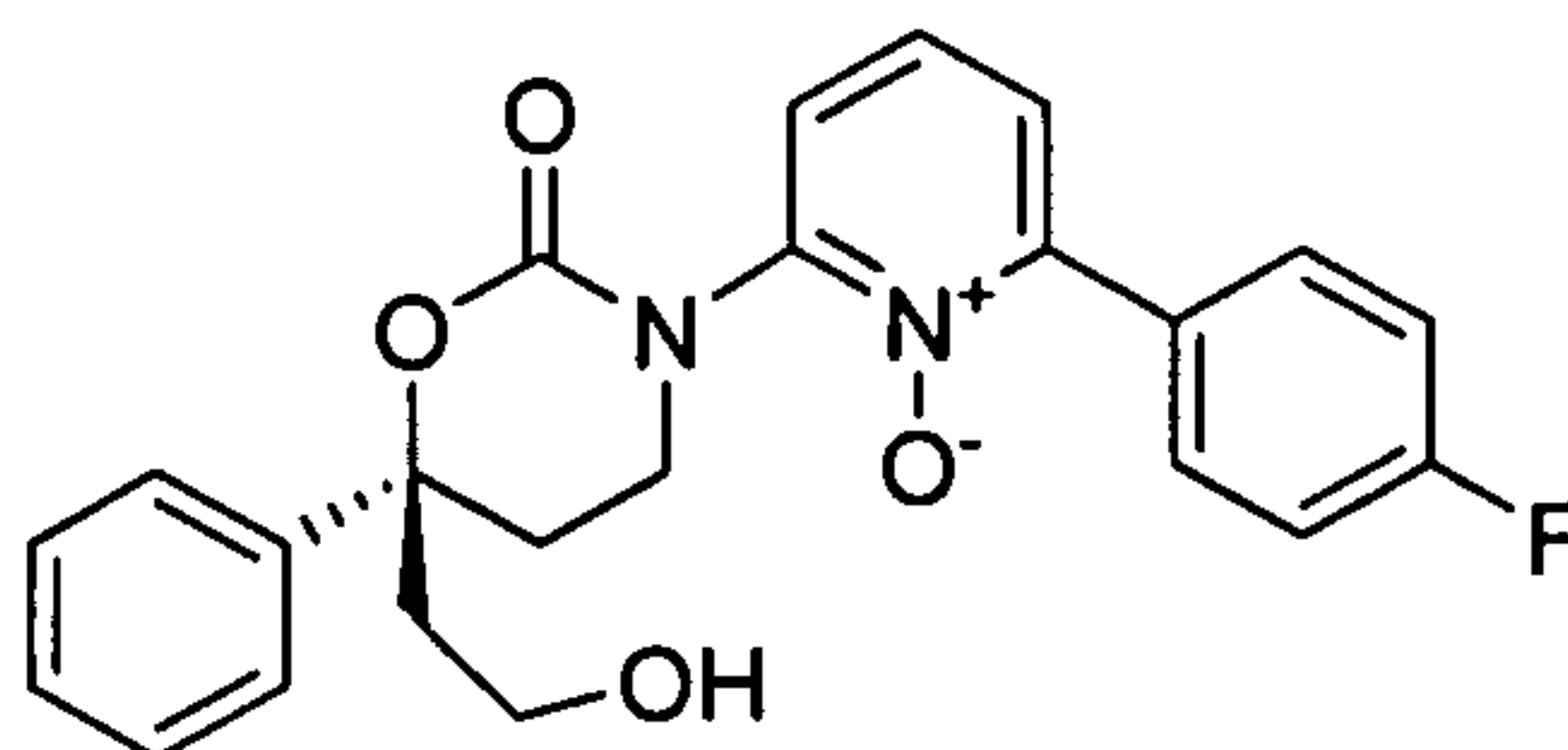
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that described in Example 78. LC-MS Method 1, $t_R = 1.71$ min, $m/z = 420$. ^1H NMR (CDCl_3) 7.31(m, 4H), 7.07(m, 2H), 6.82(d, 2H), 5.65(m, 1H), 3.96(m, 1H), 3.58(t, 2H), 1.48(t, 3H), 1.12(d, 2H), 0.92(d, 2H).

5

EXAMPLE 126

(S)-2-(4-fluorophenyl)-6-(6-(2-hydroxyethyl)-2-oxo-6-phenyl-1,3-oxazinan-3-yl)pyridine 1-oxide

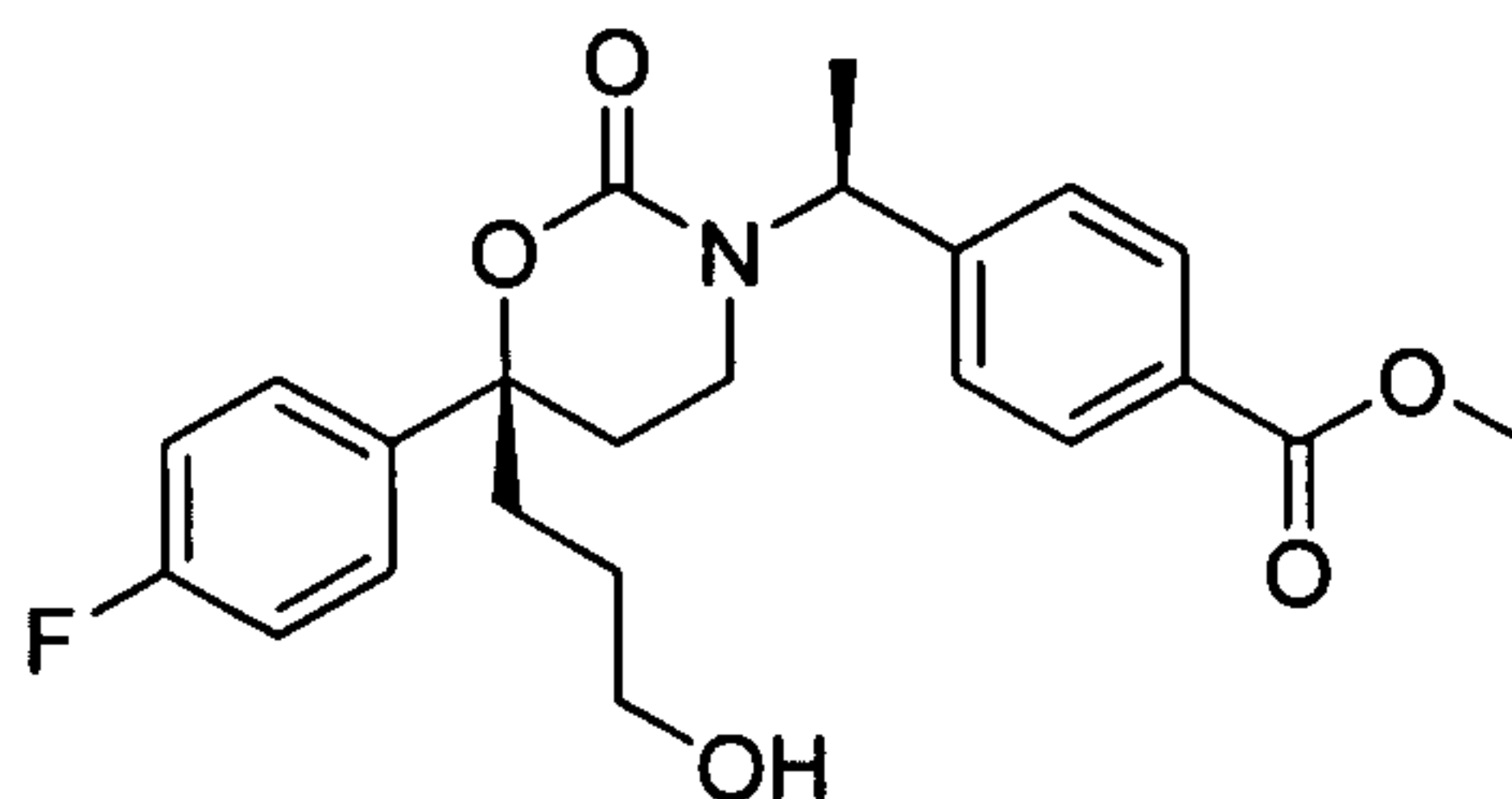


The title compound was prepared from (S)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one using a procedure analogous to that described in Example 129. LC-MS Method 2, $t_R = 1.637$ min, $m/z = 409.1$. ^1H NMR (CD_3OD) 2.25-2.40 (m, 2H), 2.56-2.70 (m, 2H), 3.05-3.14 (m, 1H), 3.32-3.40 (m, 1H), 3.62-3.80 (m, 2H), 7.15-7.26 (m, 2H), 7.30-7.68 (m, 7H), 7.70-7.88 (m, 2H).

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EXAMPLE 127

Methyl 4-((S)-1-((R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoate



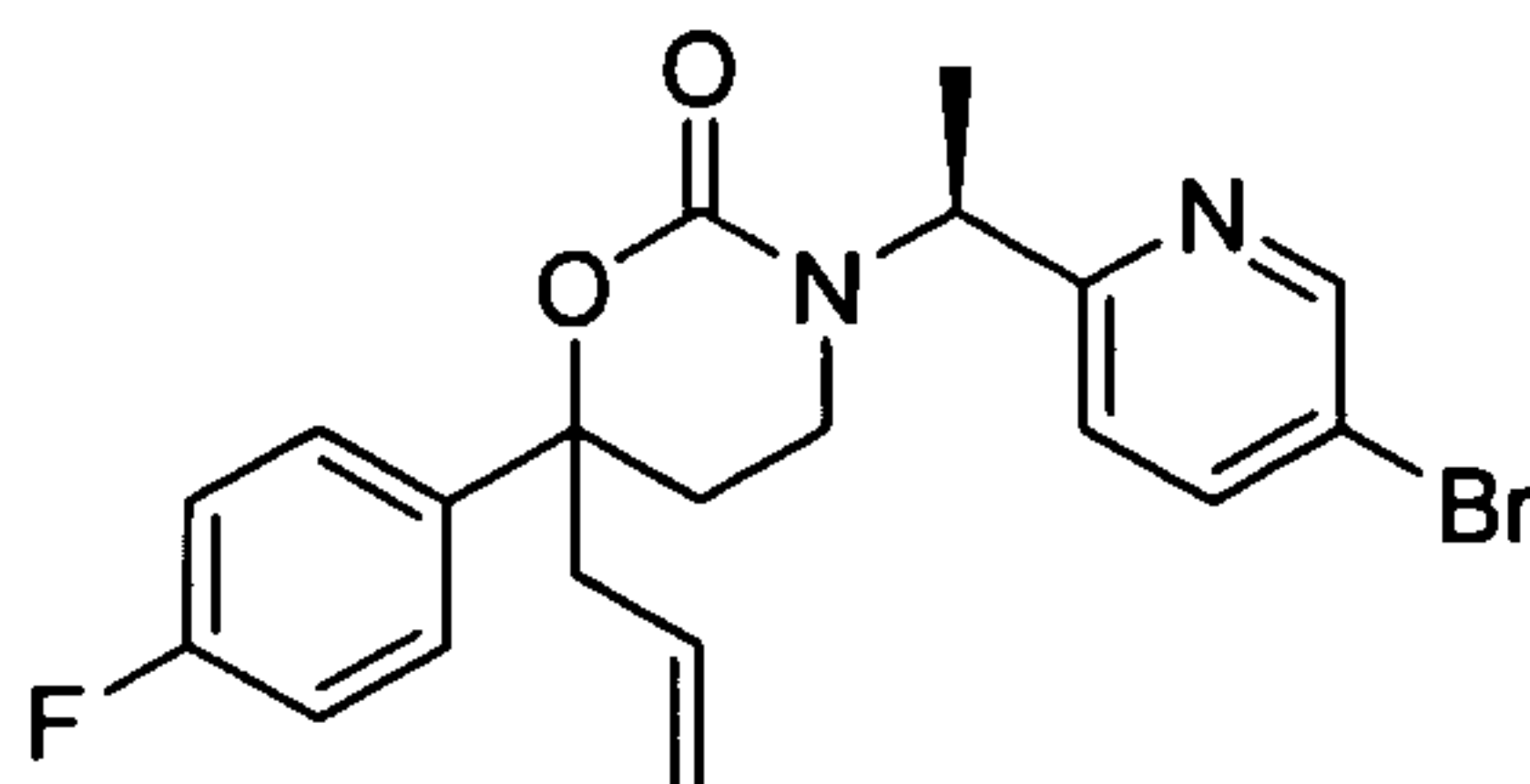
The title compound was prepared from methyl 4-((S)-1-((R)-6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoate using a procedure analogous to that described in Example 78. LC-MS Method 1, $t_R = 1.49$ min, $m/z = 416$. ^1H NMR (CDCl_3) 7.80(d, 2H), 7.23(m, 2H), 7.02(m, 4H), 5.67(m, 1H), 3.88(s, 3H), 3.576(t, 2H), 2.94(m, 1H), 1.65(m, 1H), 1.53(d, 3H), 1.35(m, 1H).

25

EXAMPLE 128

6-allyl-3-((S)-1-(5-bromopyridin-2-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

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The title compound was prepared following using a procedure analogous to that described in Example 95 using (S)-5-bromo-2-(1-isocyanatoethyl)pyridine in Step 2.

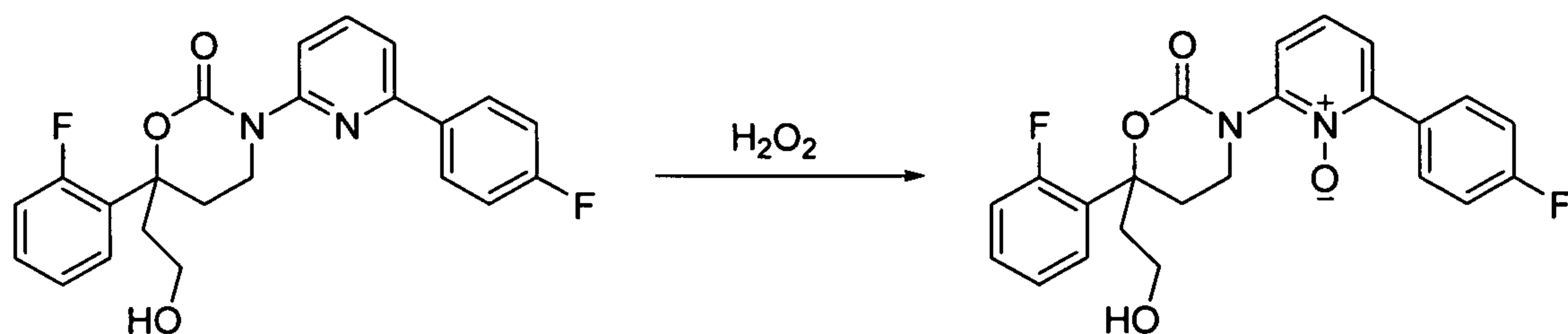
5 Isomer 1: (R)-6-allyl-3-((S)-1-(5-bromopyridin-2-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 3, $t_R = 1.281$ min, $m/z = 419$. ^1H NMR (CDCl_3) 1.25 (s, 1H), 1.60 (m, 3H), 2.25-2.33 (m, 1H), 2.35 (s, 3H), 2.46-2.55 (m, 2H), 2.60-2.70 (m, 1H), 3.80 (s, 1H), 4.48-4.59 (m, 2H), 5.06-5.14 (m, 2H), 5.52-5.65 (m, 1H), 6.30 (d, 2H), 6.95 (m, 3H), 7.27 (m, 1H), 7.35 (m, 2H).

10 Isomer 2: (S)-6-allyl-3-((S)-1-(5-bromopyridin-2-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 3, $t_R = 1.242$ min, $m/z = 419$. ^1H NMR (CDCl_3) 2.05 (m, 1H), 2.13 (d, 3H), 2.24 (m, 1H), 2.36 (m, 3H), 2.52 (m, 1H), 3.63 (m, 1H), 3.85 (m, 1H), 4.09 (m, 1H), 4.99 (m, 2H), 5.55 (m, 1H), 6.13 (d, 1H), 6.48 (m, 1H), 6.83 (m, 1H), 6.98 (m, 1H), 7.22 (m, 2H), 7.33 (m, 1H).

15

EXAMPLE 129

2-(4-fluorophenyl)-6-(6-(2-fluorophenyl)-6-(2-hydroxyethyl)-2-oxo-1,3-oxazinan-3-yl)pyridine 1-oxide



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6-(2-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one (680 mg, 1.66 mmol) was added to acetic acid (20 mL), 30% aq hydrogen peroxide (50 mL) was added at rt and the reaction mixture was stirred for about 5 h at 80 °C. The mixture was extracted with CH_2Cl_2 and the organic phase washed with Na_2SO_3 solution, then dried over Na_2SO_4 . Removal of the solvent gave the crude product, which was purified by HPLC and give 2-(4-fluorophenyl)-6-(6-(2-fluorophenyl)-6-(2-hydroxyethyl)-2-oxo-1,3-oxazinan-3-yl)pyridine 1-oxide (80 mg, 11%). LC-MS Method 2, $t_R = 1.704$ min, $m/z = 427.1$. ^1H NMR (CD_3OD) 2.33-2.50 (m, 2H), 2.60-2.77 (m, 2H), 3.08-3.20 (m, 1H), 3.32-3.40 (m, 1H), 3.40-3.52 (m, 1H),

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3.70-3.85 (m, 1H), 7.08-7.37 (m, 5H), 7.40-7.69 (m, 4H), 7.70-7.86 (m, 2H). ¹H NMR (400MHz, CDCl₃): δ=2.5 (s, 2H), 2.6 (m, 2H), 3.05 (m, 1H), 3.3 (m, 1H), 3.35-3.6 (m, 1H), 3.75 (m, 1H), 7.0-7.8 (m, 11H).

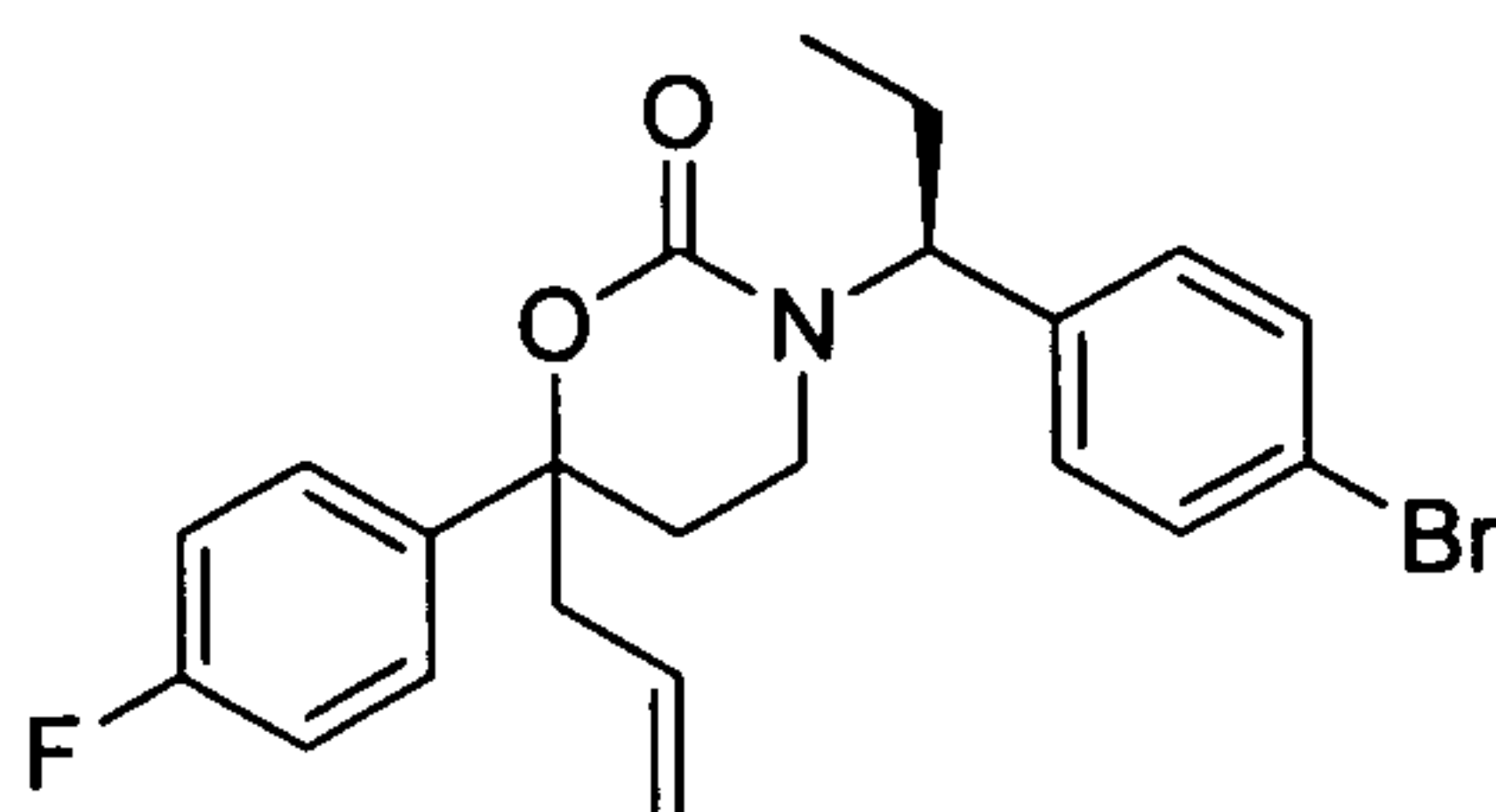
The enantiomers were separated by chiral SFC.

5 Isomer 1: LC-MS Method 2, *t_R* = 1.843 min, *m/z* = 427.1. ¹H NMR (CD₃OD) 2.40-2.52 (m, 2H), 2.62-2.80 (m, 2H), 3.12-3.23 (m, 1H), 3.35-3.45 (m, 1H), 3.58-3.65 (m, 1H), 3.72-3.88 (m, 1H), 7.12-7.49 (m, 5H), 7.50-7.70 (m, 4H), 7.72-7.90 (m, 2H).

10 Isomer 2: LC-MS Method 2, *t_R* = 1.841 min, *m/z* = 427.1. ¹H NMR (CD₃OD) 2.26-2.40 (m, 2H), 2.50-2.70 (m, 2H), 3.06 (m, 1H), 3.23-3.32 (m, 1H), 3.23-3.58 (m, 1H), 3.62-3.75 (m, 1H), 6.98-7.30 (m, 1H), 7.30-7.60 (m, 4H), 7.62-7.78 (m, 2H).

EXAMPLE 130

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



15

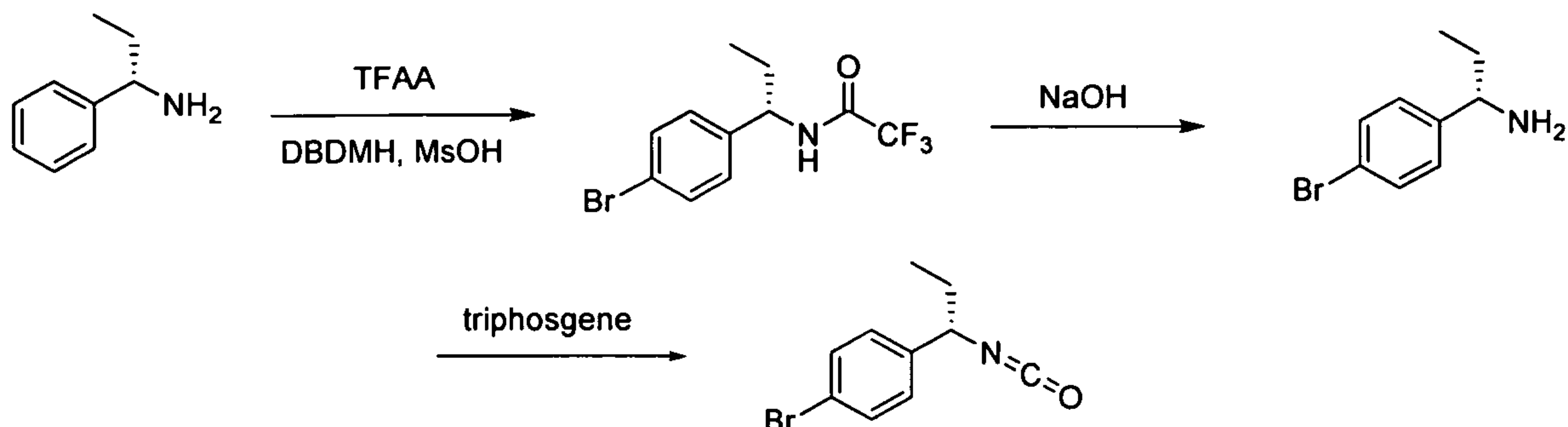
The title compound was prepared following using a procedure analogous to that described in Example 95 using (S)-1-bromo-4-(1-isocyanatopropyl)benzene in Step 2.

20 Isomer 1: (R)-6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 3, *t_R* = 1.415 min, *m/z* = 432. ¹H NMR (CD₃OD) 0.94 (t, 3H), 1.96 (m, 2H), 2.28 (m, 2H), 2.46 (m, 1H), 2.62 (m, 2H), 3.10 (m, 1H), 5.06 (m, 1H), 5.28 (m, 1H), 5.68 (m, 1H), 6.92 (m, 2H), 7.06 (m, 2H), 7.29 (m, 4H)

25 Isomer 2: (S)-6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 3, *t_R* = 1.454 min, *m/z* = 432. ¹H NMR (CD₃OD) 0.56 (d, 3H), 1.65-1.75 (m, 1H), 1.76-1.88 (m, 1H), 1.98-2.08 (m, 1H), 2.46-2.55 (m, 1H), 2.60 (m, 2H), 2.72-2.86 (m, 2H), 4.98-5.08 (m, 2H), 5.30 (m, 1H), 5.62-5.72 (m, 1H), 7.11-7.18 (m, 1H), 7.25 (m, 2H), 7.39 (m, 2H), 7.50 (m, 2H).

(S)-1-bromo-4-(1-isocyanatopropyl)benzene was prepared as follows.

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5 Step 1

TFAA (27 mL) was dissolved in methylene chloride (121 mL) and cooled in ice water bath. A solution of (S)-1-phenylpropan-1-amine (25 g, 0.1851 mol) in methylene chloride (41 mL) was added and the ice water removed. The reaction mixture was stirred at rt for 3 h. The reaction mixture was cooled in ice water and MsOH (32.5 mL) was added followed by 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (DBDMH) (26.16g, 0.09255 mol). The mixture was stirred overnight. The mixture was quenched with water, and the precipitate was filtered to give (S)-N-(1-(4-bromophenyl)propyl) -2,2,2-trifluoroacetamide (45.24 g, 79%).

15 Step 2

To a solution of (S)-N-(1-(4-bromophenyl)propyl)-2,2,2-trifluoroacetamide (45.24 g, 0.1464 mol) in methanol (317 mL) was added a solution of NaOH (188 mL, 13%) at 0 °C. The mixture was stirred for 2 h. The mixture was concentrated and extracted with methylene chloride. The solvent was removed to give (S)-1-(4-bromophenyl)propan-1-amine (29.65 g, 95%). ¹H NMR (CDCl₃): 0.84 (t, 3H), 1.63 (m, 2H), 3.79 (m, 1H), 7.19 (m, 2H), 7.45 (m, 2H).

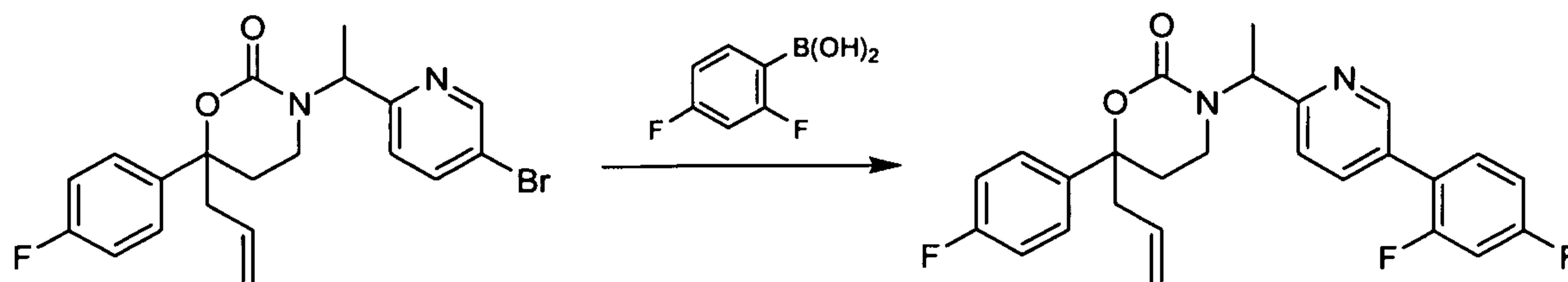
Step 3

(S)-1-(4-bromophenyl)propan-1-amine was used in a procedure analogous to that described in Example 392 Step 1 to afford (S)-1-bromo-4-(1-isocyanatopropyl)benzene.

EXAMPLE 131

6-allyl-3-(1-(5-(2,4-difluorophenyl)pyridin-2-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

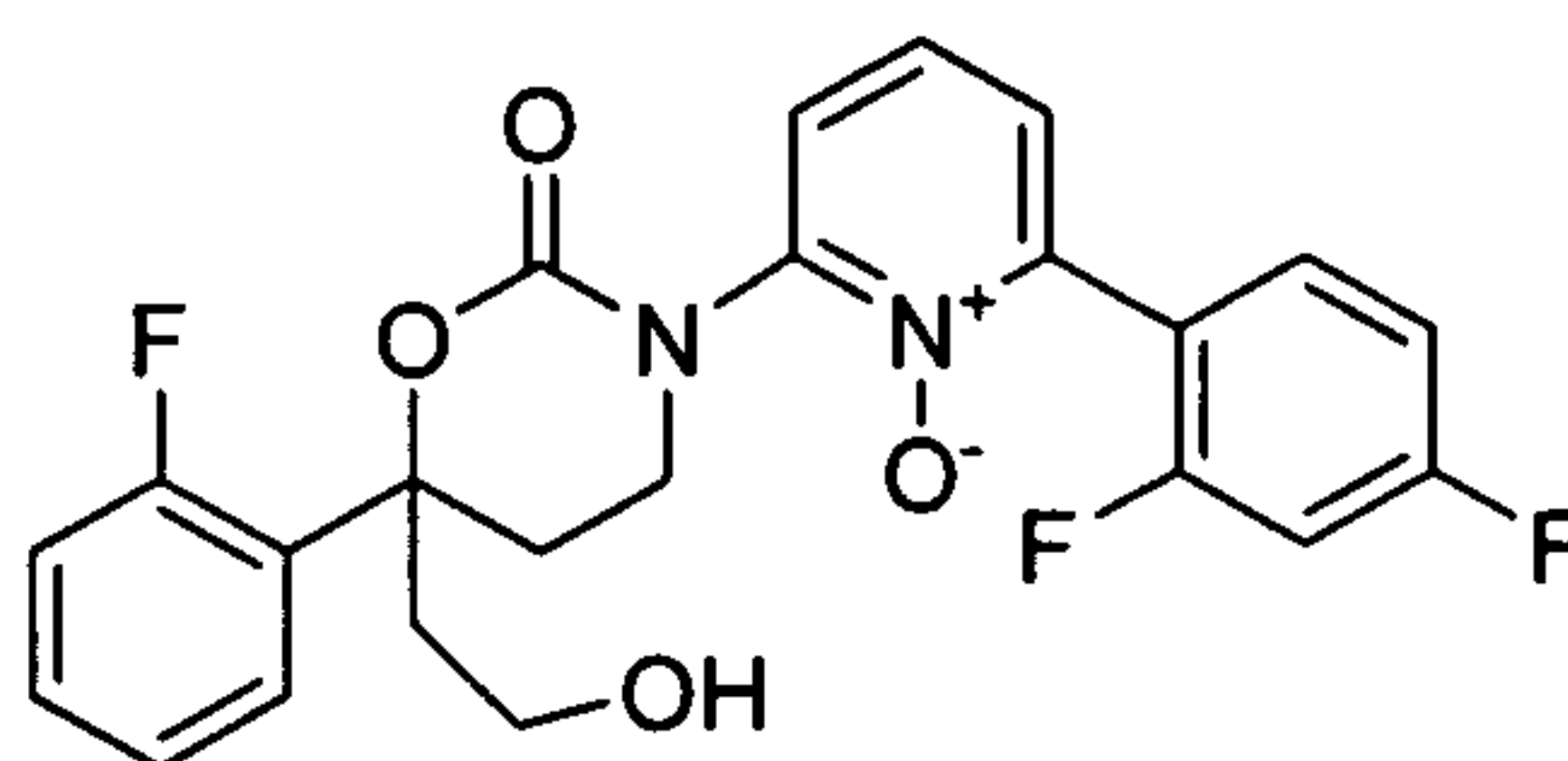
- 192 -



A solution of 6-allyl-3-(1-(5-bromopyridin-2-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (100 mg, 0.24 mmol), 2,4-difluorophenylboronic acid (56.9 mg, 0.36 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (10 mg, 10%) and aqueous solution of Cs_2CO_3 (2 M, 0.2 mL) in 1,4-dioxane (3 mL) was heated to reflux overnight. After the solvents were evaporated, the crude product was purified by preparative TLC to give 6-allyl-3-(1-(5-(2,4-difluorophenyl)pyridin-2-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (50 mg, 46%). LC-MS Method 3, $t_R = 1.336$ min, $m/z = 453.1$. ^1H NMR (CDCl_3): 2.30-2.40 (m, 1H), 2.39-2.42 (d, 3H), 2.50-2.60 (m, 2H), 2.60-2.70 (m, 2H), 4.10-4.20 (m, 1H), 4.50-4.65 (m, 2H), 5.55-5.70 (m, 2H), 6.40-6.50 (d, 1H), 6.80-7.00 (m, 4H), 7.10-7.15 (m, 1H), 7.22-7.30 (m, 2H), 7.30-7.40 (m, 3H).

EXAMPLE 132

2-(2,4-difluorophenyl)-6-(6-(2-fluorophenyl)-6-(2-hydroxyethyl)-2-oxo-1,3-oxazinan-3-yl)pyridine 1-oxide

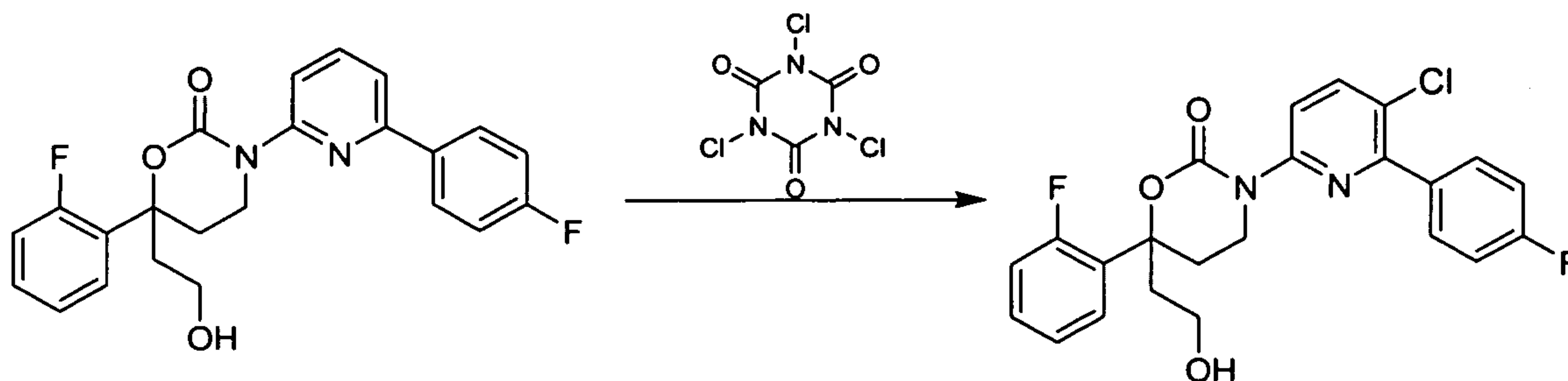


The title compound was prepared from 3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one following a procedure analogous to that described in Example 129. LC-MS Method 2, $t_R = 1.724$ min, $m/z = 445$. ^1H NMR (CD_3OD) 2.32-2.50 (m, 3H), 2.78-2.86 (m, 1H), 3.33-3.53 (m, 1H), 3.63 (m, 1H), 3.80 (m, 1H), 4.25 (m, 1H), 7.05-7.13 (m, 3H), 7.18 (m, 1H), 7.32 (m, 1H), 7.50 (m, 1H), 7.65-7.70 (m, 5H).

EXAMPLE 133

3-(5-chloro-6-(4-fluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one

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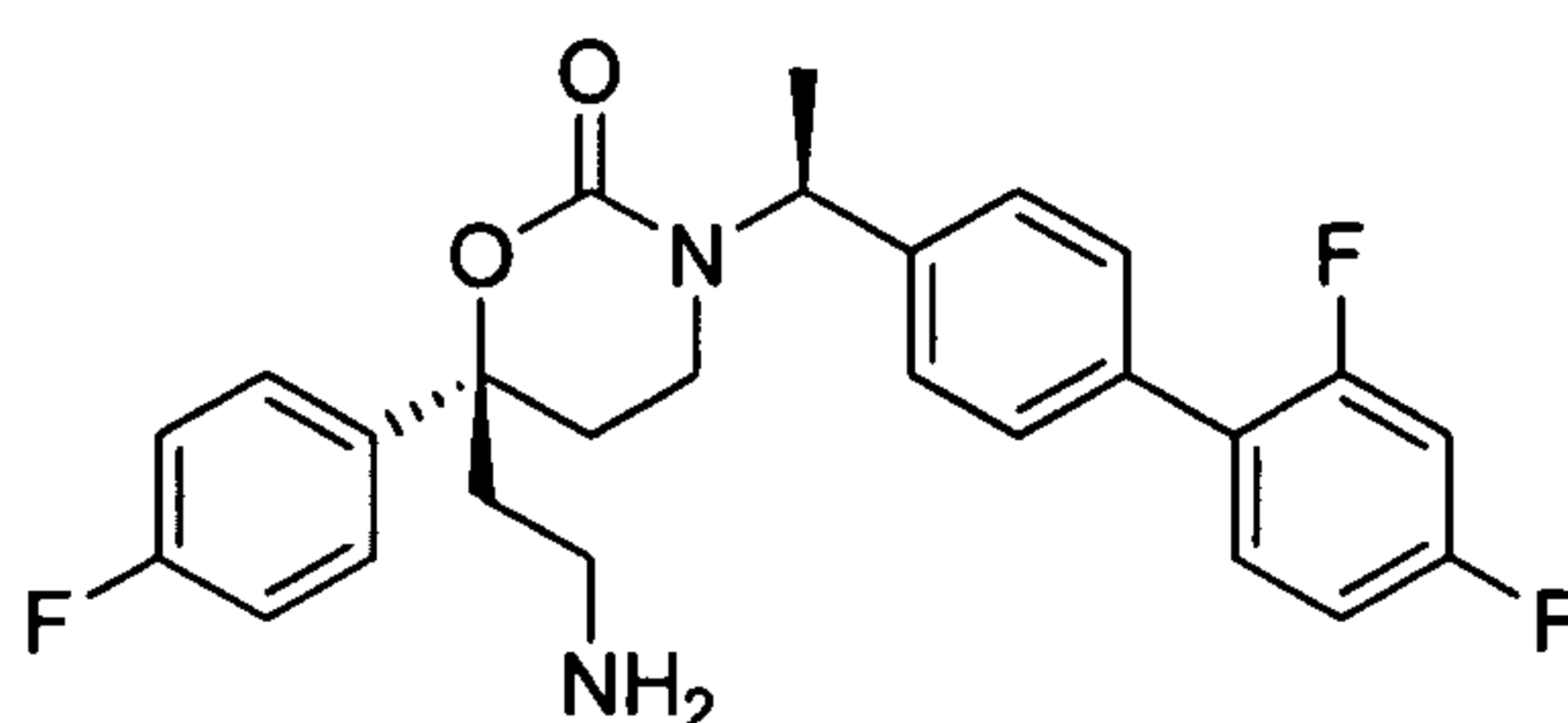


A mixture of 6-(2-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one (30 mg, 0.07 mmol), NaOAc (9 mg, 0.11 mmol) in
 5 HOAc (4 mg, 0.07 mmol), CH₃CN (2 mL), H₂O (0.1 mL) and CH₂Cl₂ (2 mL) was stirred at rt for 5 min. A solution of 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione (37 mg, 0.11 mmol) in CH₃CN (0.5 mL) was added slowly. The mixture was stirred for 20 min and heated to 40 °C for 2 h. The reaction was quenched with aq NaHSO₃ and extracted with CH₂Cl₂. The organic layer was dried with Na₂SO₄, concentrated to
 10 afford the crude product. Purification afforded 3-(5-chloro-6-(4-fluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one (15 mg, 48%). LC-MS Method 3, *t_R* = 1.331 min, *m/z* = 445. ¹H NMR (CDCl₃, 400 Hz): 2.40 (m, 3H), 2.84 (m, 1H), 3.40 (m, 1H), 3.66 (m, 1H), 3.82 (m, 1H), 4.26 (m, 1H), 7.10 (m, 3H), 7.18 (m, 1H), 7.34 (m, 1H), 7.50 (m, 1H), 7.68 (m, 2H), 7.76 (m, 1H), 8.01 (m, 1H).

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EXAMPLE 134

(R)-6-(2-aminoethyl)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

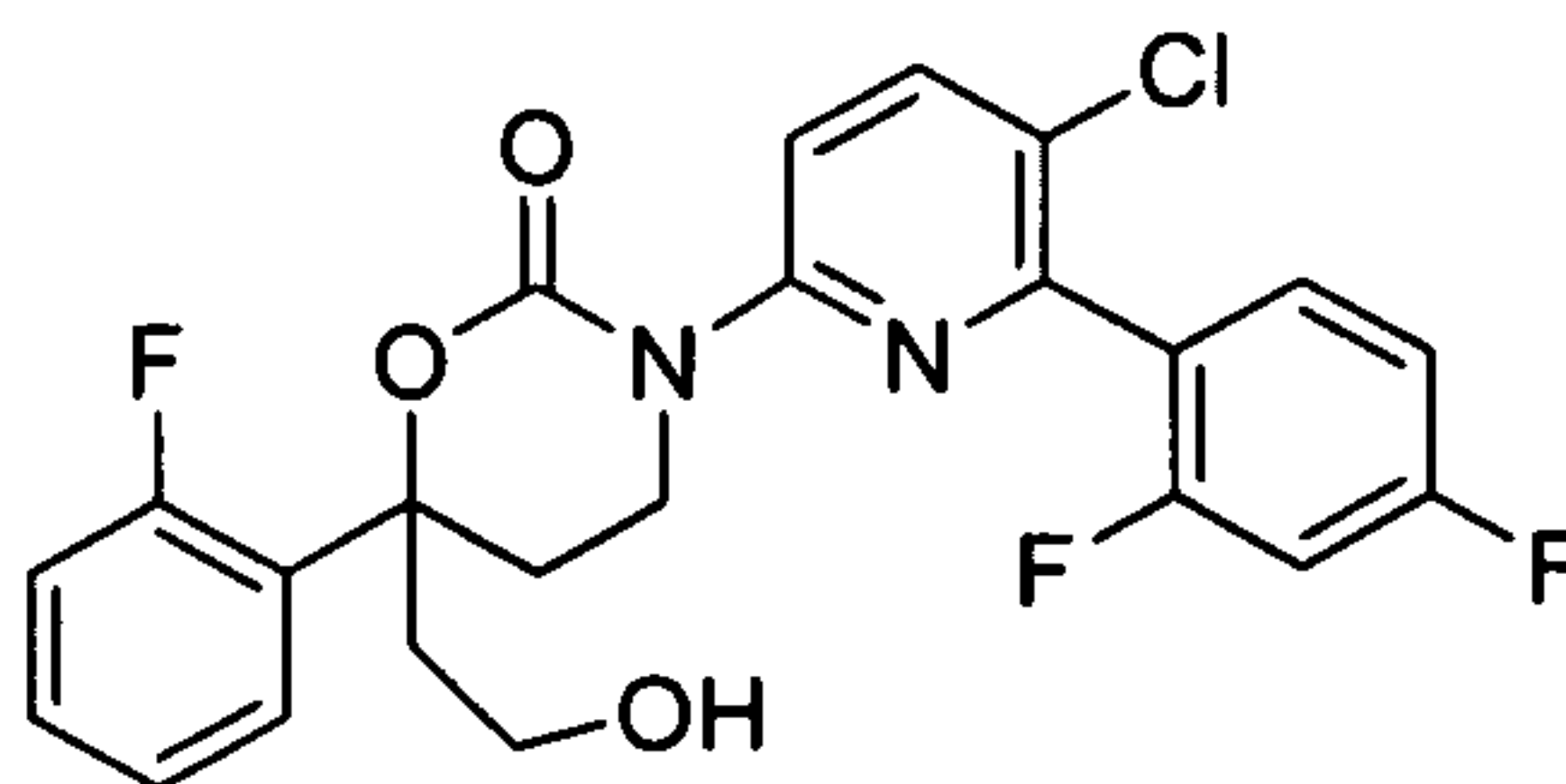


20 The title compound was prepared from (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one following procedures analogous to those described in Example 75 Steps 2, 3 and 4. LC-MS Method 2, *t_R* = 1.981 min, *m/z* = 455.2. ¹H NMR (CDCl₃) 1.50 (m, 3H), 2.29 (m, 3H), 2.34-2.50 (m, 1H), 2.80-3.18 (m, 5H), 5.60 (m, 1H), 6.85-7.09 (m, 6H), 7.21 (m, 2H),
 25 7.30 (m, 2H), 8.05-8.35 (m, 2H).

EXAMPLE 135

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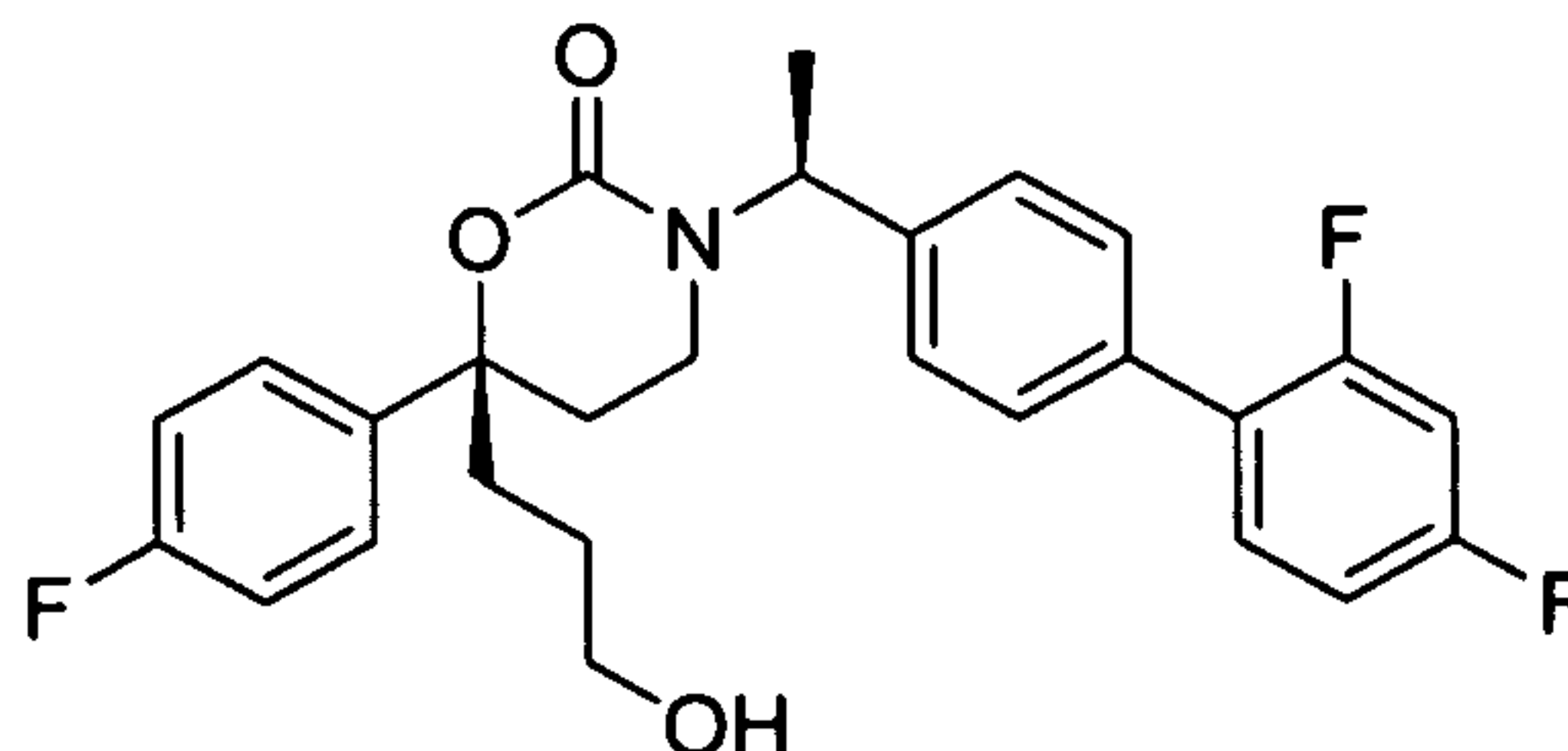
3-(5-chloro-6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one



The title compound was prepared from 3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one using a procedure analogous to that described in Example 133. LC-MS Method 3, $t_R = 1.314$ min, $m/z = 463$. ^1H NMR ($CDCl_3$) 2.42-2.53 (m, 3H), 2.64-2.86 (m, 1H), 3.29-3.40 (m, 1H), 3.65 (m, 1H), 3.78 (m, 1H), 4.20 (m, 1H), 4.30-4.58 (m, 1H), 6.83-6.95 (m, 2H), 7.09 (m, 1H), 7.18 (m, 1H), 7.30-7.40 (m, 2H), 7.42-7.51 (m, 1H), 7.76 (m, 1H), 8.05 (m, 1H).

EXAMPLE 136

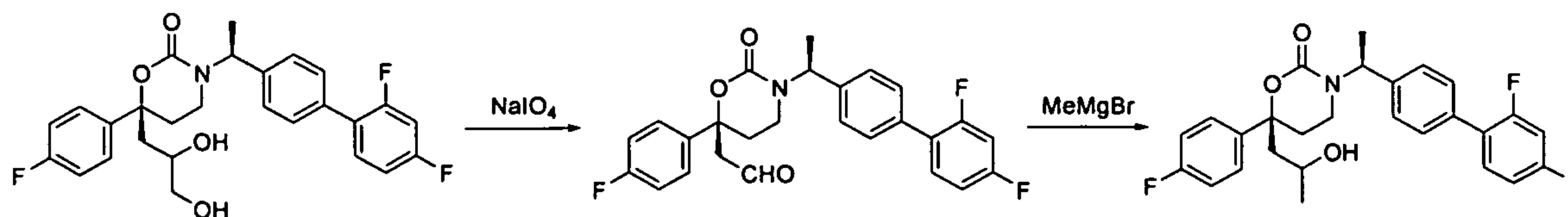
(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one



The title compound was prepared from (R)-6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one using a procedure analogous to that described in Example 78. LC-MS Method 1, $t_R = 1.84$ min, $m/z = 470$. ^1H NMR ($CDCl_3$) 7.34-7.22(m, 4H), 7.07-6.98(m, 4H), 6.96-6.85(m, 3H), 5.69(m, 1H), 3.58(t, 1H), 1.56(d, 3H).

EXAMPLE 137

(6S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxypropyl)-1,3-oxazinan-2-one



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Step 1. 2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetaldehyde

To a stirred solution of crude (6S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (0.2726 g, 0.56 mmol) in acetone/water (4:1, 5 mL) was added NaIO₄ (0.3070 g, 1.43 mmol) at rt. The white suspension was stirred for 1 h and treated with EtOAc, dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give crude aldehyde (0.2669 g) as a foam. The crude aldehyde was directly used in the next step without further purification. LC-MS Method 1 *t_R* = 1.93 min, *m/z* 454 (MH⁺).

Step 2. (6S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxypropyl)-1,3-oxazinan-2-one

To a stirred solution of 2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetaldehyde in THF (3 mL) was added MeMgBr (1.4 M in toluene/THF, 3 mL, 4.2 mmol) at 0 °C. The mixture was warmed up to rt and stirred for 1.5 h before quenching with satd aq NH₄Cl (3 mL). The mixture was diluted with CH₂Cl₂ and dried over Na₂SO₄. Removal of the solvent gave the crude alcohol as a mixture of diastereomers.

Analytical samples were purified by reversed-phase HPLC (SunFire™ Prep C₁₈ OBD™ 5μm 19 × 50 mm column, 10% → 90% CH₃CN/H₂O, 0.1% CF₃COOH over 8 min and then 90% CH₃CN/H₂O, 0.1% CF₃COOH over 2 min, flow rate 20 mL/min) to afford two diastereoisomers.

Isomer 1: (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxypropyl)-1,3-oxazinan-2-one. LC-MS Method 1, *t_R* = 1.87 min, *m/z* = 470. ¹H NMR (CD₃OD) 7.34-7.16 (m, 5H), 7.03-6.87 (m, 6H), 5.47 (q, *J* = 7.0 Hz, 1H), 3.47-3.43 (m, 1H), 3.07-3.02 (m, 1H), 2.63-2.58 (m, 1H), 2.35-2.28 (m, 1H), 2.19-2.12 (m, 1H), 2.01 (dd, *J* = 14.3, 7.6 Hz, 1H), 1.86 (dd, *J* = 14.3, 4.4 Hz, 1H), 1.46 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 3H).

Isomer 2: (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxypropyl)-1,3-oxazinan-2-one. LC-MS Method 1, *t_R* = 1.88 min, *m/z* = 470. ¹H NMR (CD₃OD) 7.35-7.19 (m, 5H), 7.03-6.92 (m, 6H), 5.50 (q, *J* = 7.0 Hz, 1H), 3.90-3.86 (m, 1H), 3.04-2.99 (m, 1H), 2.40-2.36 (m, 2H), 2.23-2.16 (m, 1H), 1.95 (dd, *J* = 15.1, 7.5 Hz, 1H), 1.85 (dd, *J* = 15.1, 3.4 Hz, 1H), 1.48 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H).

EXAMPLE 138

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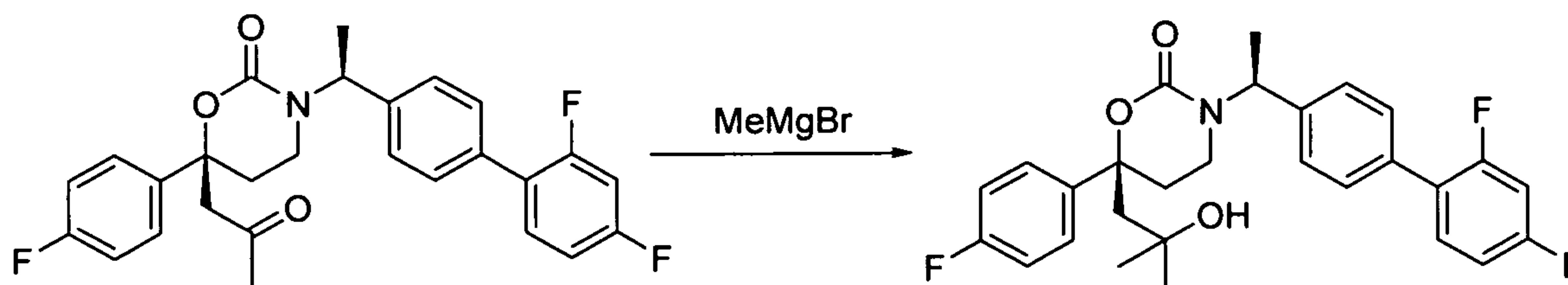
(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-oxopropyl)-1,3-oxazinan-2-one



- 5 A mixture of the above alcohol (0.1830 g, 0.39 mmol) and Dess-Martin periodinane (0.1760 g, 0.41 mmol) in CH₂Cl₂ was stirred at rt for 2 h. The mixture was treated with satd aq NaHCO₃, diluted with EtOAc, and dried over Na₂SO₄. After the solvent was evaporated under reduced pressure, the residue was purified by preparative HPLC (SunFire™ Prep C₁₈ OBD™ 5μm 19 × 50 mm column, 10% → 90%
 10 CH₃CN/H₂O, 0.1% CF₃COOH over 8 min and then 90% CH₃CN/H₂O, 0.1% CF₃COOH over 2 min, flow rate 20 mL/min) to afford (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-oxopropyl)-1,3-oxazinan-2-one.
 LC-MS Method 1 *t_R* = 1.94 min, *m/z* 468 (MH⁺); ¹H NMR (400 MHz, CD₃OD) δ 7.34-7.27 (m, 3H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.01-6.90 (m, 6H), 5.49 (q, *J* = 7.0 Hz, 1H),
 15 3.06-3.02 (m, 1H), 2.99 (s, 2H), 2.54-2.49 (m, 1H), 2.38-2.24 (m, 2H), 1.97 (s, 3H), 1.46 (d, *J* = 7.3 Hz, 3H); ¹⁹F NMR (376 MHz, CD₃OD) δ -113.66 (m), -115.74 (m), -116.72 (m).

EXAMPLE 139

- 20 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one



- To a stirred solution of (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-oxopropyl)-1,3-oxazinan-2-one (0.0303 g, 0.0648 mmol) in THF (5
 25 mL) was added MeMgBr (1.4 M in toluene/THF, 1 mL, 1.4 mmol) at 0 °C. The mixture was warmed to rt and stirred for 1 h before quenching with satd aq NH₄Cl (1 mL). The mixture was diluted with CH₂Cl₂ and dried over Na₂SO₄. After the solvent was evaporated under reduced pressure, the residue was purified by preparative HPLC (SunFire™ Prep C₁₈ OBD™ 5μm 19 × 50 mm column, 10% → 90%

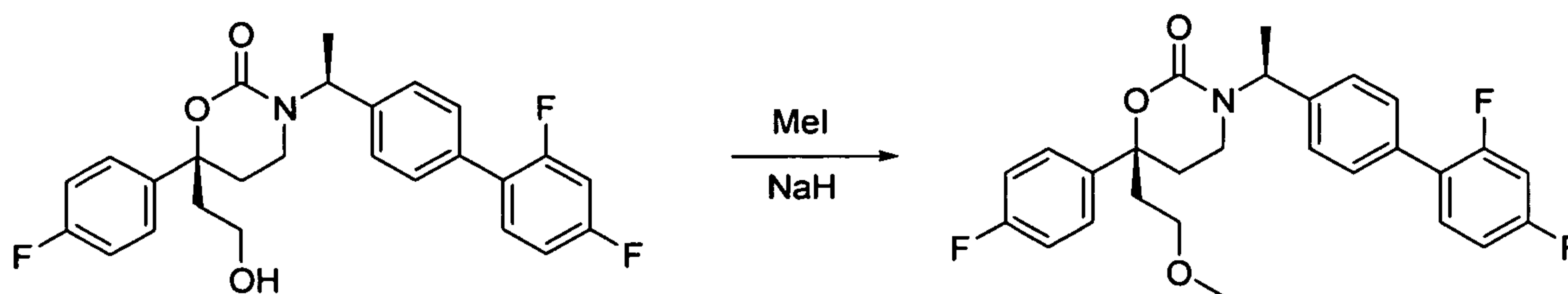
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CH₃CN/H₂O, 0.1% CF₃COOH over 8 min and then 90% CH₃CN/H₂O, 0.1% CF₃COOH over 2 min, flow rate 20 mL/min) to afford (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one. LC-MS Method 1 *t_R* = 1.91 min, *m/z* 484 (MH⁺), 426; ¹H NMR (400 MHz, CD₃OD) δ 7.36-7.20 (m, 5H), 7.02-6.92 (m, 6H), 5.52 (q, *J* = 7.0 Hz, 1H), 3.05-3.00 (m, 1H), 2.49-2.35 (m, 2H), 2.22-2.15 (m, 1H), 2.06 (s, 2H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.19 (s, 3H), 0.90 (s, 3H); ¹⁹F NMR (376 MHz, CD₃OD) δ -113.78 (m), -115.82 (m), -117.50 (m).

10

EXAMPLE 140

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-methoxyethyl)-1,3-oxazinan-2-one



15

A mixture of NaH 6 mg, 0.21 mmol in THF (2 mL) was added dropwise to a mixture of (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one (80 mg, 0.196 mmol) in THF (5 mL) at -20 °C. The mixture was stirred at -20 °C for 1 h, then iodomethane (30 mg, 0.21 mmol) was added dropwise. The mixture was refluxed overnight. The reaction was quenched with water and the mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to give the residue, which was purified by preparative TLC to give (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one (30 mg, 37%. ¹H NMR (400MHz, CD₃OD): δ=1.5 (m, 3H), 2.1 (m, 2H), 2.3 (m, 2H), 2.5 (m, 1H), 3.1 (m, 2H), 3.2 (s, 3H), 3.53 (m, 1H), 5.5 (m, 1H), 7.0 (m, 4H), 7.15 (m, 2H), 7.30 (m, 2H), 7.42 (m, 2H), 7.50 (m, 1H); LC-MS Method 3, *t_R* = 1.393 min, *m/z* = 470.2.

20

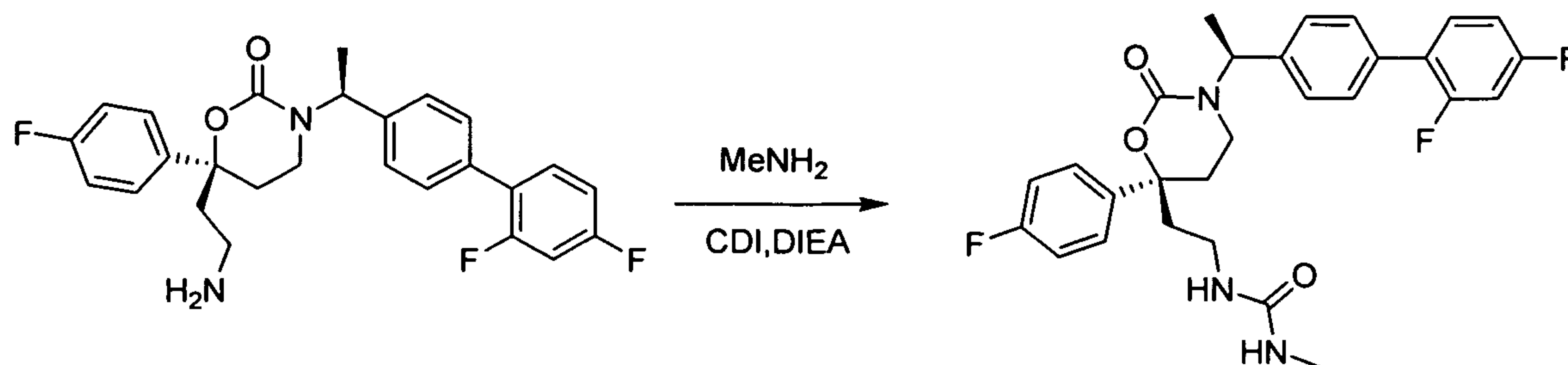
25

30

EXAMPLE 141

1-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-3-methylurea

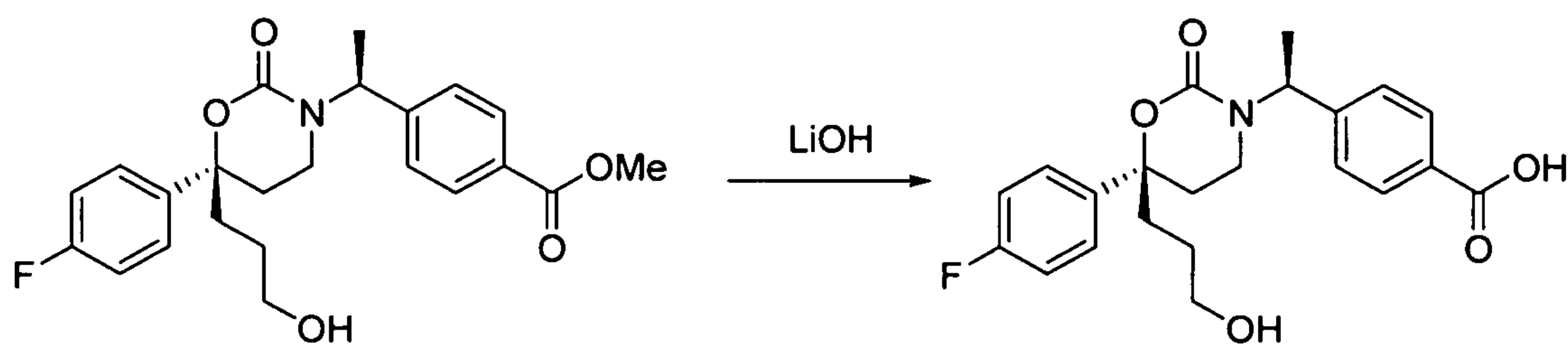
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To a solution of methylamine (11 mg, 0.11 mmol) and CDI (20 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (3 mL) was added DIEA (130 mg, 1.00 mmol) at 0 °C under nitrogen. The resulting mixture was stirred at ambient temperature for 1 h. (R)-6-(2-aminoethyl)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (40 mg, 0.088 mmol) was added to the above mixture, and the mixture was stirred at rt overnight. The mixture was concentrated in *vacuo* to give a residue, which was purified by preparative HPLC to afford 1-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-3-methylurea (5 mg, 12%). ^1H NMR (CDCl_3): 1.56 (m, 3H), 2.10-2.30 (m, 4H), 2.35 (m, 1H), 2.75 (s, 3H), 3.01 (m, 1H), 3.09 (m, 1H), 3.30 (m, 1H), 5.69 (m, 1H), 6.86-6.96 (m, 2H), 7.08 (m, 4H), 7.25 (m, 2H), 7.30 (m, 3H).

EXAMPLE 142

4-((S)-1-((R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoic acid

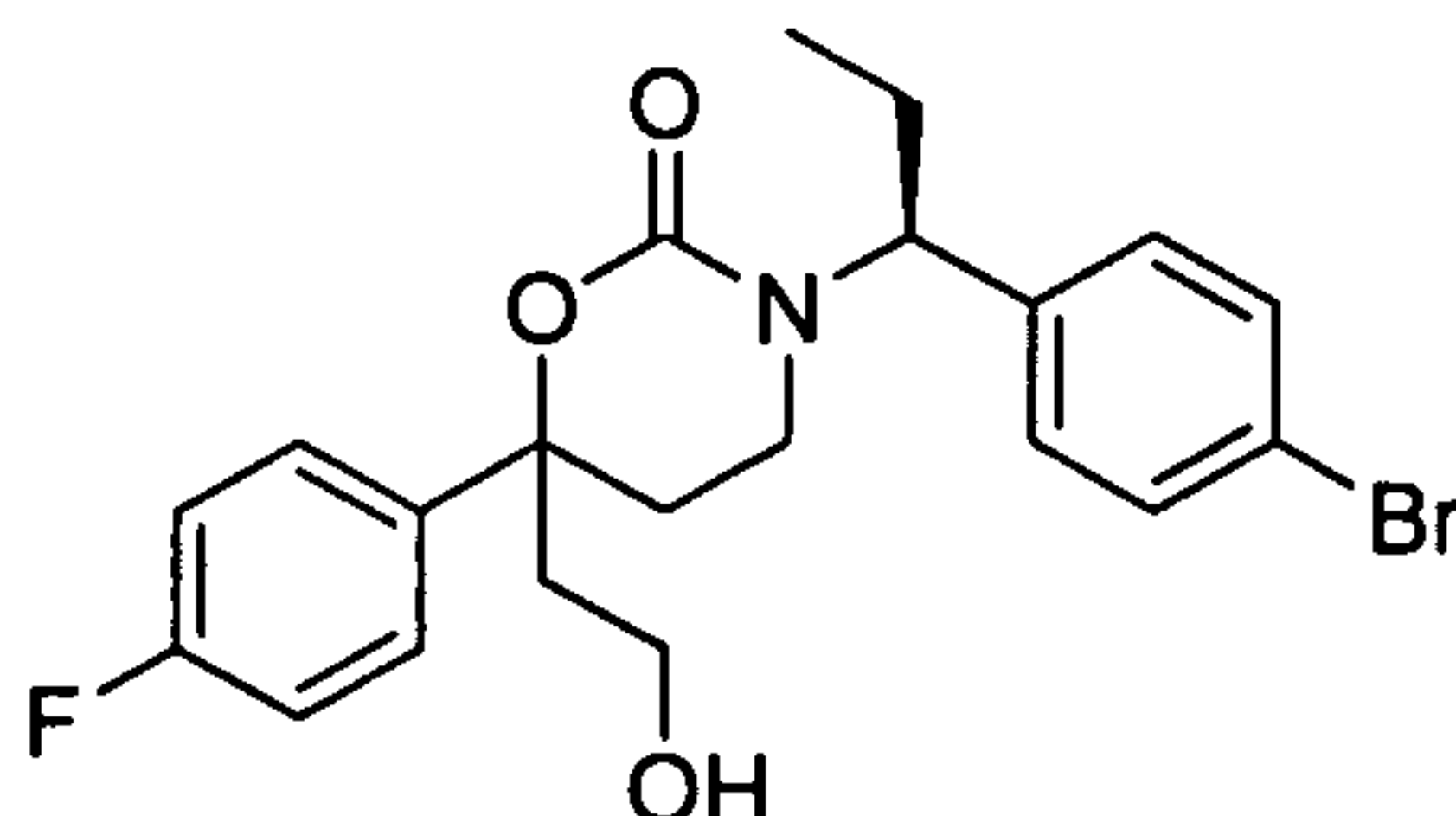


The title compound was prepared following a procedure analogous to that described in Example 94 Step 1. LC-MS Method 1 t_R = 1.18 min, m/z = 424($M+Na$); ^1H NMR (CD_3OD) 7.79(d, 2H), 7.32(m, 2H), 7.13-6.97(m, 4H), 5.57(q, 1H), 3.47(t, 2H), 3.14(m, 2H), 2.48(d, 1H), 2.34(td, 1H), 2.23(m, 1H), 1.55(d, 3H).

EXAMPLE 143

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

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The title compound was prepared from 6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one following a procedure analogous to that described in Example 74. The isomers were separated to afford:

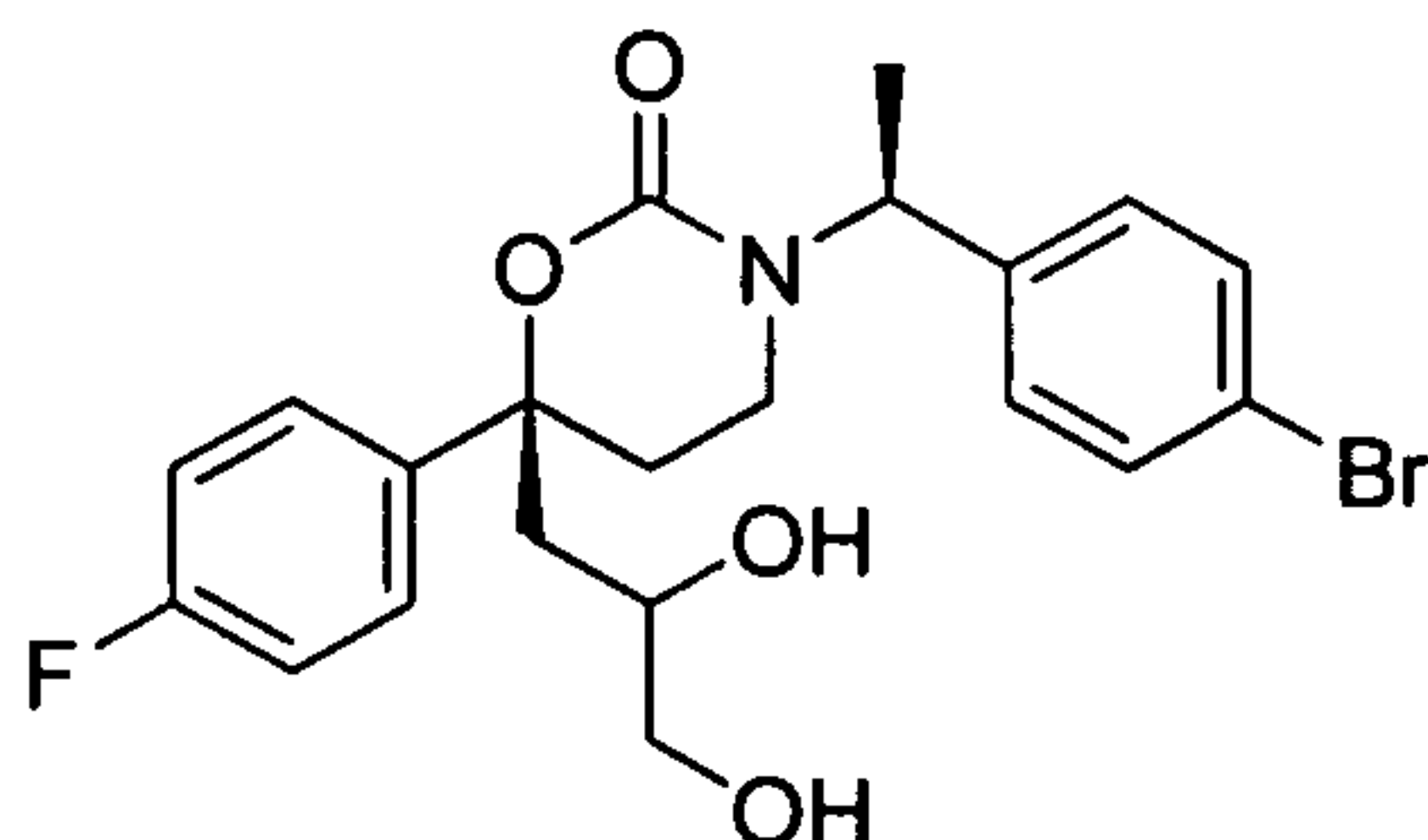
5 Isomer 1: (R)-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one. LC-MS Method 3 t_R = 1.206 min, m/z = 435.9; ^1H NMR (CD_3OD) 0.58 (m, 3H), 1.67-1.87 (m, 2H), 2.08 (m, 3H), 2.56 (m, 1H), 2.71-2.89 (m, 2H), 3.69 (m, 1H), 5.30 (m, 1H), 7.15-7.25 (m, 2H), 7.28 (m, 2H), 7.43 (m, 2H), 7.50 (m, 2H).

10 Isomer 2: (S)-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one. LC-MS Method 3 t_R = 1.287 min, m/z = 460.1; ^1H NMR (CD_3OD) 0.97 (m, 3H), 1.94-2.04 (m, 2H), 2.12 (m, 2H), 2.30 (m, 2H), 2.49 (m, 1H), 3.09 (m, 1H), 3.66 (m, 1H), 5.28 (m, 1H), 6.94 (m, 2H), 7.05 (m, 2H), 7.28 (m, 4H).

15

EXAMPLE 144

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



The title compound was prepared from (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one following a procedure analogous to that described in Example 77. The two isomers were separated by chromatography.

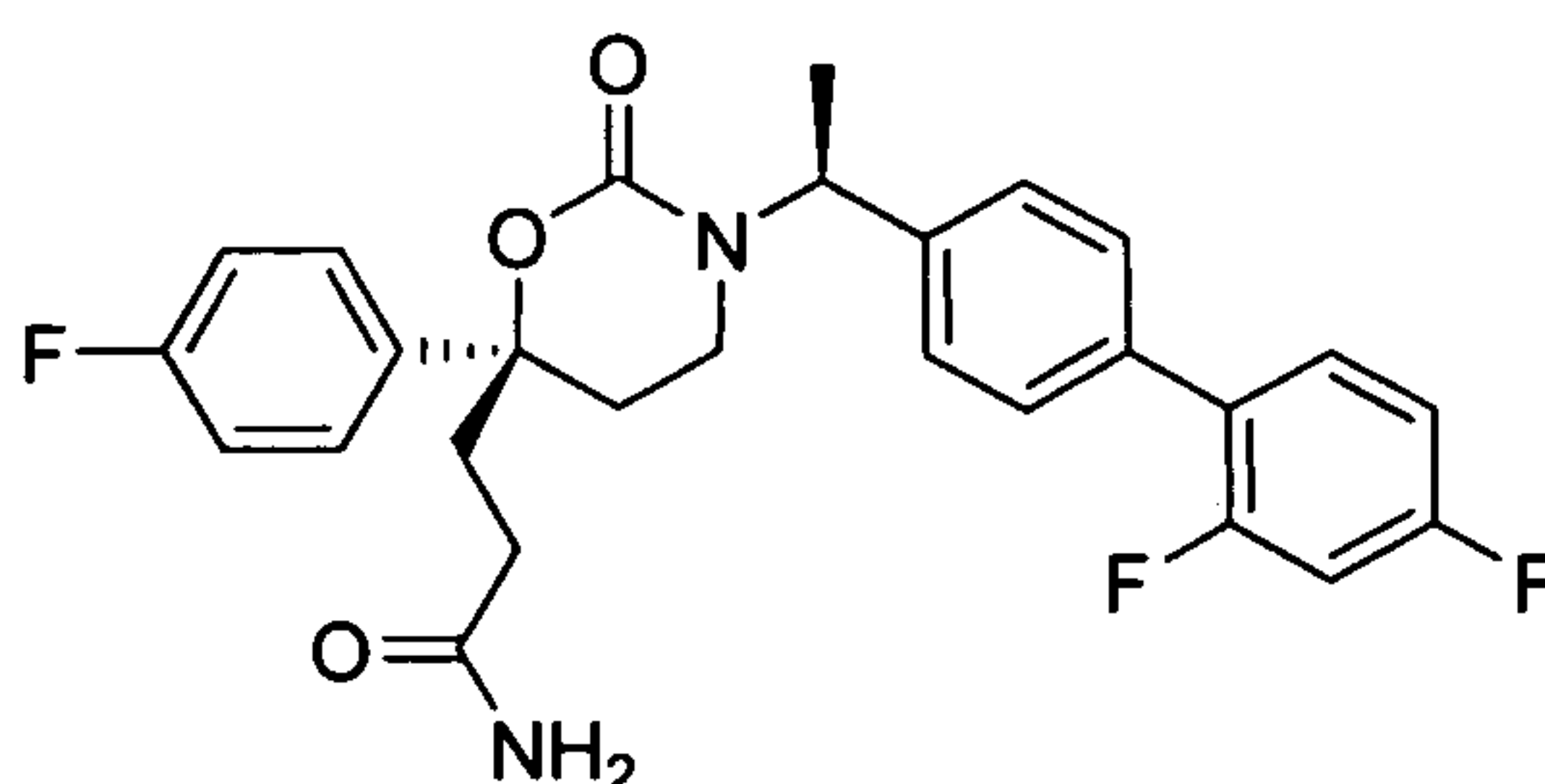
20 Isomer 1: LC-MS Method 1 t_R = 1.55 min, m/z = 452, 454; ^1H NMR (CD_3OD) 7.27-7.24 (m, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.04 (t, J = 8.8 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 5.42 (q, J = 7.0 Hz, 1H), 3.75-3.71 (m, 1H), 3.22 (m, 2H), 3.04-2.99 (m, 1H), 2.44-2.39 (m, 2H), 2.21-2.14 (m, 1H), 2.00-1.95 (m, 1H), 1.87-1.81 (m, 1H), 1.44 (d, J = 7.0 Hz, 3H).

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Isomer 2: LC-MS Method 1 t_R = 1.52 min, m/z = 452, 454; ^1H NMR (CD_3OD) 7.34-7.30 (m, 2H), 7.19 (d, J = 8.5 Hz, 2H), 7.04 (t, J = 8.6 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 5.40 (q, J = 7.0 Hz, 1H), 3.38-3.27 (m, 3H), 3.08-3.04 (m, 1H), 2.67-2.61 (m, 1H), 2.34-2.27 (m, 1H), 2.23-2.15 (m, 1H), 2.03-1.91 (m, 2H), 1.43 (d, J = 7.0 Hz, 3H).

EXAMPLE 145

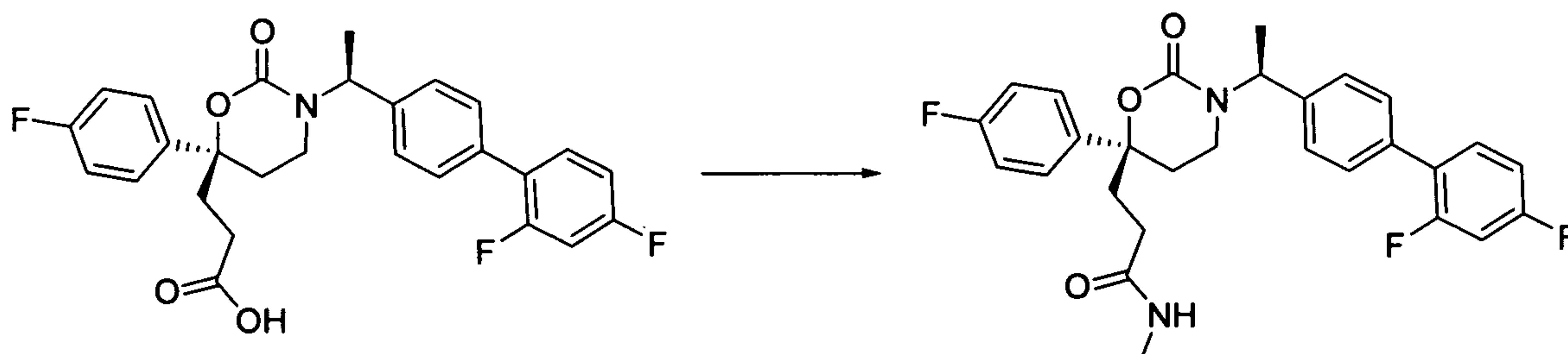
3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanamide



The title compound was prepared from 3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanoic acid following a procedure analogous to that described in Example 76. LC-MS Method 3 t_R = 1.212 min, m/z = 483.1; ^1H NMR (CD_3OD) 1.50 (m, 3H), 1.92-2.08 (m, 1H), 2.10-2.39 (m, 5H), 2.43 (m, 1H), 5.63 (m, 1H), 5.85 (s, 1H), 6.02 (s, 1H), 6.84 (m, 2H), 6.98 (m, 4H), 7.20 (m, 2H), 7.26 (m, 3H).

EXAMPLE 146

3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-N-methylpropanamide



The title compound was prepared from 3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanoic acid following a procedure analogous to that described in Example 76 using methylamine in place of ammonia. LC-MS Method 3 t_R = 1.249 min, m/z = 497.2; ^1H NMR (CD_3OD) 1.51 (m, 3H), 1.97 (s, 1H), 2.07-2.31 (m, 6H), 2.64-2.74 (s, 3H), 2.94 (d, 1H), 5.62 (m, 1H), 6.13 (s, 1H), 6.79-6.89 (m, 2H), 6.97 (m, 4H), 7.15 (s, 2H), 7.23 (m, 3H).

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __3__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __3__

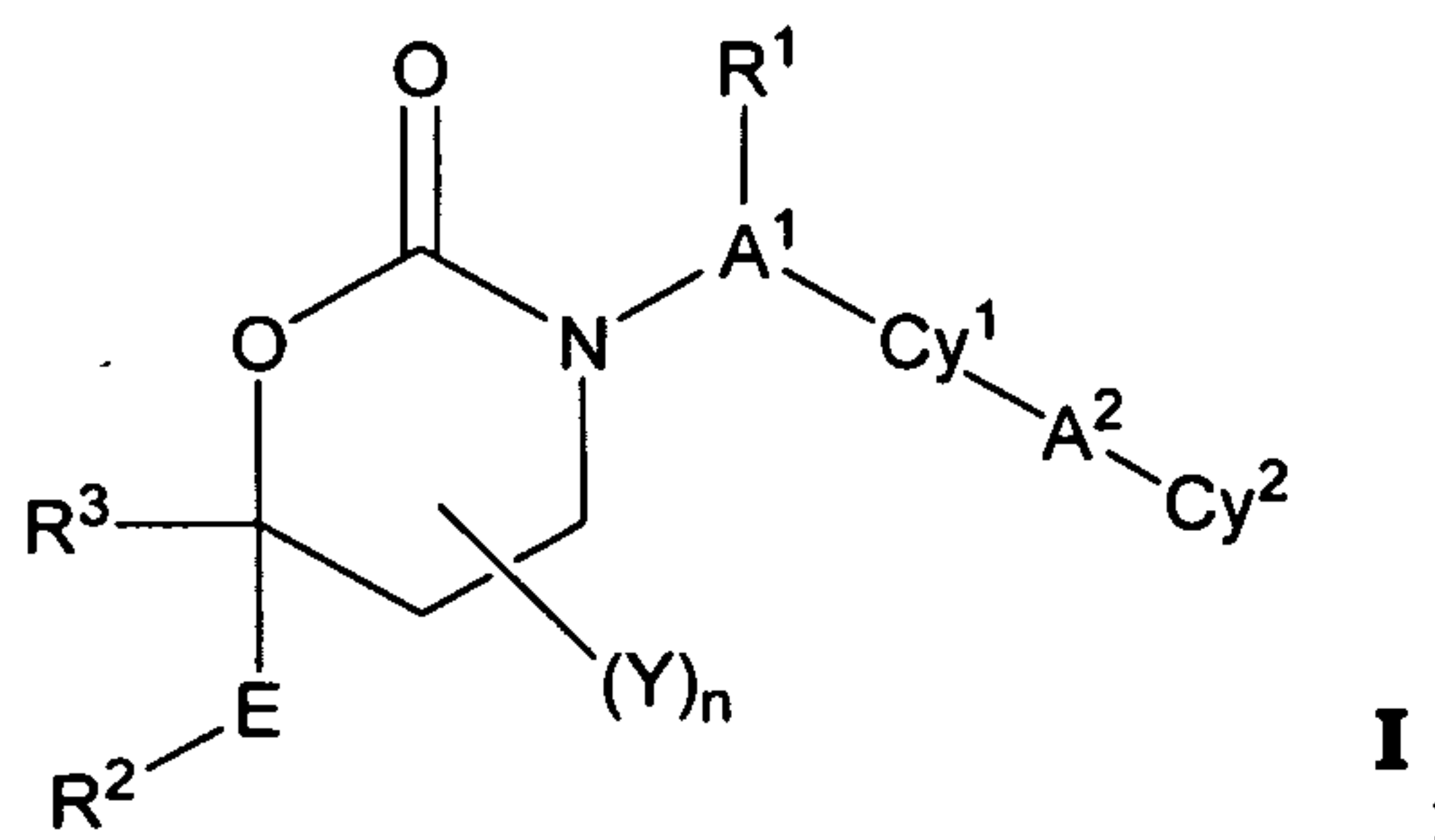
NOTE: For additional volumes please contact the Canadian Patent Office.

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What is claimed is:

1. A compound of Formula (I)

5



wherein:

- R^1 is (a) absent or (b) is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and 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 , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, heterocyclyl, heteroaryl, arylamino and heteroarylamino;
- A^1 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;
- Cy¹ is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl and 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-

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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)alkyl-
 sulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-
 15 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-
 20 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 and 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-
 35 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,

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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,
 5 halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkyl-
 alkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkyl-
 alkanesulfonyl, 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,
 10 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-
 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, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-
 C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-
 20 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.

In one aspect, the heterocyclyl represented by Cy² is other than optionally substituted thiazolidine-2,4-dionyl;

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

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;

R² is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl and is optionally
 35 substituted with up to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-

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C_6)alkyl, (C_3-C_6) cycloalkyl, hydroxy (C_3-C_6) cycloalkyl, (C_4-C_7) cycloalkylalkyl, (C_2-C_6) alkenyl, halo (C_2-C_6) alkenyl, hydroxy (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_3-C_6) cycloalkyl (C_2-C_4) alkynyl, halo (C_1-C_6) alkyl, halo (C_3-C_6) cycloalkyl, halo (C_4-C_7) cycloalkylalkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkoxy, (C_4-C_7) cycloalkylalkoxy,

 5 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-C_7) cycloalkylalkanesulfinyl, halo (C_1-C_6) alkanesulfinyl, halo (C_3-C_6) cycloalkanesulfinyl, halo (C_4-C_7) cycloalkyl-

 10 alkanesulfinyl, (C_1-C_6) alkanesulfonyl, (C_3-C_6) cycloalkanesulfonyl, (C_4-C_7) cycloalkyl-alkanesulfonyl, halo (C_1-C_6) alkanesulfonyl, halo (C_3-C_6) cycloalkanesulfonyl, halo (C_4-C_7) cyclo-alkylalkanesulfonyl, (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, (C_1-C_6) alkoxy (C_1-C_6) alkoxy, halo (C_1-C_6) alkoxy (C_1-C_6) alkoxy, (C_1-C_6) alkoxycarbonyl, H_2NCO , H_2NSO_2 , (C_1-C_6) alkylaminocarbonyl, di (C_1-C_6) alkylaminocarbonyl, (C_1-C_6) 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) alkylcarbonylamino (C_1-C_6) alkyl, (C_1-C_6) alkylsulfonylamino, (C_1-C_6) alkylsulfonylamino (C_1-C_6) alkyl, (C_1-C_6) alkoxycarbonyl (C_1-C_6) alkoxy, (C_1-C_6) alkoxy (C_1-C_6) alkyl, halo (C_1-C_6) alkoxy (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkoxy,

 20 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 $\}(C_1-C_6)$ alkylaminocarbonyl, di (C_3-C_6) cycloalkylaminocarbonyl, (C_3-C_6) cycloalkylaminosulfonyl, $\{(C_3-C_6)$ cycloalkyl $\}(C_1-C_6)$ alkylaminosulfonyl, 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 $\}(C_1-C_6)$ alkylaminocarbonyl (C_1-C_6) alkyl and di (C_3-C_6) cycloalkylaminocarbonyl (C_1-C_6) alkyl;

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R^3 is selected from (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_3-C_5) cycloalkyl (C_1-C_4) alkyl, (C_1-C_3) alkoxy (C_1-C_3) alkoxy, or (C_1-C_3) alkoxy (C_1-C_3) alkyl and is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R^4 , R^4O- , $(R^4)_2N-$, R^4O_2C- , $R^4C(=O)O-$, R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=N)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$,

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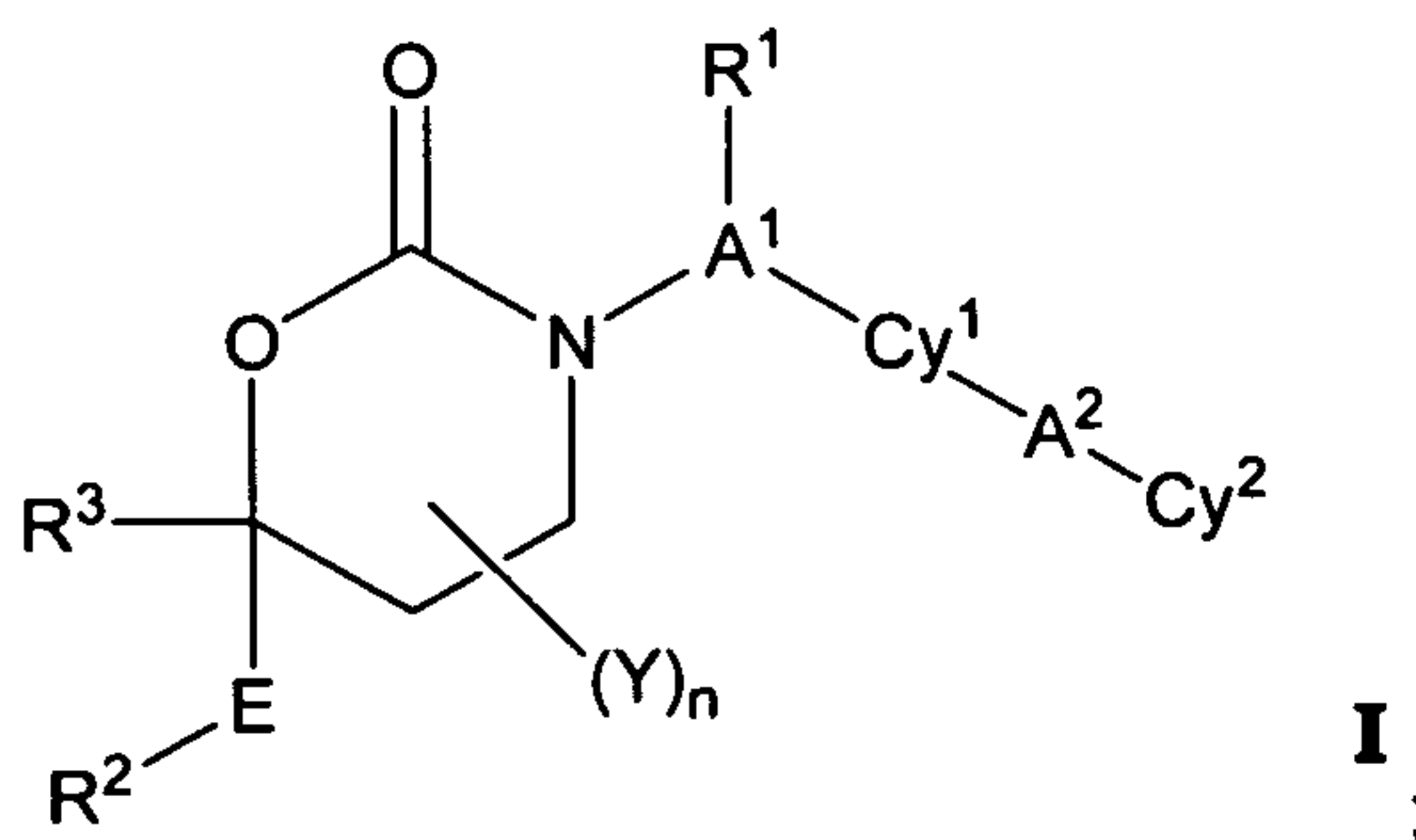
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$(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$,
 $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$,
 $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$,
 $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$,
5 $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$,
 $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$,
 $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, spirocycloalkyl; heterocyclyl
(which in turn may be optionally substituted with alkyl, haloalkyl, halogen or oxo),
heteroaryl (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy,
10 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 heteroarylamino
15 (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); and

R^4 is independently selected from H, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, amino $(C_1-$
20 $C_6)$ alkyl, (C_1-C_6) alkylamino (C_1-C_6) alkyl, di (C_1-C_6) alkylamino (C_1-C_6) alkyl, hydroxy $(C_1-$
 $C_6)$ alkyl and (C_1-C_6) alkoxy (C_1-C_6) alkyl;
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

2. A compound of Formula (I)

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wherein:

R^1 is (a) absent or (b) is selected from (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl,
30 (C_1-C_3) alkoxy (C_1-C_3) alkoxy, or (C_1-C_3) alkoxy (C_1-C_3) alkyl and is optionally substituted
with up to four groups independently selected from fluorine, cyano, oxo, R^4 , R^4O- ,

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$(R^4)_2N-$, R^4O_2C- , R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$,
 $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$,
 $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$,
 $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$,
5 $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$,
 $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$,
 $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$,
 $R^4C(=O)NHS(=O)_2NR^4$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$,
 $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$,
10 $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, 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 ;

15 Cy^1 is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl and is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, hydroxy (C_3-C_6) cycloalkyl, (C_4-C_7) cycloalkylalkyl, (C_2-C_6) alkenyl, halo (C_2-C_6) alkenyl, hydroxy (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_3-C_6) cycloalkyl (C_2-C_4) alkynyl, halo (C_1-C_6) alkyl, halo (C_3-C_6) cycloalkyl, halo (C_4-C_7) cycloalkylalkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkoxy, (C_4-C_7) cycloalkylalkoxy, halo (C_1-C_6) alkoxy, halo (C_3-C_6) cycloalkoxy, halo (C_4-C_7) cycloalkylalkoxy, (C_1-C_6) alkylthio, (C_3-C_6) 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-C_7) cycloalkylalkanesulfinyl, halo (C_1-C_6) alkanesulfinyl, halo (C_3-C_6) cycloalkanesulfinyl, halo (C_4-C_7) cycloalkylalkanesulfinyl, (C_1-C_6) alkanesulfonyl, (C_3-C_6) cycloalkanesulfonyl, (C_4-C_7) cycloalkylalkanesulfonyl, halo (C_1-C_6) alkanesulfonyl, halo (C_3-C_6) cycloalkanesulfonyl, halo (C_4-C_7) cycloalkylalkanesulfonyl, (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, (C_1-C_6) alkoxy (C_1-C_6) alkoxy, halo (C_1-C_6) alkoxy (C_1-C_6) alkoxy, (C_1-C_6) alkoxycarbonyl, H_2NCO , H_2NSO_2 , (C_1-C_6) alkylaminocarbonyl, di (C_1-C_6) alkylaminocarbonyl, (C_1-C_3) alkoxy (C_1-C_3) alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6) alkylaminosulfonyl, di (C_1-C_6) alkylaminosulfonyl, heterocyclosulfonyl, (C_1-C_6) alkylcarbonylamino, (C_1-C_6) alkylcarbonylamino (C_1-C_6) alkyl, (C_1-C_6) alkylsulfonylamino, (C_1-C_6) alkylsulfonylamino (C_1-C_6) alkyl, (C_1-C_6) alkoxycarbonyl (C_1-C_6) alkoxy, (C_1-C_6) alkoxy $(C_1-$
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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;

5

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;

- 10 Cy² is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl or heterocyclyl and 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;

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

n is 0, 1 or 2;

E is (a) a bond or (b) (C₁-C₃)alkylene or (C₁-C₂)alkylenyloxy, wherein the O is
 5 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 and is optionally substituted with up to 4 groups independently selected from fluorine, chlorine,
 10 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,
 15 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)cycloalkyl-
 20 alkanesulfinyl, (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, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-
 25 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,
 30 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;

R³ is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₅)cycloalkyl(C₁-
 35 C₄)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo,

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R^4 , R^4O- , $(R^4)_2N-$, R^4O_2C- , $R^4C(=O)O-$, R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$,
 $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=N)NR^4-$,
 $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$,
 $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$,
 $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$,
 $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$,
 $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$,
 $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, spirocycloalkyl; heterocyclyl
 (which in turn may be optionally substituted with alkyl, haloalkyl, halogen or oxo), heteroaryl (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), 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 heteroarylamino
 (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); and

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

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

3. The compound of Claim 2 wherein:

R^1 is (a) absent or (b) is selected from (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_3) alkoxy (C_1-C_3) alkoxy, or (C_1-C_3) alkoxy (C_1-C_3) alkyl and 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 , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$,
 $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=N)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$,
 $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$,
 $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$,

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$(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$,
 $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$,
 $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$,
 $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, heterocyclyl, heteroaryl, arylamino and heteroarylamino;

5 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 monocyclic heterocyclyl and 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,
 10 hydroxy (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, hydroxy (C_3-C_6) cycloalkyl, (C_4-C_7) cycloalkylalkyl, (C_2-C_6) alkenyl, halo (C_2-C_6) alkenyl, hydroxy (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_3-C_6) cycloalkyl (C_2-C_4) alkynyl, halo (C_1-C_6) alkyl, halo (C_3-C_6) cycloalkyl, halo (C_4-C_7) cycloalkylalkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkoxy, (C_4-C_7) cycloalkylalkoxy, halo (C_1-C_6) alkoxy, halo (C_3-C_6) cycloalkoxy, halo (C_4-C_7) cycloalkylalkoxy,
 15 (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-C_7) cycloalkylalkanesulfinyl, halo (C_1-C_6) alkanesulfinyl, halo (C_3-C_6) cycloalkanesulfinyl, halo (C_4-C_7) cycloalkylalkanesulfinyl, (C_1-C_6) alkanesulfonyl, (C_3-C_6) cycloalkanesulfonyl, (C_4-C_7) cycloalkylalkanesulfonyl, halo (C_1-C_6) alkanesulfonyl, halo (C_3-C_6) cycloalkanesulfonyl, halo (C_4-C_7) cycloalkylalkanesulfonyl, (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, (C_1-C_6) alkoxy (C_1-C_6) alkoxy, halo (C_1-C_6) alkoxy (C_1-C_6) alkoxy, (C_1-C_6) alkoxycarbonyl, H_2NCO , H_2NSO_2 , (C_1-C_6) alkylaminocarbonyl, di (C_1-C_6) alkylaminocarbonyl, (C_1-C_6) 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) alkylcarbonylamino (C_1-C_6) alkyl, (C_1-C_6) alkylsulfonylamino, (C_1-C_6) alkylsulfonylamino (C_1-C_6) alkyl, (C_1-C_6) alkoxycarbonyl (C_1-C_6) alkoxy, (C_1-C_6) alkoxy (C_1-C_6) alkyl, halo (C_1-C_6) alkoxy (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkoxy, heteroaryl, oxo,
 30 amino (C_1-C_6) alkyl, (C_1-C_6) alkylamino (C_1-C_6) alkyl, di (C_1-C_6) alkylamino (C_1-C_6) alkyl, amino (C_2-C_6) alkoxy, (C_1-C_6) alkylamino (C_2-C_6) alkoxy, di (C_1-C_6) alkylamino (C_2-C_6) alkoxy and (C_1-C_6) alkylcarbonyl;

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

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Cy² is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl or heterocyclyl and 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;

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

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;

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R^2 is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl and 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;

R^3 is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy or (C₁-C₃)alkoxy(C₁-C₃)alkyl and 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 , $R^4S(=O)$ -, $R^4S(=O)_2$ -, $R^4C(=O)NR^4$ -, $(R^4)_2NC(=O)$ -, $(R^4)_2NC(=O)O$ -, $(R^4)_2NC(=O)NR^4$ -, $R^4OC(=O)NR^4$ -, $(R^4)_2NC(=NCN)NR^4$ -, $(R^4O)_2P(=O)O$ -, $(R^4O)_2P(=O)NR^4$ -, $R^4OS(=O)_2NR^4$ -, $(R^4)_2NS(=O)_2O$ -, $(R^4)_2NS(=O)_2NR^4$ -, $R^4S(=O)_2NR^4$ -, $R^4S(=O)_2NHC(=O)$ -, $R^4S(=O)_2NHC(=O)O$ -, $R^4S(=O)_2NHC(=O)NR^4$ -, $R^4OS(=O)_2NHC(=O)$ -, $R^4OS(=O)_2NHC(=O)O$ -, $R^4OS(=O)_2NHC(=O)NR^4$ -, $(R^4)_2NS(=O)_2NHC(=O)$ -, $(R^4)_2NS(=O)_2NHC(=O)O$ -, $(R^4)_2NS(=O)_2NHC(=O)NR^4$ -, $R^4C(=O)NHS(=O)_2$ -, $R^4C(=O)NHS(=O)_2O$ -, $R^4C(=O)NHS(=O)_2NR^4$ -,

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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 heteroarylamino
 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); and

R^4 is independently selected from H, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, amino $(C_1-$
 15 $C_6)$ alkyl, (C_1-C_6) alkylamino (C_1-C_6) alkyl, di (C_1-C_6) alkylamino (C_1-C_6) alkyl, hydroxy $(C_1-$
 $C_6)$ alkyl and (C_1-C_6) alkoxy (C_1-C_6) alkyl;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

20 4. The compound of Claim 2 wherein:

R^1 is absent or is selected from (C_1-C_6) alkyl or (C_2-C_6) alkenyl, (C_2-C_6) alkynyl or $(C_1-$
 $C_3)$ alkoxy (C_1-C_3) alkoxy and 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 ,
 $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$,
 25 , $R^4OC(=O)NR^4-$, $(R^4)_2NC(=N)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$,
 $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$,
 $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$,
 $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$,
 $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$,
 30 $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$,
 $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$,
 $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$,
 heterocyclyl, heteroaryl, arylamino and heteroarylamino;

35 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 ;

Cy¹ is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl each 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)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 and oxo;

25

A² is (a) a bond, O, S or NR⁴; or (b) (C₁-C₃)alkylene, (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 each 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)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,

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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 and oxo;

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

20 n is 0, 1 or 2;

E is (a) a bond or (b) (C₁-C₃)alkylene, (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;

25

R² is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl and 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-
 30 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-
 35 C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-
 C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-

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C_6)cycloalkanesulfinyl, halo(C_4 - C_7)cycloalkylalkanesulfinyl, (C_1 - C_6)alkanesulfonyl,
 $(C_3$ - C_6)cycloalkanesulfonyl, (C_4 - C_7)cycloalkylalkanesulfonyl, halo(C_1 -
 C_6)alkanesulfonyl, halo(C_3 - C_6)cycloalkanesulfonyl, halo(C_4 - C_7)cyclo-
alkylalkanesulfonyl, (C_1 - C_6)alkylamino, di(C_1 - C_6)alkylamino, (C_1 - C_6)alkoxy(C_1 -
5 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)alkylcarbonylamino(C_1 - C_6)alkyl, (C_1 - C_6)alkylsulfonylamino, (C_1 -
10 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 or oxo;

R^3 is selected from (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl or (C_1 - C_3)alkoxy(C_1 -
15 C_3)alkoxy and 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) $_2NS(=O)_2NR^4$ -, $R^4S(=O)_2NR^4$ -, $R^4S(=O)_2NHC(=O)$ -,
20 $R^4S(=O)_2NHC(=O)O$ -, $R^4S(=O)_2NHC(=O)NR^4$ -, $R^4OS(=O)_2NHC(=O)$ -,
 $R^4OS(=O)_2NHC(=O)O$ -, $R^4OS(=O)_2NHC(=O)NR^4$ -, (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) $_2NC(=O)NHS(=O)_2$ -,
25 (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, CO_2H , $CONH_2$, N-monoalkyl-
substituted amido, N,N-dialkyl-substituted amido, or oxo), arylamino (which in turn
30 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 (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
35 amido, N,N-dialkyl-substituted amido, or oxo); and

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

5 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

5. The compound of Claim 2, wherein

R^1 is (a) absent or (b) is selected from (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_3) alkoxy (C_1-C_3) alkoxy, or (C_1-C_3) alkoxy (C_1-C_3) alkyl and is optionally substituted
 10 with up to four groups independently selected from fluorine, cyano, oxo, R^4 , R^4O- , $(R^4)_2N-$, R^4O_2C- , R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$,
 15 $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$,
 20 $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, heterocyclyl, heteroaryl, arylamino and heteroarylamino;

A^1 is (a) a bond, or (b) (C_1) 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 ;

25 Cy^1 is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl, each optionally substituted with 1 to 4 groups independently selected from nitro, amino, hydroxy, carboxy, (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, 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_4-C_7) cycloalkylalkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkoxy, (C_4-C_7) cycloalkylalkoxy,
 30 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-C_7) cycloalkylalkanesulfinyl,
 35 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,

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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-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, 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 if the substitution is either meta or para to A¹, the substituents may also include optionally substituted cycloalkyl, optionally substituted halocycloalkyl or optionally substituted heteroaryl.

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;

20

Cy² is *meta* or *para* to A₁ and is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl 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-thiaoxazole 1,1-dioxide, tetrahydro-2H-1,2-thiazine 1,1-dioxide, hexahydro-1,2,6-thiadiazine 1,1-dioxide, tetrahydro-1,2,5-thiadiazole 1,1-dioxide isothiazolidine 1,1-dioxide, 6-oxo-1,6-dihydropyridazin-3-yl, 6-oxo-1,6-dihydropyridazin-4-yl, 5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl and 5-oxo-4,5-dihydro-1H-imidazol-2-yl optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, hydroxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-

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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, (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;

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

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;

R² is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl and 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-

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

R^3 is selected from (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, (C_3 - C_5)cycloalkyl(C_1 - C_4)alkyl, (C_1 - C_3)alkoxy(C_1 - C_3)alkoxy, or (C_1 - C_3)alkoxy(C_1 - C_3)alkyl and is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo,

R^4 , R^4O- , $(R^4)_2N-$, R^4O_2C- , $R^4C(=O)O-$, R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4$, $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, spirocycloalkyl; heterocyclyl (which in turn may be optionally substituted with alkyl, haloalkyl, halogen or oxo), heteroaryl (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy,

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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 heteroarylamino (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); and

10 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;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

15 6. The compound of claim 2, wherein A¹ is a bond.

7. The compound of claim 2 wherein A¹ is (C₁-C₃)alkylene.

8. The compound of claim 7, wherein A¹ is methylene.

9. The compound of claim 2, wherein R¹ is (C₁-C₆)alkyl.

10. The compound of claim 9, wherein R¹ is methyl or ethyl.

20 11. The compound of claim 10, wherein R¹ is unsubstituted methyl or ethyl.

12. The compound of claim 2, wherein Cy¹ is optionally substituted aryl or optionally substituted heteroaryl.

25 13. The compound of claim 2, wherein Cy¹ is optionally substituted phenyl or optionally substituted pyridyl.

14. The compound of claim 12, wherein Cy¹ is optionally substituted phenyl.

15. The compound of claim 14, wherein Cy¹ is substituted with fluorine or bromine.

30 16. The compound of claim 14, wherein A² is a bond and Cy² is hydrogen.

17. The compound of claim 14, wherein A² is a bond and Cy² is cyclopropyl.

18. The compound of claim 14, wherein A² is a bond and Cy² is optionally substituted aryl or optionally substituted heteroaryl.

35 19. The compound of claim 14, wherein A² is a bond and Cy² is optionally substituted phenyl or optionally substituted pyridyl.

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20. The compound of claim 19, wherein Cy^2 is optionally substituted phenyl.
21. The compound of claim 20, wherein Cy^2 is substituted with 1 to 4 groups independently selected from chlorine or fluorine.
- 5 22. The compound of claim 20, wherein Cy^2 is difluorophenyl.
23. The compound of claim 2, wherein R^3 is hydroxy(C_2 - C_4)alkyl.
24. The compound of claim 2, wherein R^3 is dihydroxy(C_3 - C_4)alkyl.
25. The compound of claim 2, wherein R^3 is ω - H_2NCO (C_1 - C_3)alkyl.
26. The compound of claim 2, wherein R^3 is (C_1 - C_2)alkoxy(C_1 - C_3)alkyl.
- 10 27. The compound of claim 2, wherein R^3 is H_2NSO_2O (C_2 - C_4)alkyl.
28. The compound of claim 2, wherein R^3 is H_2NSO_2NH (C_2 - C_4)alkyl.
29. The compound of claim 2, wherein R^3 is oxo(C_2 - C_4)alkyl.
30. The compound of claim 2, wherein R^3 is $MeC(=O)NH$ (C_2 - C_4)alkyl.
31. The compound of claim 2, wherein R^3 is 2-hydroxy-2-methylpropyl.
- 15 32. The compound of claim 2, wherein R^3 is 2-(4-morpholino)ethyl.
33. The compound of claim 2, wherein R^3 is $MeSO_2NH$ (C_2 - C_4)alkyl.
34. The compound of claim 2, wherein R^3 is $MeSO_2NHCH_2CH_2CH_2$ -.
35. The compound of claim 2, wherein R^2 is optionally substituted aryl, optionally substituted heteroaryl or cycloalkyl.
- 20 36. The compound of claim 35, wherein R^2 is optionally substituted phenyl, optionally substituted thienyl or optionally substituted pyridyl.
37. The compound of claim 36, wherein R^2 is optionally substituted phenyl.
38. The compound of claim 37, wherein R^2 is fluorophenyl.
- 25 39. The compound of any one of claims 1-5, wherein;
- R^1 is absent or is methyl or ethyl;
- A^1 is a bond or CH_2 ; or CH if R^1 is present;
- Cy^1 is phenyl, cyclohexyl, pyridyl, N-oxo-pyridyl, thiazolyl or pyrimidinyl each optionally substituted with 1 to 4 groups independently selected from halo, methyl, trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy and 2-hydroxy-2-methylpropoxy;
- 30 A^2 is a bond, O or OCH_2CO ;
- Cy^2 is (a) hydrogen or (b) phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl or piperazinyl each optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl,
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acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonylaminomethyl or tetrazolyl;

n is 0;

5 E is a bond or CH₂;

R² is phenyl or pyridyl each optionally substituted with one group selected from halo, methyl, methylthio or (4-morpholino)methyl; and

R³ is methyl, ethyl, propyl, vinyl or allyl each optionally substituted with up to two groups independently selected from methyl, HO-, MeO-, H₂N-, MeC(=O)NH-,
 10 MeS(=O)₂NH-, H₂NC(=O)-, MeNHC(=O)-, HO₂C-, (HO)₂P(=O)O-, H₂NS(=O)₂O-,
 H₂NS(=O)₂NH-, MeNHC(=O)NH-, MeNHC(=O)O-, cyano, HO₂C-, HOCH₂CH₂NH-, 4-morpholino, HOCH₂C(=O)NH-, H₂NCH₂C(=O)NH-, EtNHC(=O)NH-, MeOC(=O)NH-, MeNHC(=NC≡N)NH-, or oxo;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

15

40. The compound of any one of claims 1-5, wherein;

R¹ is absent or is methyl or ethyl;

A¹ is a bond, CH₂, CH₂CH₂, or CH when R¹ is present;

Cy¹ is phenyl, cyclopropyl, cyclohexyl, pyrrolidinyl, pyridyl, N-oxo-pyridyl, thiazolyl or
 20 pyrimidinyl each optionally substituted with 1 to 4 groups independently selected from halo, methyl, trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy, 2-hydroxy-2-methylpropoxy, cyano, difluoromethoxy, t-butoxycarbonyl, hydroxy, hydroxymethyl, 2-hydroxyethyl, 2-hydroxy-2-propyl, methoxymethyl, methylsulfonyl and methylsulfonylamino;

25 A² is a bond, O, OCH₂CO or C=O;

Cy² is (a) hydrogen or (b) phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl, piperazinyl, morpholinyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, S,S-dioxothiazinyl, 2-oxo-1,2-dihydropyridyl each optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl,
 30 methoxycarbonyl, amino, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonylaminomethyl, tetrazolyl, methyl, trifluoromethyl, acetyl, 2-hydroxyethyl and 1-aminoethyl;

35 n is 0;

E is a bond or CH₂;

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R^2 is phenyl, thienyl, pyridyl or isopropyl each optionally substituted with halo, methyl, methylthio or (4-morpholino)methyl; and

R^3 is methyl, ethyl, propyl, butyl, vinyl, allyl or ethoxyethyl each optionally substituted with up to two groups independently selected from Methyl, HO-, MeO-, H_2N -,

- 5 MeC(=O)NH-, MeS(=O)₂NH-, $H_2NC(=O)$ -, MeNHC(=O)-, HO₂C-, (HO)₂P(=O)O-, $H_2NS(=O)_2O$ -, $H_2NS(=O)_2NH$ -, MeNHC(=O)NH-, MeNHC(=O)O-, oxo, cyano, HO₂C-, HOCH₂CH₂NH-, 4-morpholino, HOCH₂C(=O)NH-, $H_2NCH_2C(=O)NH$ -, EtNHC(=O)NH-, MeOC(=O)NH-, MeNHC(=NC≡N)NH-, Me-, MeS-, MeSO₂-, MeSO₂N(Me)-, MeS(=O)₂NHC(=O)-, imidazolylamino-, imidazolyl, tetrazolyl, H_2NCONH -, H_2NCO_2 -,
- 10 HOCH₂CH₂O-, MeNH-, Me₂N- and MeCONMe;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

41. The compound of any one of claims 1-5, wherein

R^1 is absent or is methyl or ethyl;

- 15 A^1 is a bond, CH₂ or CH₂CH₂ or CH when R^1 is present;

Cy^1 is phenyl, cyclopropyl, cyclohexyl, pyrrolidinyl, pyridyl, N-oxo-pyridyl, thiazolyl, piperidinyl or pyrimidinyl each optionally substituted with 1 to 4 groups independently selected from halo, methyl, trifluoromethyl, hydroxy, methoxy, methoxycarbonyl, carboxy, ethoxycarbonylmethoxy, 2-hydroxy-2-methylpropoxy, cyano, difluoromethoxy, t-butoxycarbonyl, hydroxy, hydroxymethyl, 2-hydroxyethyl, 2-hydroxy-2-propyl, methoxymethyl, methylsulfonyl, methylsulfonylamino and benzyloxycarbonyl;

A^2 is a bond, CH₂, O, OCH₂CO or C=O;

- 25 Cy^2 is (a) hydrogen or (b) phenyl, thienyl, pyridyl, N-oxo-pyridyl, cyclopropyl, piperidinyl, piperazinyl, morpholinyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, S,S-dioxothiazinyl, 2-oxo-1,2-dihydropyridyl each optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino, aminomethyl, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonylaminomethyl, tetrazolyl, methyl, trifluoromethyl, acetyl, 2-hydroxyethyl and 1-aminoethyl;

n is 0;

E is a bond or CH₂;

- 35 R^2 is phenyl, thienyl, pyridyl, t-butyl or isopropyl each optionally substituted with halo, methyl, methylthio, hydroxymethyl or (4-morpholino)methyl; and

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R³ is methyl, ethyl, propyl, butyl, vinyl, allyl or ethoxyethyl each optionally substituted with up to two groups independently selected from methyl, HO-, MeO-, H₂N-, MeC(=O)NH-, MeS(=O)₂NH-, H₂NC(=O)-, MeNHC(=O)-, HO₂C-, (HO)₂P(=O)O-, H₂NS(=O)₂O-, H₂NS(=O)₂NH-, MeNHC(=O)NH-, MeNHC(=O)O-, oxo, cyano, HO₂C-,
 5 HOCH₂CH₂NH-, 4-morpholino, HOCH₂C(=O)NH-, H₂NCH₂C(=O)NH-, EtNHC(=O)NH-, MeOC(=O)NH-, MeNHC(=NC≡N)NH-, Me-, MeS-, MeSO₂-, MeSO₂N(Me)-, MeS(=O)₂NHC(=O)-, imidazolylamino-, imidazolyl, tetrazolyl, spirocyclopropyl, FCH₂CH₂NH-, 1-pyrrolidinyl, 3-fluoro-1-pyrrolidinyl, 3-oxo-1-piperazinyl, 1-azetidiny, 1,1-dioxo-2-isothiazolidinyl, 2-oxo-1-pyrrolidinyl, H₂NCONH-, H₂NCO₂-,
 10 HOCH₂CH₂O-, MeNH-, Me₂N- and MeCONMe;
 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

42. A compound selected from the group consisting of:

- 6-methyl-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one;
- 15 3-(4-chlorophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
- 3-(2-chlorophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
- 3-(3-chlorophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
- 6-methyl-6-phenyl-3-(4-(trifluoromethyl)phenyl)-1,3-oxazinan-2-one;
- 3-(3-bromophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
- 20 6-methyl-3,6-diphenyl-1,3-oxazinan-2-one;
- 3-cyclohexyl-6-methyl-6-phenyl-1,3-oxazinan-2-one;
- 3-(biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
- 3-(2'-chlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
- 3-(4'-Methanesulfonyl-biphenyl-3-yl)-6-methyl-6-phenyl-[1,3]oxazinan-2-one;
- 25 3'-(6-Methyl-2-oxo-6-phenyl-[1,3]oxazinan-3-yl)-biphenyl-2-carbonitrile;
- N-isopropyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-sulfonamide;
- N,N-dimethyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-sulfonamide;
- 6-methyl-3-(2'-(methylsulfonyl)biphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one;
- 6-methyl-6-phenyl-3-(4'-(pyrrolidin-1-ylsulfonyl)biphenyl-3-yl)-1,3-oxazinan-2-one;
- 30 3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-carbonitrile;
- N-(2-methoxyethyl)-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-carboxamide;
- N-((3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-yl)methyl)methanesulfonamide;
- 35 6-methyl-6-phenyl-3-(3-(pyridin-3-yl)phenyl)-1,3-oxazinan-2-one;
- 3-(2'-methoxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

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- 3-(2',6'-dichlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 3-(2',4'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 3-(3'-chlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 3-(3'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 5 3-(2',5'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 3-(3',5'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 3-(4'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (S)-3-(4'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(4'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 10 N-(3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-yl)methanesulfonamide;
 N-methyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-sulfonamide;
 N-methyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-carboxamide;
 3-(3'-aminobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 6-methyl-6-phenyl-3-(3-(pyridin-4-yl)phenyl)-1,3-oxazinan-2-one;
 15 3-(3'-methoxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 3-(2'-(hydroxymethyl)biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 6-methyl-6-phenyl-3-(3-(thiophen-2-yl)phenyl)-1,3-oxazinan-2-one;
 3-(2'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 methyl 3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-carboxylate;
 20 3-(3'-(hydroxymethyl)biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 6-methyl-3-(3'-(methylsulfonyl)biphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one;
 N-((3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-yl)methyl)acetamide;
 N,N-dimethyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-carboxamide;
 3-(4'-hydroxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 25 3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-carboxamide;
 N-(3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-2-yl)methanesulfonamide;
 methyl 3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-carboxylate;
 N-methyl-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-4-sulfonamide;
 3-(4'-(hydroxymethyl)biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 30 3-(3'-(1H-tetrazol-5-yl)biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
 2-(3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetamide;
 35 (6S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

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- 6-(3-chlorophenyl)-6-methyl-3-(6-(piperidin-1-yl)pyridin-2-yl)-1,3-oxazinan-2-one;
3-(2-(3-chlorophenyl)pyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(2-(4-fluorophenyl)pyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(2-(3-fluorophenyl)pyrimidin-4-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
5 3-(4-chloropyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(4-(3-chlorophenyl)pyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(4-(2,4-difluorophenyl)pyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(4-(2,6-dichlorophenyl)pyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(4-(4-fluorophenyl)pyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
10 3-(4-(3-fluorophenyl)pyrimidin-2-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
6-allyl-3-(3-bromophenyl)-6-phenyl-1,3-oxazinan-2-one;
6-allyl-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one;
3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
(S)-3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
15 (R)-3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
3-(4',6-difluorobiphenyl-3-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
3-(4',6-difluorobiphenyl-3-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
20 3-(2'-chloro-4'-fluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
3-(2',6'-dichlorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetic acid;
3-(3-bromobenzyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(2-bromobenzyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
25 3-(4-bromobenzyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(3-bromophenyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
6-(2-aminoethyl)-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one;
2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetamide;
3-(2',4'-difluorobiphenyl-3-yl)-6-(2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;
30 3-(2',4'-difluorobiphenyl-3-yl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;
3-(biphenyl-3-yl)-6-(3-chlorophenyl)-6-methyl-1,3-oxazinan-2-one;
3-(2',4'-difluorobiphenyl-3-yl)-6-methyl-6-(pyridin-2-yl)-1,3-oxazinan-2-one;
6-methyl-3-(3-phenoxyphenyl)-6-phenyl-1,3-oxazinan-2-one;
(S)-6-methyl-6-phenyl-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;
35 6-methyl-6-phenyl-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;
(R)-6-methyl-6-phenyl-3-((R)-1-phenylethyl)-1,3-oxazinan-2-one;

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- 6-methyl-6-phenyl-3-((R)-1-phenylethyl)-1,3-oxazinan-2-one;
 (S)-3-((S)-1-(3-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-((S)-1-(3-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (S)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 5 (R)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (S)-6-methyl-3-((S)-1-phenylethyl)-6-o-tolyl-1,3-oxazinan-2-one;
 (R)-6-methyl-3-((S)-1-phenylethyl)-6-o-tolyl-1,3-oxazinan-2-one;
 (S)-6-methyl-3-((S)-1-phenylethyl)-6-m-tolyl-1,3-oxazinan-2-one;
 (R)-6-methyl-3-((S)-1-phenylethyl)-6-m-tolyl-1,3-oxazinan-2-one;
 10 (S)-6-methyl-3-((S)-1-phenylethyl)-6-p-tolyl-1,3-oxazinan-2-one;
 (R)-6-methyl-3-((S)-1-phenylethyl)-6-p-tolyl-1,3-oxazinan-2-one;
 (S)-3-((S)-1-(3-hydroxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (S)-6-methyl-6-(4-(methylthio)phenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;
 ethyl 2-(3-((S)-1-((S)-6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-
 15 yl)ethyl)phenoxy)acetate;
 (S)-6-methyl-6-(4-(morpholinomethyl)phenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-
 one;
 (S)-3-((S)-1-(3-(2-hydroxy-2-methylpropoxy)phenyl)ethyl)-6-methyl-6-phenyl-1,3-
 oxazinan-2-one;
 20 (S)-6-methyl-3-((S)-1-(3-(2-oxo-2-(piperazin-1-yl)ethoxy)phenyl)ethyl)-6-phenyl-1,3-
 oxazinan-2-one;
 (R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;
 (S)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;
 3-(4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
 25 (S)-3-(4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
 (R)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;
 (S)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;
 N-(2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-
 30 yl)ethyl)acetamide;
 N-(2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-
 yl)ethyl)methanesulfonamide;
 3-(2'-chloro-4',6-difluorobiphenyl-3-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-
 oxazinan-2-one;
 35 3-(2'-chloro-4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-
 one;

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3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

(R)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

(S)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-

5 one;

6-(4-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

6-(2-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

10 (R)-6-(2-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

(S)-6-(2-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-(2',4',6-trifluorobiphenyl-3-yl)-1,3-oxazinan-2-

15 one;

6-(2-fluorophenyl)-6-(2-hydroxyethyl)-3-(2',4',6-trifluorobiphenyl-3-yl)-1,3-oxazinan-2-one;

3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-

20 oxazinan-2-one;

3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

(R)-3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

25 (S)-3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

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

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

(S)-6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-

30 2-one;

(R)-6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

35 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

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6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-6-vinyl-1,3-oxazinan-2-one;

6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-6-vinyl-1,3-oxazinan-2-one;

6-(4-fluorophenyl)-6-(hydroxymethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;

6-(4-fluorophenyl)-6-(hydroxymethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;

5 (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

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

10 3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one;

3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

15 (S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

(R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

(R)-6-allyl-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

20 (S)-6-allyl-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

6-methyl-6-phenyl-3-(4-phenylthiazol-2-yl)-1,3-oxazinan-2-one;

(R)-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one;

25 (R)-6-allyl-3-((S)-1-(4-cyclopropylphenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

methyl 4-((S)-1-((R)-6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoate;

(R)-3-((S)-1-(4-cyclopropylphenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one;

30 (S)-2-(4-fluorophenyl)-6-(6-(2-hydroxyethyl)-2-oxo-6-phenyl-1,3-oxazinan-3-yl)pyridine 1-oxide;

methyl 4-((S)-1-((R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoate;

(R)-6-allyl-3-((S)-1-(5-bromopyridin-2-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

35 (S)-6-allyl-3-((S)-1-(5-bromopyridin-2-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

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2-(4-fluorophenyl)-6-(6-(2-fluorophenyl)-6-(2-hydroxyethyl)-2-oxo-1,3-oxazinan-3-yl)pyridine 1-oxide;

(S)-2-(4-fluorophenyl)-6-(6-(2-fluorophenyl)-6-(2-hydroxyethyl)-2-oxo-1,3-oxazinan-3-yl)pyridine 1-oxide;

5 (R)-2-(4-fluorophenyl)-6-(6-(2-fluorophenyl)-6-(2-hydroxyethyl)-2-oxo-1,3-oxazinan-3-yl)pyridine 1-oxide;

(R)-6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

(S)-6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

6-Allyl-3-{1-[5-(2,4-difluoro-phenyl)-pyridin-2-yl]-ethyl}-6-(4-fluoro-phenyl)-

10 [1,3]oxazinan-2-one;

2-(2,4-difluorophenyl)-6-(6-(2-fluorophenyl)-6-(2-hydroxyethyl)-2-oxo-1,3-oxazinan-3-yl)pyridine 1-oxide;

3-(5-chloro-6-(4-fluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

15 (R)-6-(2-aminoethyl)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

3-(5-chloro-6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-

20 1,3-oxazinan-2-one;

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxypropyl)-1,3-oxazinan-2-one;

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxypropyl)-1,3-oxazinan-2-one;

25 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-oxopropyl)-1,3-oxazinan-2-one;

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one;

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-methoxyethyl)-

30 1,3-oxazinan-2-one;

1-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-3-methylurea;

4-((S)-1-((R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoic acid;

35 (R)-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

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(S)-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

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

5 (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-((R)-2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanamide;

3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-N-methylpropanamide;

10 N-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)acetamide;

2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl methylcarbamate;

15 (6S)-6-(2-(aminosulfonylamino)ethyl)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl sulfamate; and

2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl dihydrogen phosphate;

20 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

43. A compound selected from the group consisting of:

6-methyl-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one;

25 3-(2-chlorophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

3-(3-bromophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

3-(biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

3-(2'-chlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

3'-(6-Methyl-2-oxo-6-phenyl-[1,3]oxazinan-3-yl)-biphenyl-2-carbonitrile;

30 3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-carbonitrile;

6-methyl-6-phenyl-3-(3-(pyridin-3-yl)phenyl)-1,3-oxazinan-2-one;

3-(2'-methoxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

3-(2',6'-dichlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

3-(2',4'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

35 3-(3'-chlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

3-(3'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

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- 3-(2',5'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(3',5'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(4'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(3'-methoxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
5 6-methyl-6-phenyl-3-(3-(thiophen-2-yl)phenyl)-1,3-oxazinan-2-one;
3-(2'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(4'-hydroxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
10 2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetamide;
3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
6-(3-chlorophenyl)-6-methyl-3-(6-(piperidin-1-yl)pyridin-2-yl)-1,3-oxazinan-2-one;
15 6-allyl-3-(3-bromophenyl)-6-phenyl-1,3-oxazinan-2-one;
6-allyl-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one;
3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
3-(4',6-difluorobiphenyl-3-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
20 3-(4',6-difluorobiphenyl-3-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
3-(2'-chloro-4'-fluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
3-(2',6'-dichlorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
3-(2-bromobenzyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
25 3-(3-bromophenyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
6-(2-aminoethyl)-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one;
2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetamide;
3-(2',4'-difluorobiphenyl-3-yl)-6-(2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;
3-(2',4'-difluorobiphenyl-3-yl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;
30 3-(biphenyl-3-yl)-6-(3-chlorophenyl)-6-methyl-1,3-oxazinan-2-one;
3-(2',4'-difluorobiphenyl-3-yl)-6-methyl-6-(pyridin-2-yl)-1,3-oxazinan-2-one;
6-methyl-3-(3-phenoxyphenyl)-6-phenyl-1,3-oxazinan-2-one;
6-methyl-6-phenyl-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;
3-(1-(3-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
35 3-(1-(4-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
6-methyl-3-(1-phenylethyl)-6-o-tolyl-1,3-oxazinan-2-one;

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- 6-methyl-3-(1-phenylethyl)-6-m-tolyl-1,3-oxazinan-2-one;
6-methyl-3-(1-phenylethyl)-6-p-tolyl-1,3-oxazinan-2-one;
3-(1-(3-hydroxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
6-methyl-6-(4-(methylthio)phenyl)-3-(1-phenylethyl)-1,3-oxazinan-2-one;
5 6-allyl-6-(4-fluorophenyl)-3-(1-phenylethyl)-1,3-oxazinan-2-one;
3-(4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-(1-phenylethyl)-1,3-oxazinan-2-one;
N-(2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl)acetamide;
10 N-(2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl)methanesulfonamide;
3-(2'-chloro-4',6-difluorobiphenyl-3-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
3-(2'-chloro-4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-
15 one;
3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
6-(4-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
6-(2-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-
20 2-one;
6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-(2',4',6-trifluorobiphenyl-3-yl)-1,3-oxazinan-2-one;
6-(2-fluorophenyl)-6-(2-hydroxyethyl)-3-(2',4',6-trifluorobiphenyl-3-yl)-1,3-oxazinan-2-one;
25 3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
30 6-allyl-3-(1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
6-allyl-3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-6-vinyl-1,3-oxazinan-2-one;
35 6-(4-fluorophenyl)-6-(hydroxymethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;
3-(1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

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3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

5 3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

(R)-6-allyl-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

3-(1-cyclohexylethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one;

6-allyl-3-(1-(4-cyclopropylphenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

10 methyl 4-(1-(6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoate;

3-(1-(4-cyclopropylphenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one;

2-(4-fluorophenyl)-6-(6-(2-hydroxyethyl)-2-oxo-6-phenyl-1,3-oxazinan-3-yl)pyridine 1-oxide;

15 methyl 4-(1-(6-(4-fluorophenyl)-6-(3-hydroxypropyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoate;

6-allyl-3-(1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

3-(5-chloro-6-(4-fluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

20 6-(2-aminoethyl)-3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

3-(5-chloro-6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one;

25 3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxypropyl)-1,3-oxazinan-2-one;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxypropyl)-1,3-oxazinan-2-one;

30 3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-oxopropyl)-1,3-oxazinan-2-one;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-methoxyethyl)-1,3-oxazinan-2-one;

35

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1-(2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-3-methylurea;

3-(1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

5 3-(1-(4-bromophenyl)ethyl)-6-((R)-2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

3-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanamide;

10 3-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-N-methylpropanamide;

N-(2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)acetamide;

2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl methylcarbamate;

15 6-(2-(aminosulfonylamino)ethyl)-3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl sulfamate;

20 2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl dihydrogen phosphate;

2-amino-N-(2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)acetamide;

4-(1-(6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzamide;

25 6-(4-fluorophenyl)-3-(1-(4-(hydroxymethyl)phenyl)ethyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one;

4-(1-(6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)-N-methylbenzamide;

6-allyl-6-(4-fluorophenyl)-3-(1-(4-(2-hydroxypropan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one;

6-allyl-3-(1-(4-bromophenyl)ethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

30 6-allyl-6-(4-fluorophenyl)-3-((1-phenylpiperidin-4-yl)methyl)-1,3-oxazinan-2-one;

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

6-allyl-3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

6-allyl-3-(1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-4-methyl-1,3-oxazinan-2-one;

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

35 3-(1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-4-methyl-1,3-oxazinan-2-one;

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3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

6-allyl-3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

6-(2,3-dihydroxypropyl)-3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-phenyl-1,3-oxazinan-2-one;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetic acid;

3-(1-(2',4'-difluorobiphenyl-4-yl)propyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-(dimethylamino)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

3-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanoic acid;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-(2-hydroxyethylamino)ethyl)-1,3-oxazinan-2-one;

N-(2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-2-hydroxyacetamide;

methyl 2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethylcarbamate;

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-morpholinoethyl)-1,3-oxazinan-2-one;

1-(2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-3-ethylurea;

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2-cyano-1-(2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-3-methylguanidine;

3-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-N-(methylsulfonyl)propanamide;

5 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

44. A compound selected from the group consisting of:

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

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one

N-(3-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propyl)methanesulfonamide

6-(3-hydroxypropyl)-3-phenethyl-6-phenyl-1,3-oxazinan-2-one

3-(1-(4-chlorophenyl)ethyl)-6-(3-hydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

6-(3-hydroxypropyl)-6-phenyl-3-(2-phenylcyclopropyl)-1,3-oxazinan-2-one

6-allyl-6-(4-fluorophenyl)-3-(1-p-tolyethyl)-1,3-oxazinan-2-one

6-allyl-6-(4-fluorophenyl)-3-(1-(4-hydroxyphenyl)ethyl)-1,3-oxazinan-2-one

6-(2-hydroxyethyl)-3-(1-(4-methoxyphenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

4-(1-(6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzonitrile

6-allyl-6-(4-fluorophenyl)-3-(1-(4-methoxyphenyl)ethyl)-1,3-oxazinan-2-one

3-(1-(4-(hydroxymethyl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-(1-(4-methoxyphenyl)ethyl)-1,3-oxazinan-2-one

6-allyl-3-(1-(4-chlorophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

3-(1-cyclohexylethyl)-6-(2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

3-(1-(4-(2-hydroxyethyl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

6-(3-hydroxypropyl)-3-(1-(4-(methoxymethyl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

3-(1-(4-bromophenyl)ethyl)-6-(3-hydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-(1-(4-methoxyphenyl)ethyl)-1,3-oxazinan-2-one

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3-(1-(4-chlorophenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

3-(1-(4-chlorophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxypropyl)-1,3-oxazinan-2-one

5 6-allyl-3-(1-(4-bromophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

6-(2-hydroxyethyl)-6-phenyl-3-(1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

6-(2,3-dihydroxypropyl)-6-(4-fluorophenyl)-3-(1-(4-methoxyphenyl)ethyl)-1,3-oxazinan-2-one

10 3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-isopropyl-1,3-oxazinan-2-one

tert-butyl 3-(6-(3-hydroxypropyl)-2-oxo-6-phenyl-1,3-oxazinan-3-yl)pyrrolidine-1-carboxylate

N-(2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)methanesulfonamide

15 6-(3-hydroxypropyl)-6-phenyl-3-(1-(4-(pyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one

6-(3-hydroxypropyl)-6-phenyl-3-(1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

20 3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-(1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

6-allyl-6-(4-fluorophenyl)-3-(1-(4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one

25 6-(3-hydroxypropyl)-6-phenyl-3-(1-(4-(thiophen-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one

6-allyl-6-(4-fluorophenyl)-3-(1-(4-morpholinophenyl)ethyl)-1,3-oxazinan-2-one

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one

3-(3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanenitrile

30 3-(1-(4-bromophenyl)propyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

6-(3-hydroxypropyl)-3-(1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

3-(4-(1-(6-(3-hydroxypropyl)-2-oxo-6-phenyl-1,3-oxazinan-3-yl)ethyl)phenyl)pyridine 1-oxide

35 3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

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3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-(1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-

5 oxazinan-2-one

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-phenyl-6-propyl-1,3-oxazinan-2-one

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

N-(4-(1-(6-(4-fluorophenyl)-6-(2-hydroxyethyl)-2-oxo-1,3-oxazinan-3-

10 yl)ethyl)phenyl)methanesulfonamide

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-(methylsulfonyl)ethyl)-1,3-oxazinan-2-one

6-allyl-6-(4-fluorophenyl)-3-(1-(4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one

15 6-allyl-6-(4-fluorophenyl)-3-(1-(4-(4-methylpiperazin-1-yl)phenyl)ethyl)-1,3-oxazinan-2-one

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-(thiophen-2-yl)-1,3-

20 oxazinan-2-one

3-(3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide

6-(3-hydroxypropyl)-3-(1-(4-(6-methoxypyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

3-(6-(4-fluorophenyl)-2-oxo-3-(1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-6-

25 yl)propanamide

3-(1-(4'-fluorobiphenyl-4-yl)propyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

3-(1-(4-bromophenyl)propyl)-6-(2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

30 3-(3-(1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanamide

3-(1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-

35 yl)acetonitrile

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6-allyl-6-(4-fluorophenyl)-3-(1-(4-(piperidine-1-carbonyl)phenyl)ethyl)-1,3-oxazinan-2-one

6-allyl-3-(1-(4-(2,4-dimethylthiazol-5-yl)phenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

5 3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

10 3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxy-3-methylbutyl)-6-phenyl-1,3-oxazinan-2-one

3-(1-(4-(5-acetylthiophen-2-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

15 3-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide

3-(1-(4-(5-(1-aminoethyl)thiophen-2-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

20 3-(1-(4'-fluorobiphenyl-4-yl)propyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

3-(1-(2',4'-difluorobiphenyl-4-yl)propyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

3-(1-(4-(5-(1-hydroxyethyl)thiophen-2-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

25 3-(1-(4-bromophenyl)propyl)-6-(2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

6-(3-aminopropyl)-3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

30 3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-(methylamino)ethyl)-1,3-oxazinan-2-one

6-allyl-6-(4-fluorophenyl)-3-(1-(4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)ethyl)-1,3-oxazinan-2-one

6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-(1-(4-(1,1-dioxo-hexahydro-1,2-thiazin-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one

35 3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxy-3-methylbutyl)-6-phenyl-1,3-oxazinan-2-one

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3-(1-(2',4'-difluorobiphenyl-4-yl)propyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-(methylthio)ethyl)-1,3-oxazinan-2-one

5 1-(2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)urea

2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl carbamate

10 3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-3-(methylamino)propyl)-1,3-oxazinan-2-one

3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-(2-hydroxyethoxy)ethyl)-1,3-oxazinan-2-one

6-(2-(1H-imidazol-1-yl)ethyl)-3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

15 6-(2-(2H-tetrazol-5-yl)ethyl)-3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

N-(2-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-N-methylacetamide

20 N-(3-(3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl)methanesulfonamide

1-(3-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propyl)urea

3-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propyl carbamate

25 3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-(dimethylamino)-2-hydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

6-(2-(2-amino-1H-imidazol-1-yl)ethyl)-3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

30 1-(3-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propyl)-3-methylurea

1-(3-(3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-hydroxypropyl)urea

N-(3-(3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-hydroxypropyl)methanesulfonamide

35 N-(3-(3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-hydroxypropyl)-N-methylmethanesulfonamide

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3-(1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one

3-(1-(4-(2-hydroxypropan-2-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

5 6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-(1-(4-(6-(trifluoromethyl)pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

6-(3-hydroxypropyl)-3-(1-(4-methoxyphenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

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

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

10 6-(4-fluorophenyl)-3-(1-(4-fluorophenyl)ethyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

6-(2,3-dihydroxypropyl)-3-(1-(4-methoxyphenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

3-(3-(1-(4-chlorophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide

3-(6-(4-fluorophenyl)-3-(1-(3-fluorophenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)propanamide

15 3-(6-(4-fluorophenyl)-3-(1-(4-methoxyphenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)propanamide

6-allyl-3-(1-(4-(difluoromethoxy)phenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

3-(1-(4-(1H-pyrazol-3-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

20 6-allyl-3-(1-(4-(5-fluoropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,3-oxazinan-2-one

6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-(1-(4-(trifluoromethyl)phenyl)ethyl)-1,3-oxazinan-2-one

25 3-(2-oxo-6-phenyl-3-(1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanamide

3-(2-oxo-6-phenyl-3-(1-(4-(pyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanamide

3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

3-(1-(4-(5-fluoropyridin-3-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

30 3-(6-(4-fluorophenyl)-2-oxo-3-(1-(3-(trifluoromethyl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanamide

3-(4-(1-(6-(3-amino-3-oxopropyl)-2-oxo-6-phenyl-1,3-oxazinan-3-yl)ethyl)phenyl)pyridine 1-oxide

N-(2-(6-(4-fluorophenyl)-3-(1-(4-methoxyphenyl)ethyl)-2-oxo-1,3-oxazinan-6-

35 yl)ethyl)methanesulfonamide

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6-(4-fluorophenyl)-3-(1-(4-(5-fluoropyridin-3-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

3-(3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile

5 3-(3-(1-(4-(6-methoxypyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide

6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-(1-(4-(5-methoxypyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

10 3-(1-(4-(5-chloropyridin-3-yl)phenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

N-(2-(2-oxo-6-phenyl-3-(1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)ethyl)methanesulfonamide

6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-(1-(4-(methylsulfonyl)phenyl)ethyl)-1,3-oxazinan-2-one

15 3-(1-(4-(difluoromethoxy)phenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

3-(3-(1-(4'-fluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl dihydrogen phosphate

20 6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-(1-(4-(2-methylpyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one

3-(1-(4-(2-hydroxy-2-methylpropyl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

6-(3-hydroxypropyl)-3-(1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

25 N-(3-(6-(4-fluorophenyl)-3-(1-(4-methoxyphenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)propyl)methanesulfonamide

3-(3-(1-(4-methoxyphenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide

3-(6-(4-fluorophenyl)-3-(1-(4-fluorophenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)propanamide

30 3-(3-(1-cyclohexylethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanamide

N-(2-(3-(1-cyclohexylethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)methanesulfonamide

N-(3-(3-(1-cyclohexylethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propyl)methanesulfonamide

35

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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45. A compound selected from the group consisting of:

- (R)-6-methyl-6-phenyl-3-m-tolyl-1,3-oxazinan-2-one;
 (R)-3-(2-chlorophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(3-bromophenyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 5 (R)-3-(biphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(2'-chlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-2-carbonitrile;
 (R)-3'-(6-methyl-2-oxo-6-phenyl-1,3-oxazinan-3-yl)biphenyl-3-carbonitrile;
 (R)-6-methyl-6-phenyl-3-(3-(pyridin-3-yl)phenyl)-1,3-oxazinan-2-one;
 10 (R)-3-(2'-methoxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(2',6'-dichlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(2',4'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(3'-chlorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(3'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 15 (R)-3-(2',5'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(3',5'-difluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(4'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (S)-3-(4'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(4'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 20 (R)-3-(3'-methoxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-6-methyl-6-phenyl-3-(3-(thiophen-2-yl)phenyl)-1,3-oxazinan-2-one;
 (R)-3-(2'-fluorobiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(4'-hydroxybiphenyl-3-yl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;
 (S)-3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-
 25 1,3-oxazinan-2-one;
 2-(3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetamide;
 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-((R)-2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
 30 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-((S)-2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
 (R)-6-(3-chlorophenyl)-6-methyl-3-(6-(piperidin-1-yl)pyridin-2-yl)-1,3-oxazinan-2-one;
 (R)-6-allyl-3-(3-bromophenyl)-6-phenyl-1,3-oxazinan-2-one;
 (R)-6-allyl-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one;
 35 (S)-3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
 (R)-3-(2',4'-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

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(S)-3-(4',6-difluorobiphenyl-3-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

(S)-3-(4',6-difluorobiphenyl-3-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

5 (S)-3-(2'-chloro-4'-fluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

(S)-3-(2',6'-dichlorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

(R)-3-(2-bromobenzyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

(S)-3-(3-bromophenyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

10 (R)-6-(2-aminoethyl)-3-(2',4'-difluorobiphenyl-3-yl)-6-phenyl-1,3-oxazinan-2-one;

(S)-2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)acetamide;

(S)-3-(2',4'-difluorobiphenyl-3-yl)-6-((R)-2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

15 (S)-3-(2',4'-difluorobiphenyl-3-yl)-6-((S)-2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

(R)-3-(2',4'-difluorobiphenyl-3-yl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

(R)-3-(biphenyl-3-yl)-6-(3-chlorophenyl)-6-methyl-1,3-oxazinan-2-one;

(R)-3-(2',4'-difluorobiphenyl-3-yl)-6-methyl-6-(pyridin-2-yl)-1,3-oxazinan-2-one;

(R)-6-methyl-3-(3-phenoxyphenyl)-6-phenyl-1,3-oxazinan-2-one;

20 (R)-6-methyl-6-phenyl-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;

(S)-6-methyl-6-phenyl-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;

(S)-3-((S)-1-(3-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

(R)-3-((S)-1-(3-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

(S)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

25 (R)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

(R)-6-methyl-3-((S)-1-phenylethyl)-6-o-tolyl-1,3-oxazinan-2-one;

(R)-6-methyl-3-((S)-1-phenylethyl)-6-m-tolyl-1,3-oxazinan-2-one;

(R)-6-methyl-3-((S)-1-phenylethyl)-6-p-tolyl-1,3-oxazinan-2-one;

(R)-3-((S)-1-(3-hydroxyphenyl)ethyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one;

30 (R)-6-methyl-6-(4-(methylthio)phenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;

(R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;

(S)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;

(S)-3-(4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

(S)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;

35 (R)-N-(2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl)acetamide;

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- (S)-N-(2-(3-(2',4'-difluorobiphenyl-3-yl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl)methanesulfonamide;
- (6S)-3-(2'-chloro-4',6-difluorobiphenyl-3-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
- 5 (6S)-3-(2'-chloro-4',6-difluorobiphenyl-3-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
- (S)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
- (S)-6-(4-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
- 10 (S)-6-(2-fluorophenyl)-3-(6-(4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
- (6S)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-(2',4',6-trifluorobiphenyl-3-yl)-1,3-oxazinan-2-one;
- 15 (6S)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-3-(2',4',6-trifluorobiphenyl-3-yl)-1,3-oxazinan-2-one;
- (S)-3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
- (S)-3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
- 20 (R)-3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
- (S)-3-(6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
- 25 (S)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
- (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
- (S)-6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
- (R)-6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
- 30 (R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
- (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
- 35 (R)-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-6-vinyl-1,3-oxazinan-2-one;
- (S)-6-(4-fluorophenyl)-3-((S)-1-phenylethyl)-6-vinyl-1,3-oxazinan-2-one;

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- (R)-6-(4-fluorophenyl)-6-(hydroxymethyl)-3-((S)-1-phenylethyl)-1,3-oxazinan-2-one;
(S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
(S)-3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;
5 (S)-3-(6-(2-chloro-4-fluorophenyl)pyridin-2-yl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
(S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
10 (R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
(R)-6-allyl-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
(S)-6-allyl-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
(R)-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one;
15 one;
(R)-6-allyl-3-((S)-1-(4-cyclopropylphenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
methyl 4-((S)-1-((R)-6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoate;
20 (R)-3-((S)-1-(4-cyclopropylphenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one;
(S)-6-allyl-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
methyl 4-((S)-1-((R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzoate;
25 (R)-6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
(S)-6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
(S)-3-(5-chloro-6-(4-fluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
(R)-6-(2-aminoethyl)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;
30 oxazinan-2-one;
(S)-3-(5-chloro-6-(2,4-difluorophenyl)pyridin-2-yl)-6-(2-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;
(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one;
35 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-((S)-2-hydroxypropyl)-1,3-oxazinan-2-one;

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(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-((R)-2-hydroxypropyl)-1,3-oxazinan-2-one;

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-oxopropyl)-1,3-oxazinan-2-one;

5 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one;

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-methoxyethyl)-1,3-oxazinan-2-one;

10 1-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-3-methylurea;

(S)-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

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

15 (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-((R)-2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanamide;

20 3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-N-methylpropanamide;

N-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)acetamide;

2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl methylcarbamate;

25 (6S)-6-(2-(aminosulfonylamino)ethyl)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl sulfamate; and

30 2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl dihydrogen phosphate;

2-amino-N-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)acetamide;

4-((S)-1-((R)-6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzamide;

35 (R)-6-(4-fluorophenyl)-3-((S)-1-(4-(hydroxymethyl)phenyl)ethyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one;

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4-((S)-1-((R)-6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)-N-methylbenzamide;

(R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(2-hydroxypropan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one;

5 (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

(S)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

(R)-6-allyl-6-(4-fluorophenyl)-3-((1-phenylpiperidin-4-yl)methyl)-1,3-oxazinan-2-one;

(S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

10 (S)-6-allyl-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

(R)-6-allyl-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

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

(4R,6R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-4-methyl-1,3-

15 oxazinan-2-one;

(4R,6S)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-4-methyl-1,3-oxazinan-2-one;

(4S,6R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-4-methyl-1,3-oxazinan-2-one;

20 (R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

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

(4R,6S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-4-

25 methyl-1,3-oxazinan-2-one;

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one;

(S)-6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

30 (R)-6-allyl-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

(S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

(R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-(thiophen-2-yl)-1,3-

35 oxazinan-2-one;

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(6R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-((R)-2-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

(6S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-((R)-2-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

5 (6R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-((S)-2-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

(6S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-((S)-2-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

10 (S)-6-((S)-2,3-dihydroxypropyl)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-phenyl-1,3-oxazinan-2-one;

(S)-6-((R)-2,3-dihydroxypropyl)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-phenyl-1,3-oxazinan-2-one;

(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

15 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-((R)-2-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-((S)-2-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

20 (R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one;

3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanenitrile;

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-((S)-2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

25 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-((R)-2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one;

2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetic acid;

30 (R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)propyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)propyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one;

(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-(dimethylamino)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one;

35 3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanoic acid;

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(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-(2-hydroxyethylamino)ethyl)-1,3-oxazinan-2-one;

N-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-2-hydroxyacetamide;

5 methyl 2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethylcarbamate;

(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-morpholinoethyl)-1,3-oxazinan-2-one;

10 1-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-3-ethylurea;

2-cyano-1-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-3-methylguanidine;

3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-N-(methylsulfonyl)propanamide;

15 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

46. A compound selected from the group consisting of:

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

20 3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-4-methyl-1,3-oxazinan-2-one

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one

25 N-(3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propyl)methanesulfonamide

6-(3-hydroxypropyl)-3-phenethyl-6-phenyl-1,3-oxazinan-2-one

6-(3-hydroxypropyl)-3-phenethyl-6-phenyl-1,3-oxazinan-2-one

3-((S)-1-(4-chlorophenyl)ethyl)-6-(3-hydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

3-((S)-1-(4-chlorophenyl)ethyl)-6-(3-hydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

30 6-(3-hydroxypropyl)-6-phenyl-3-(2-phenylcyclopropyl)-1,3-oxazinan-2-one

6-(3-hydroxypropyl)-6-phenyl-3-(2-phenylcyclopropyl)-1,3-oxazinan-2-one

6-allyl-6-(4-fluorophenyl)-3-((S)-1-p-tolyethyl)-1,3-oxazinan-2-one

6-allyl-6-(4-fluorophenyl)-3-((S)-1-p-tolyethyl)-1,3-oxazinan-2-one

(R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-hydroxyphenyl)ethyl)-1,3-oxazinan-2-one

35 (S)-6-(2-hydroxyethyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

(R)-6-(2-hydroxyethyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

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4-((S)-1-((R)-6-allyl-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)benzonitrile

(R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-1,3-oxazinan-2-one

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

(R)-3-((S)-1-(4-(hydroxymethyl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-

5 oxazinan-2-one

(S)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-1,3-

oxazinan-2-one

(R)-6-allyl-3-((S)-1-(4-chlorophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

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

10 (S)-3-((S)-1-cyclohexylethyl)-6-((R)-2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-

oxazinan-2-one

(S)-3-((S)-1-cyclohexylethyl)-6-((S)-2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-

oxazinan-2-one

(R)-3-((S)-1-(4-(2-hydroxyethyl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-

15 oxazinan-2-one

(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(methoxymethyl)phenyl)ethyl)-6-phenyl-1,3-

oxazinan-2-one

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

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

20 (R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-1,3-

oxazinan-2-one

(S)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-1,3-

oxazinan-2-one

(R)-3-((S)-1-(4-chlorophenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-

25 oxazinan-2-one

(6S)-3-((S)-1-(4-chlorophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxypropyl)-1,3-

oxazinan-2-one

(R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

(S)-6-(2-hydroxyethyl)-6-phenyl-3-((S)-1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-

30 2-one

(S)-6-((R)-2,3-dihydroxypropyl)-6-(4-fluorophenyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-

1,3-oxazinan-2-one

(S)-6-((S)-2,3-dihydroxypropyl)-6-(4-fluorophenyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-

1,3-oxazinan-2-one

35 (R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-isopropyl-1,3-

oxazinan-2-one

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(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-isopropyl-1,3-oxazinan-2-one

(S)-tert-butyl 3-((R)-6-(3-hydroxypropyl)-2-oxo-6-phenyl-1,3-oxazinan-3-yl)pyrrolidine-1-carboxylate

5 N-(2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)methanesulfonamide

(R)-6-(3-hydroxypropyl)-6-phenyl-3-((S)-1-(4-(pyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one

10 (R)-6-(3-hydroxypropyl)-6-phenyl-3-((S)-1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

15 3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

(S)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

20 (R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one

(R)-6-(3-hydroxypropyl)-6-phenyl-3-((S)-1-(4-(thiophen-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one

(R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-morpholinophenyl)ethyl)-1,3-oxazinan-2-one

25 (S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one

3-((R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanenitrile

30 (R)-3-((S)-1-(4-bromophenyl)propyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

3-4-((S)-1-((R)-6-(3-hydroxypropyl)-2-oxo-6-phenyl-1,3-oxazinan-3-

35 yl)ethyl)phenyl)pyridine 1-oxide

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3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

5 3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2,3-dihydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one

10 (6S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

(S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-((S)-2-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

(S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-((R)-2-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

15 (R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-phenyl-6-propyl-1,3-oxazinan-2-one

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

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

N-(4-((S)-1-((S)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-2-oxo-1,3-oxazinan-3-yl)ethyl)phenyl)methanesulfonamide

25 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-(methylsulfonyl)ethyl)-1,3-oxazinan-2-one

(R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(5-methyl-1,3,4-thiadiazol-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one

(R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(4-methylpiperazin-1-yl)phenyl)ethyl)-1,3-oxazinan-2-one

30 (R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one

35 (R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(2-hydroxyethyl)-6-(thiophen-2-yl)-1,3-oxazinan-2-one

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3-((R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide

(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(6-methoxypyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

5 3-((R)-6-(4-fluorophenyl)-2-oxo-3-((S)-1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanamide

(R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)propyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

10 (S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

(S)-3-((S)-1-(4-bromophenyl)propyl)-6-((S)-2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

(S)-3-((S)-1-(4-bromophenyl)propyl)-6-((R)-2,3-dihydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

15 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanamide

(R)-3-((S)-1-(4-bromophenyl)propyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

20 2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetonitrile

(R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(piperidine-1-carbonyl)phenyl)ethyl)-1,3-oxazinan-2-one

(R)-6-allyl-3-((S)-1-(4-(2,4-dimethylthiazol-5-yl)phenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

25 (R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

30 (S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(2-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxy-3-methylbutyl)-6-phenyl-1,3-oxazinan-2-one

35 (R)-3-((S)-1-(4-(5-acetylthiophen-2-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

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3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide

(6R)-3-((1S)-1-(4-(5-(1-aminoethyl)thiophen-2-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

5 (R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)propyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)propyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

10 (6R)-3-((1S)-1-(4-(5-(1-hydroxyethyl)thiophen-2-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

(S)-3-((S)-1-(4-bromophenyl)propyl)-6-((R)-2,3-dihydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

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

15 (R)-6-(3-aminopropyl)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-(methylamino)ethyl)-1,3-oxazinan-2-one

20 (R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)ethyl)-1,3-oxazinan-2-one

(S)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-(4-(1,1-dioxo-hexahydro-1,2-thiazin-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-hydroxy-3-methylbutyl)-6-phenyl-1,3-oxazinan-2-one

25 (R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)propyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

(S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-(methylthio)ethyl)-1,3-oxazinan-2-one

30 1-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)urea

2-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl carbamate

(6S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-3-(methylamino)propyl)-1,3-oxazinan-2-one

35 (S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-(2-hydroxyethoxy)ethyl)-1,3-oxazinan-2-one

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(S)-6-(2-(1H-imidazol-1-yl)ethyl)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

(R)-6-(2-(2H-tetrazol-5-yl)ethyl)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

5 N-(2-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)-N-methylacetamide

N-(3-((R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl)methanesulfonamide

10 1-(3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propyl)urea

3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propyl carbamate

(6S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(3-(dimethylamino)-2-hydroxypropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

15 (S)-6-(2-(2-amino-1H-imidazol-1-yl)ethyl)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

1-(3-((R)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propyl)-3-methylurea

20 1-(3-((S)-3-((S)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-hydroxypropyl)urea

N-((R)-3-((S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-hydroxypropyl)methanesulfonamide

N-((S)-3-((S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-hydroxypropyl)methanesulfonamide

25 N-((R)-3-((S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-hydroxypropyl)-N-methylmethanesulfonamide

N-((S)-3-((S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-hydroxypropyl)-N-methylmethanesulfonamide

30 (R)-3-((R)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one

(S)-3-((R)-1-(2',4'-difluorobiphenyl-4-yl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(4-(2-hydroxypropan-2-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

35 (R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(6-(trifluoromethyl)pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

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(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

(S)-6-(3-hydroxypropyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

5 (R)-6-(4-fluorophenyl)-3-((S)-1-(3-fluorophenyl)ethyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

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

10 (R)-6-(4-fluorophenyl)-3-((S)-1-(4-fluorophenyl)ethyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

(S)-6-((S)-2,3-dihydroxypropyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

(S)-6-((R)-2,3-dihydroxypropyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

15 (6R)-6-(2,3-dihydroxypropyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

3-((R)-3-((S)-1-(4-chlorophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide

3-((R)-6-(4-fluorophenyl)-3-((S)-1-(3-fluorophenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)propanamide

20 3-((R)-6-(4-fluorophenyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)propanamide

(R)-6-allyl-3-((S)-1-(4-(difluoromethoxy)phenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one

25 (R)-3-((S)-1-(4-(1H-pyrazol-3-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

(R)-6-allyl-3-((S)-1-(4-(5-fluoropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

(R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(3-(trifluoromethyl)phenyl)ethyl)-1,3-oxazinan-2-one

30 (R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(trifluoromethyl)phenyl)ethyl)-1,3-oxazinan-2-one

3-((R)-2-oxo-6-phenyl-3-((S)-1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanamide

3-((R)-2-oxo-6-phenyl-3-((S)-1-(4-(pyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanamide

35 (S)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

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(R)-3-((S)-1-(4-(5-fluoropyridin-3-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

3-((R)-6-(4-fluorophenyl)-2-oxo-3-((S)-1-(3-(trifluoromethyl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanamide

5 3-(4-((S)-1-((R)-6-(3-amino-3-oxopropyl)-2-oxo-6-phenyl-1,3-oxazinan-3-yl)ethyl)phenyl)pyridine 1-oxide

N-(2-((S)-6-(4-fluorophenyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)methanesulfonamide

10 (R)-6-(4-fluorophenyl)-3-((S)-1-(4-(5-fluoropyridin-3-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

3-((R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile

3-((R)-3-((S)-1-(4-(6-methoxypyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide

15 (R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(5-methoxypyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(4-(5-chloropyridin-3-yl)phenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

20 N-(2-((S)-2-oxo-6-phenyl-3-((S)-1-(4-(pyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)ethyl)methanesulfonamide

(S)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-(4-(methylsulfonyl)phenyl)ethyl)-1,3-oxazinan-2-one

(R)-3-((S)-1-(4-(difluoromethoxy)phenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one

25 3-((R)-3-((S)-1-(4'-fluorobiphenyl-4-yl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl dihydrogen phosphate

(R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(2-methylpyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one

30 (R)-3-((S)-1-(4-(2-hydroxy-2-methylpropyl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one

(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

N-(3-((R)-6-(4-fluorophenyl)-3-((S)-1-(4-methoxyphenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)propyl)methanesulfonamide

35 3-((R)-3-((S)-1-(4-methoxyphenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide

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3-((R)-6-(4-fluorophenyl)-3-((S)-1-(4-fluorophenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)propanamide

3-((R)-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propanamide

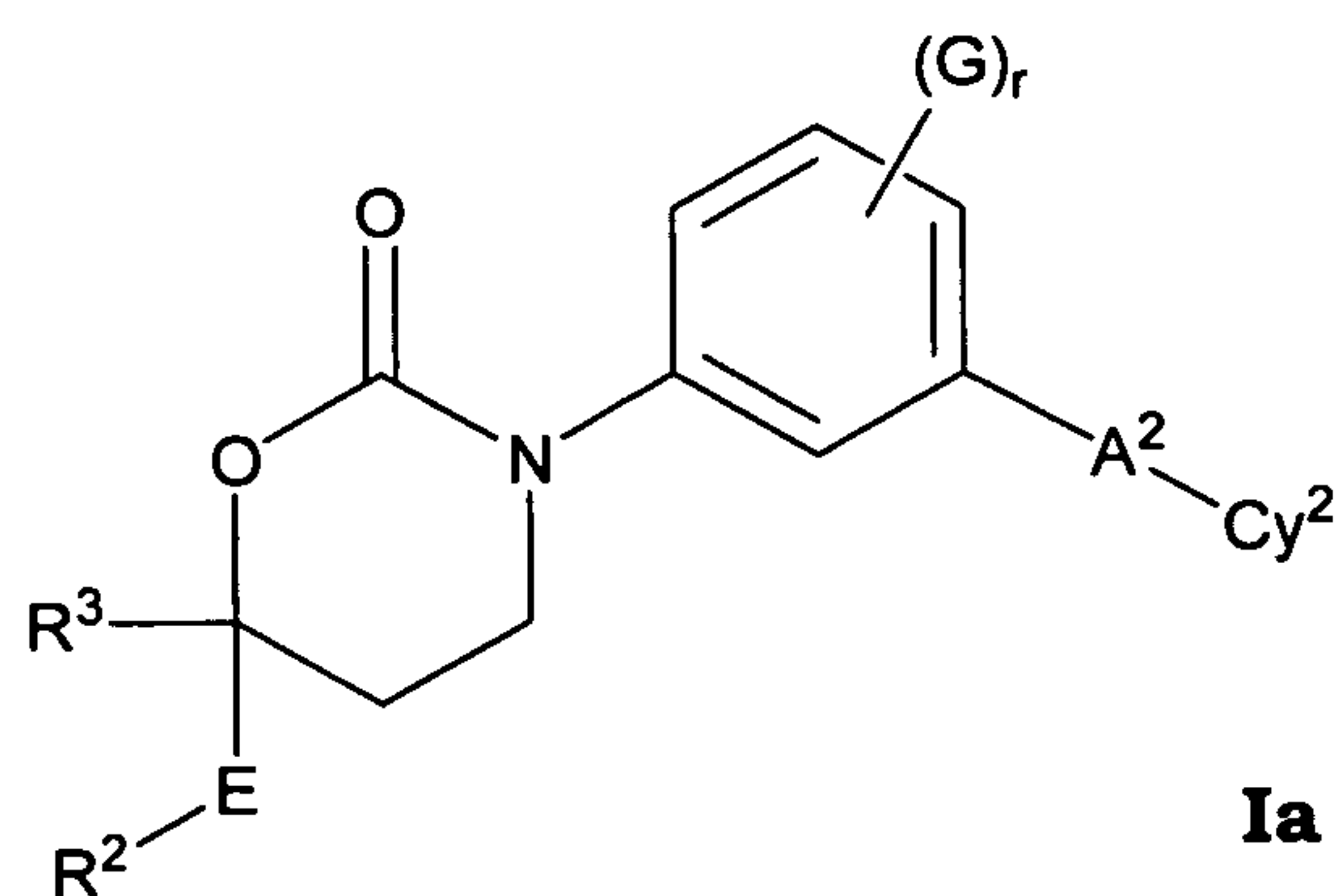
5 N-(2-((S)-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)ethyl)methanesulfonamide

N-(3-((R)-3-((S)-1-cyclohexylethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)propyl)methanesulfonamide

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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47. The compound of any one of claims 1-5, wherein the compound is of Formula (Ia):



wherein;

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

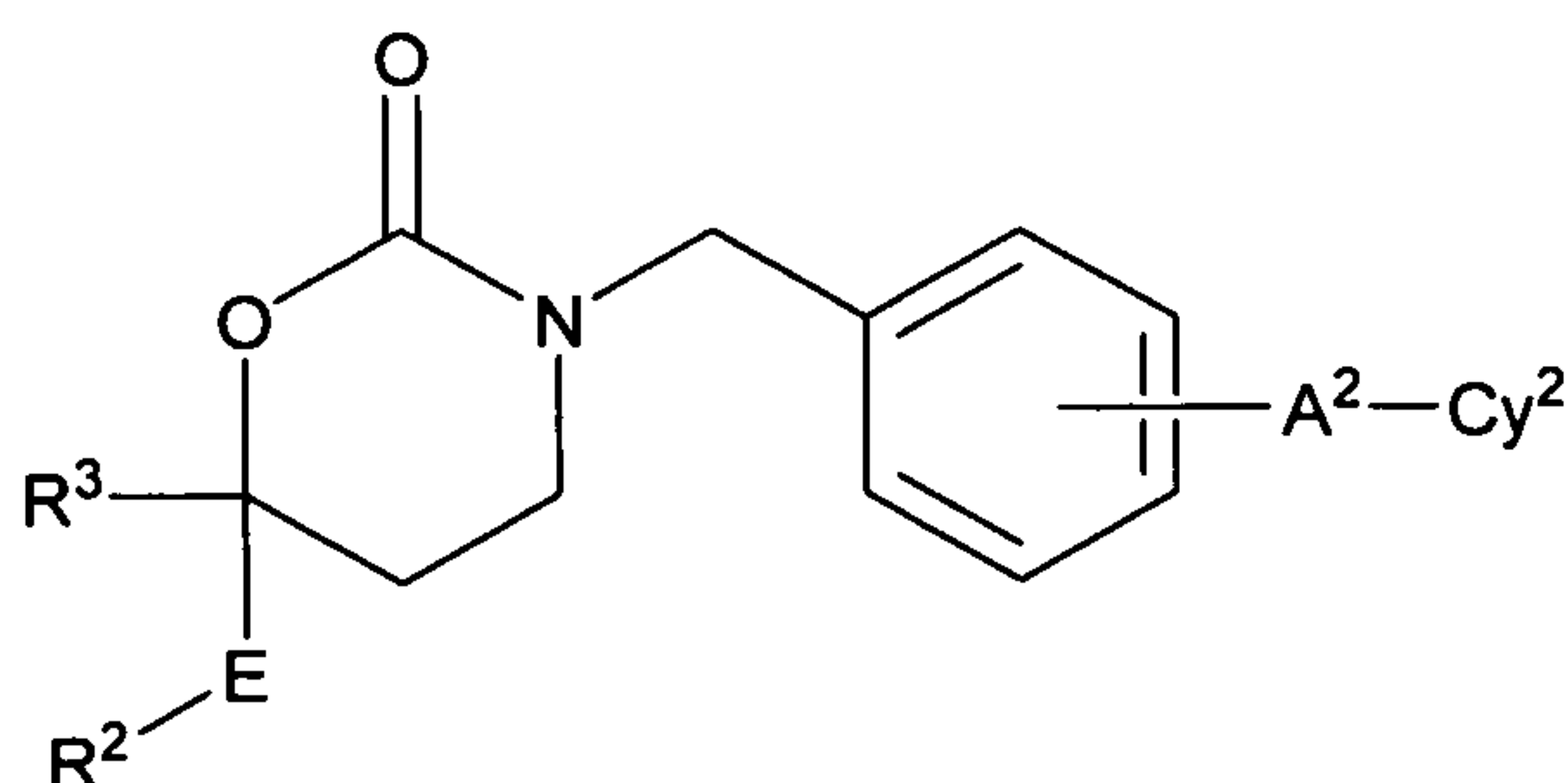
G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl,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

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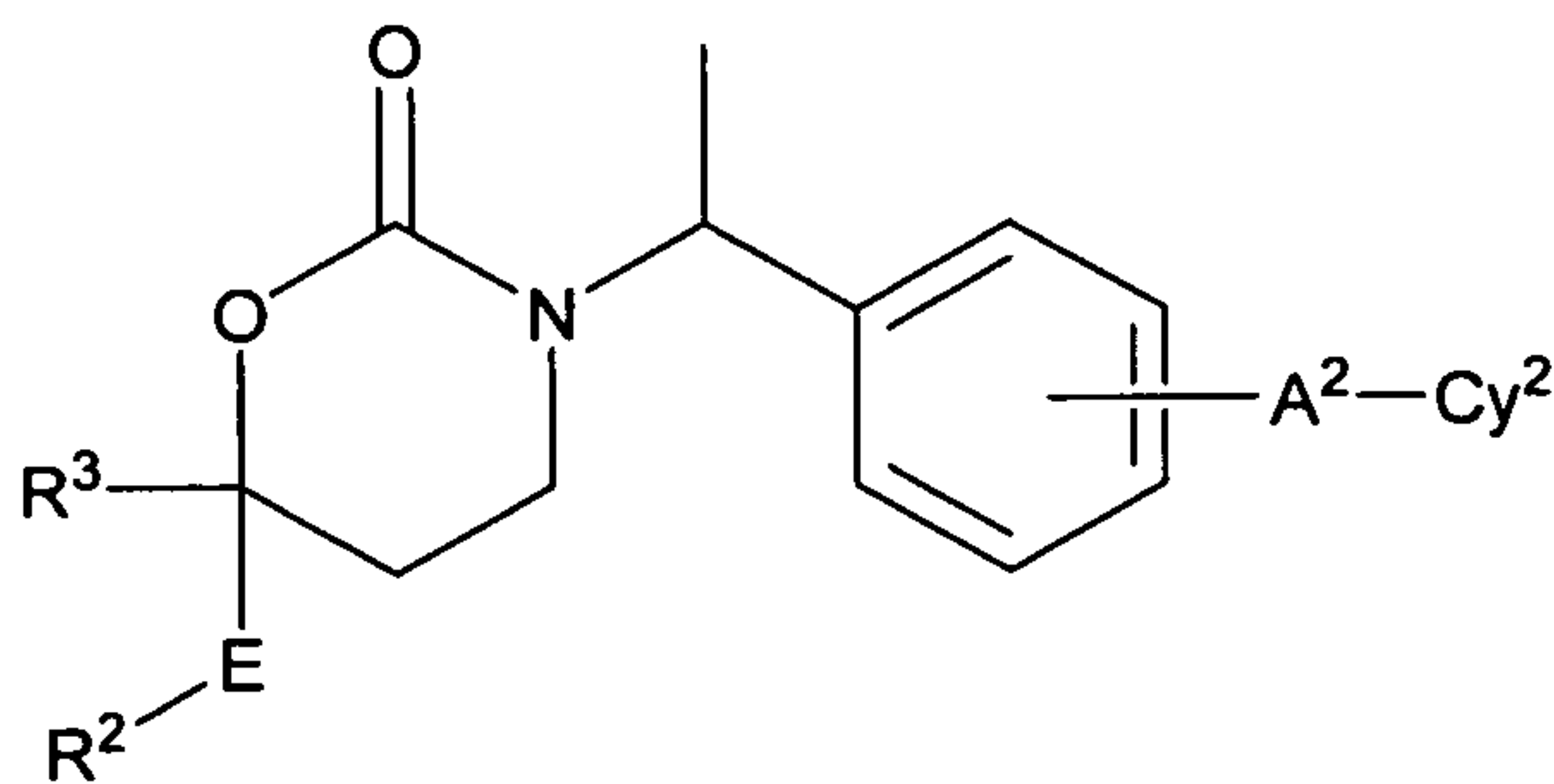
C_6)alkylaminocarbonyl, (C_1-C_3) alkoxy (C_1-C_3) alkylaminocarbonyl,
 heterocyclylcarbonyl, (C_1-C_6) alkylaminosulfonyl, di (C_1-C_6) alkylaminosulfonyl,
 heterocyclosulfonyl, (C_1-C_6) alkylcarbonylamino, (C_1-C_6) alkylcarbonylamino $(C_1-$
 $C_6)$ alkyl, (C_1-C_6) alkylsulfonylamino, (C_1-C_6) alkylsulfonylamino (C_1-C_6) alkyl, $(C_1-$
 5 $C_6)$ 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 and heteroaryl;
 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

10 48. The compound of any one of claims 1-5 wherein the compound is of Formula (Ib):

**Ib**

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

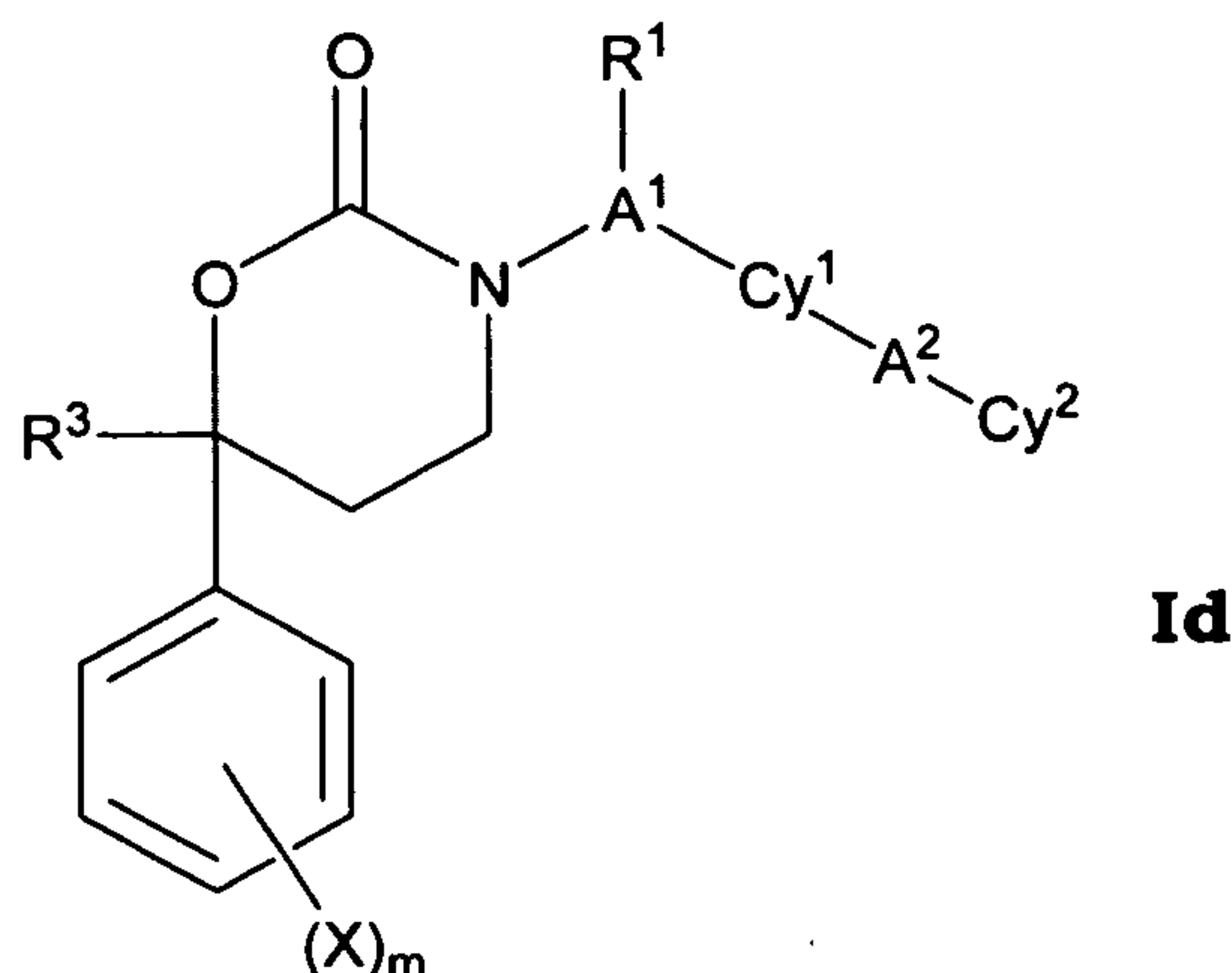
15 49. The compound of any one of claims 1-5, wherein the compound is of Formula (Ic):

**Ic**

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

20 50. The compound of any one of claims 1-5, wherein the compound is of Formula (Id):

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wherein;

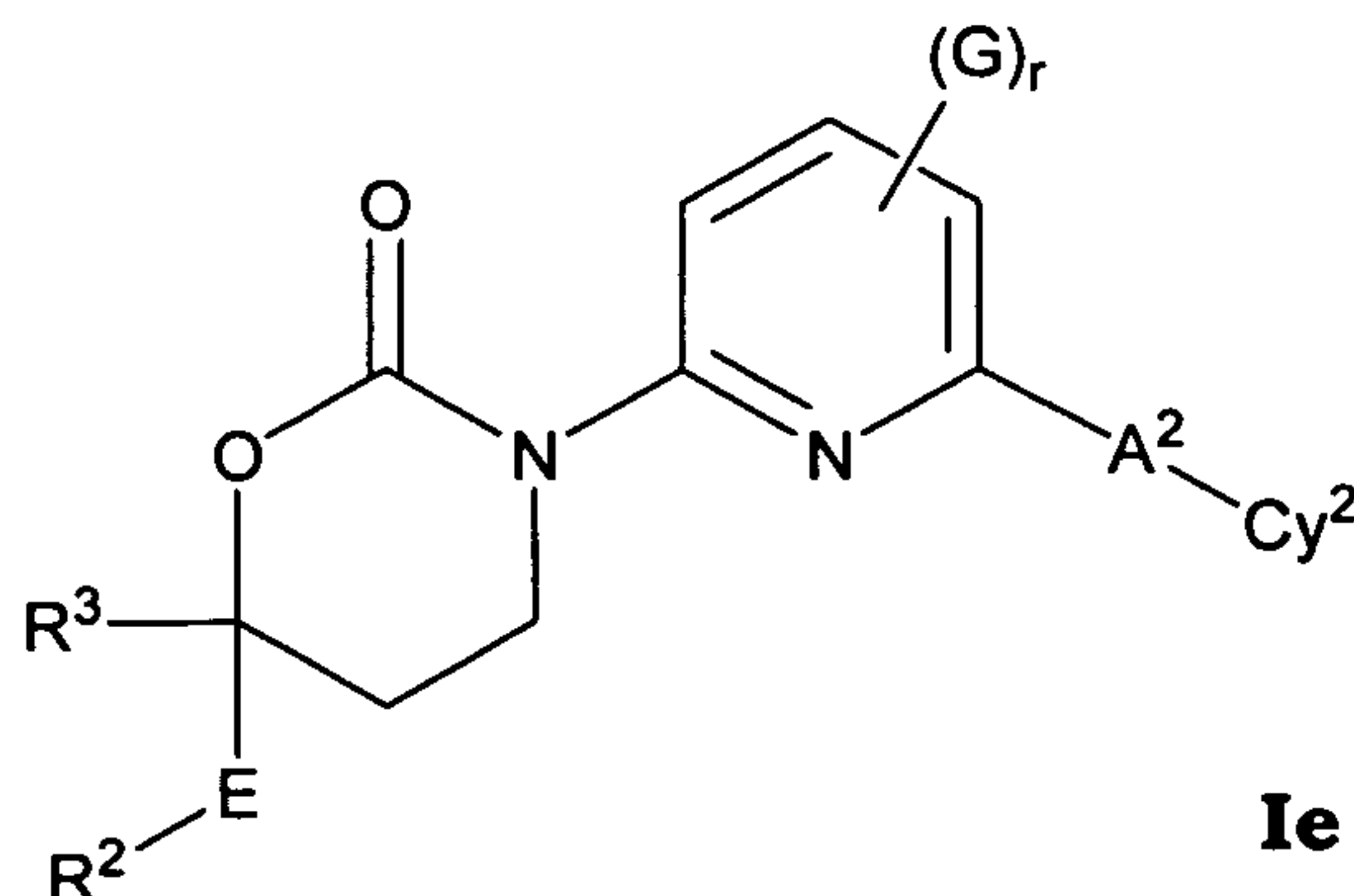
m is 0, 1, 2, 3 or 4; and

X 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, 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, 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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51. The compound of any one of claims 1-5, wherein the compound is of Formula (Ie):



wherein;

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

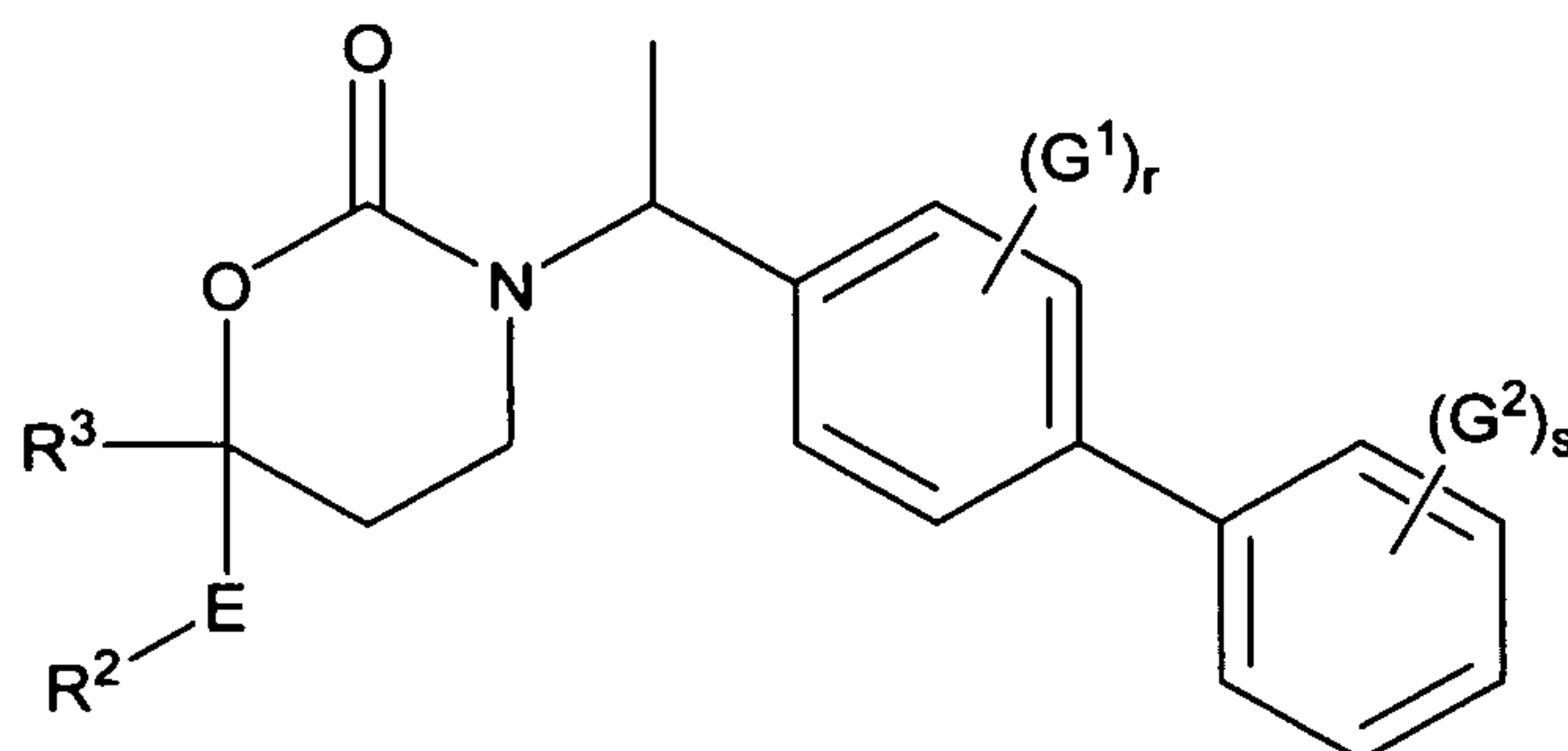
G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl,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

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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.

- 5 52. The compound of any one of claims 1-5, wherein the compound is of Formula (If):



If

wherein; and

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

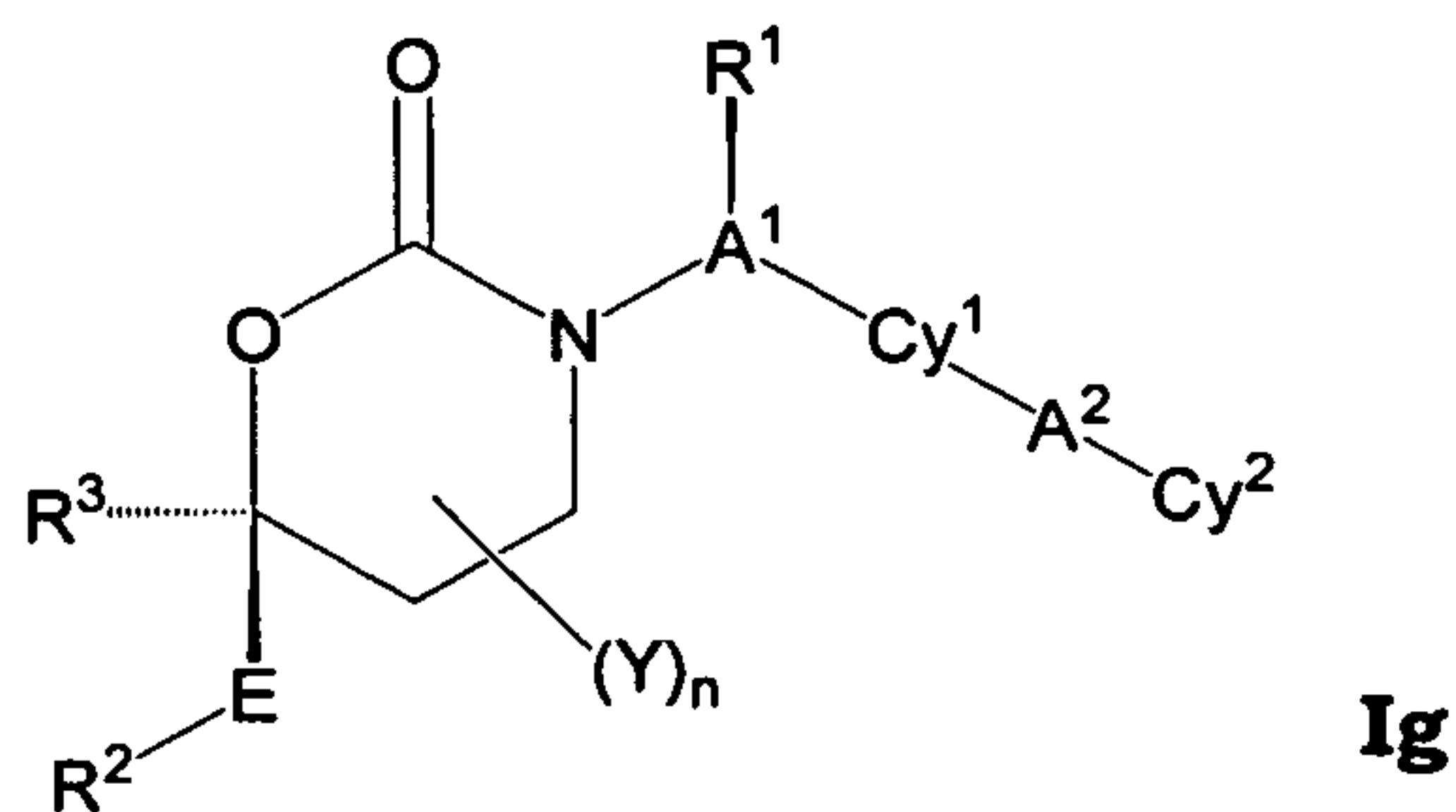
- 10 G¹ and G² are independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (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, 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-

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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)alkoxy and (C₁-C₆)alkylcarbonyl;

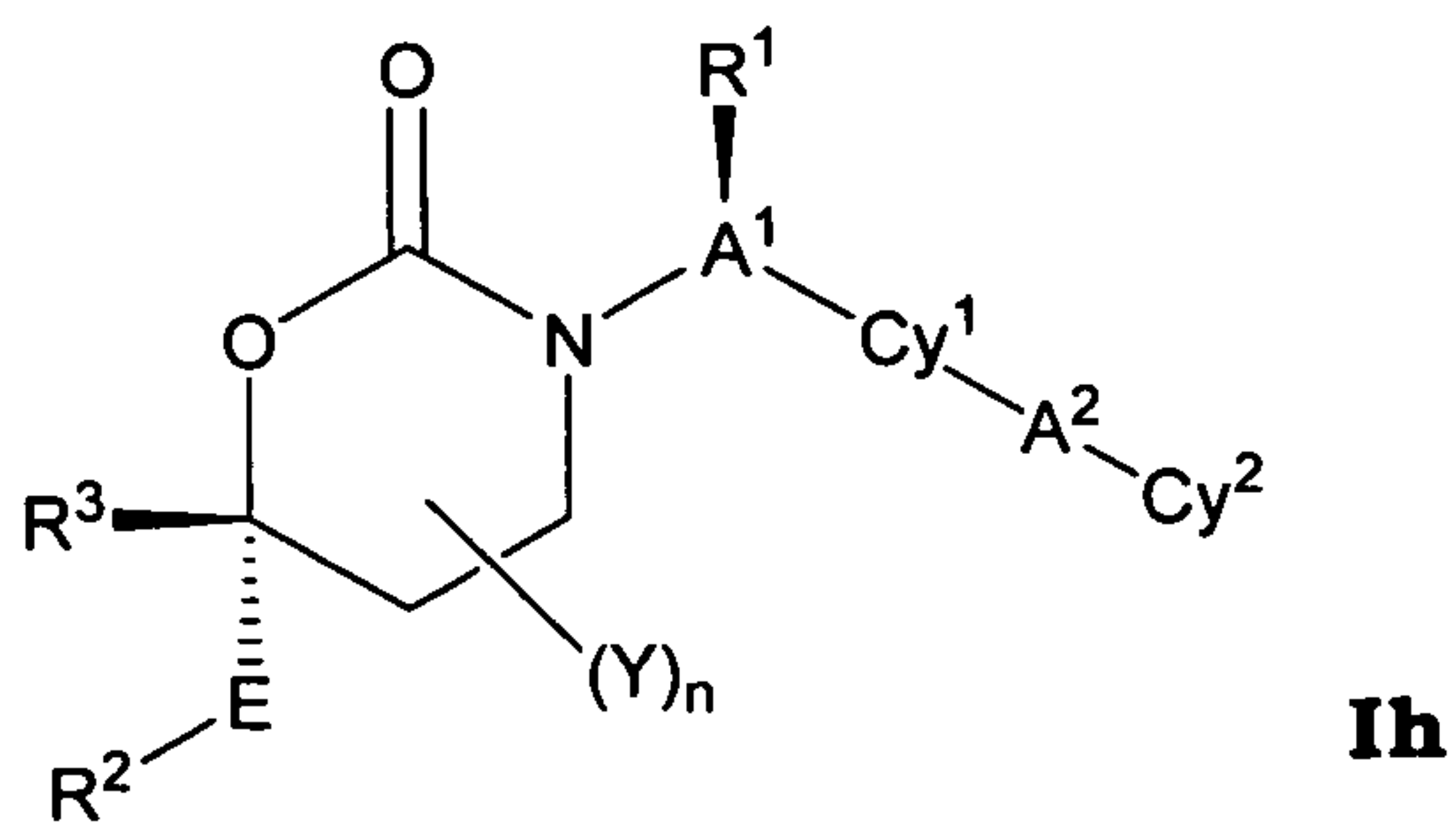
5 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

53. The compound of any one of claims 1-5, wherein the compound is of Formula (Ig):



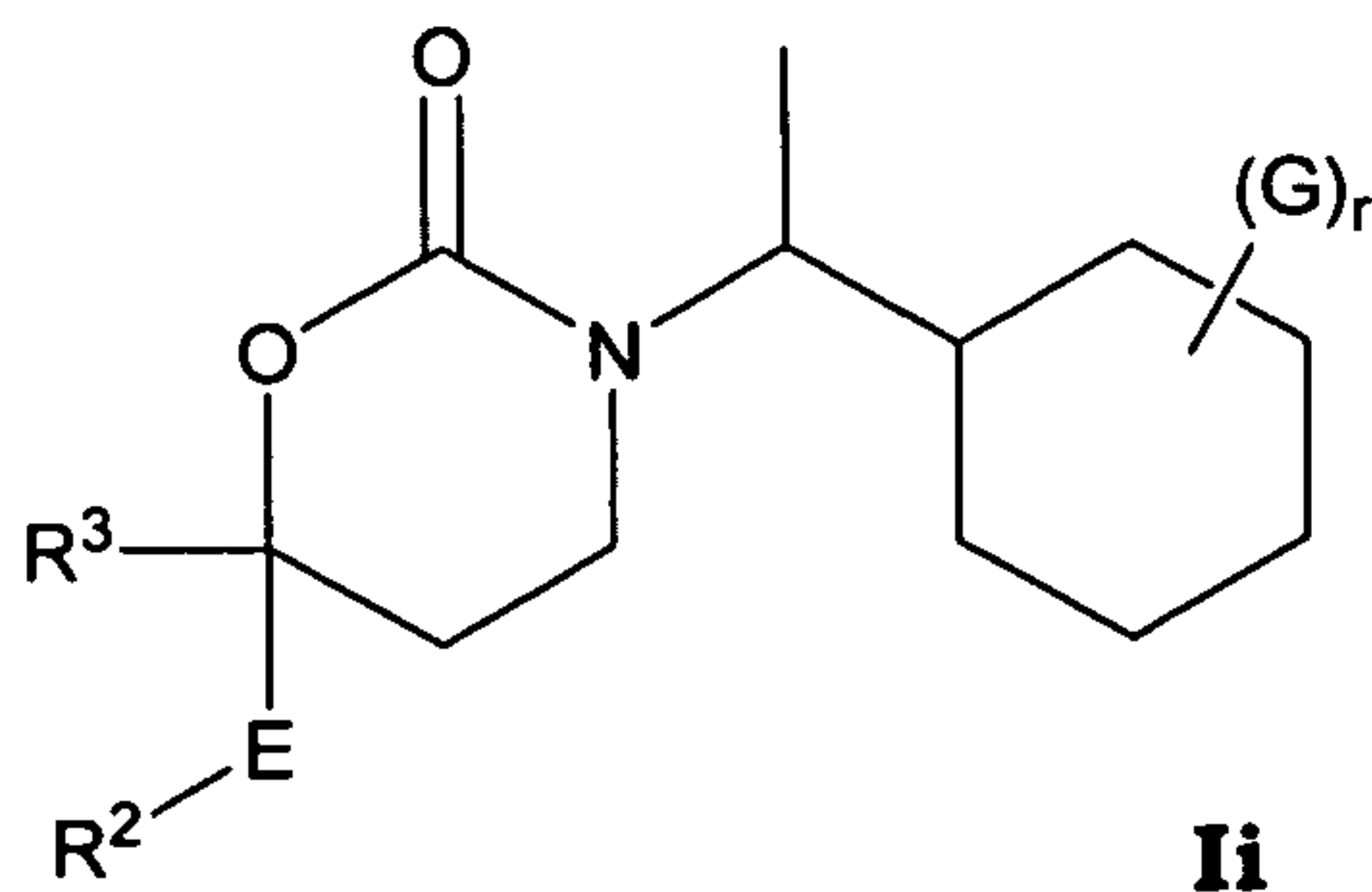
10 or a pharmaceutically acceptable salt thereof.

54. The compound of any one of claims 1-5, wherein the compound is of Formula (Ih):



15 or a pharmaceutically acceptable salt thereof.

55. The compound of any one of claims 1-5, wherein the compound is of Formula (Ii):



20 wherein;

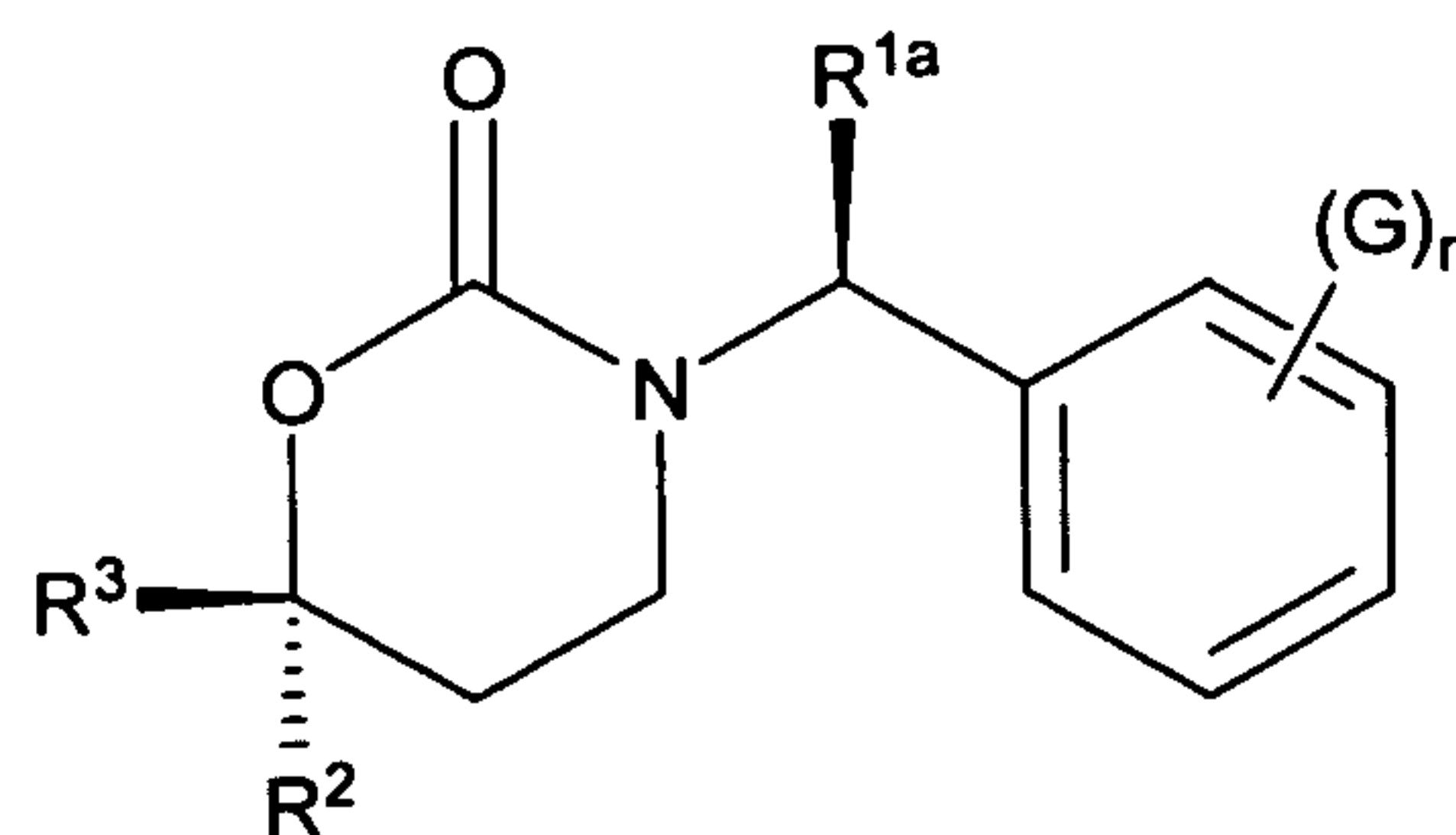
r is 0, 1, 2, 3 or 4; and

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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, 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, 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.

56. The compound of any one of claims 1-5, wherein the compound is of Formula (Ij):



Ij, wherein

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R^{1a} is methyl or ethyl;

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

each G is independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl,

5 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-

10 alkylthio, 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-

15 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, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-

20 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.

57. The compound of any one of claims 1-5, wherein the compound is of

30 Formula (Ik):

1k

30

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Cy¹ is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl, each 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, 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(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, 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 if the substitution is either meta or para to A¹, the substituents may also include optionally substituted cycloalkyl, optionally substituted halocycloalkyl or optionally substituted heteroaryl;

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;

Cy² is *meta* or *para* to A₁ and is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl 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-

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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-thiaoxazole 1,1-dioxide,
 tetrahydro-2H-1,2-thiazine 1,1-dioxide, hexahydro-1,2,6-thiadiazine 1,1-dioxide,
 tetrahydro-1,2,5-thiadiazole 1,1-dioxide isothiazolidine 1,1-dioxide, 6-oxo-1,6-
 dihydropyridazin-3-yl, 6-oxo-1,6-dihydropyridazin-4-yl, 5-oxo-4,5-dihydro-1H-1,2,4-
 triazol-3-yl and 5-oxo-4,5-dihydro-1H-imidazol-2-yl 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)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, 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;

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

n is 0, 1 or 2;

E is (a) a bond or (b) (C₁-C₃)alkylene or (C₁-C₂)alkylenyloxy, wherein the O is
 5 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 and is optionally substituted with up to 4 groups independently selected from fluorine, chlorine,
 10 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,
 15 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)cycloalkyl-
 20 alkanesulfinyl, (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-C₆)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,
 30 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;

R³ is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₅)cycloalkyl(C₁-C₄)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo,

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R^4 , R^4O- , $(R^4)_2N-$, R^4O_2C- , $R^4C(=O)O-$, R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4$,
 $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$,
 $(R^4)_2NC(=NCN)NR^4-$, $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$,
 $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$, $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$,
5 $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$, $R^4OS(=O)_2NHC(=O)-$,
 $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$, $(R^4)_2NS(=O)_2NHC(=O)-$,
 $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$, $R^4C(=O)NHS(=O)_2-$,
 $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$, $R^4OC(=O)NHS(=O)_2-$,
 $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$, $(R^4)_2NC(=O)NHS(=O)_2-$,
10 $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$, spirocycloalkyl; heterocyclyl
(which in turn may be optionally substituted with alkyl, haloalkyl, halogen or oxo),
heteroaryl (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), aryl-
15 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 heteroarylamino
(which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio,
alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H , $CONH_2$, N-
20 monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); and

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

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

61. A pharmaceutical composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) the compound in any one of claims 1-57; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

62. A pharmaceutical composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) the compound in any one of claims 1-57; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

provided that if (a) A^1 is a bond or alkylene, (b) Cy^1 is (C_3-C_7) cycloalkyl, aryl or heteroaryl, and (c) E is a bond, then R^2 is not 3, 4-dialkoxyphenyl optionally

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substituted with halogen or hydroxy, or 3, 4-dicycloalkoxyphenyl optionally substituted with halogen or 3, 4-dialkoxyalkoxyphenyl optionally substituted with halogen.

5 63. The pharmaceutical composition of Claim 61 or 62:
n is 0;

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

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Cy¹ is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl, each 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, 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(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, 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 if the substitution is either meta or para to A¹, the

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substituents may also include optionally substituted cycloalkyl, optionally substituted halocycloalkyl or optionally substituted heteroaryl;

Cy² is *meta* or *para* to A₁ and is (a) hydrogen or (b) aryl, heteroaryl, cycloalkyl
 5 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-
 10 dioxolane, 1,3-dithiolane, 1,3-dioxane, 1,4-dioxane, 1,3-dithiane, 1,4-dithiane, oxazolidin-2-one, imidazolidin-2-one, imidazolidine-2,4-dione, tetrahydropyrimidin-2(1H)-one, morpholine, N-methylmorpholine, morpholin-3-one, 1,3-oxazinan-2-one, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-1,2,5-thiaoxazole 1,1-dioxide, tetrahydro-2H-1,2-thiazine 1,1-dioxide, hexahydro-1,2,6-thiadiazine 1,1-dioxide,
 15 tetrahydro-1,2,5-thiadiazole 1,1-dioxide isothiazolidine 1,1-dioxide, 6-oxo-1,6-dihydropyridazin-3-yl, 6-oxo-1,6-dihydropyridazin-4-yl, 5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl and 5-oxo-4,5-dihydro-1H-imidazol-2-yl 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-
 20 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,
 25 (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-
 30 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,
 35 di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-

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C_6)alkylsulfonylamino(C_1 - C_6)alkyl, (C_1 - C_6)alkoxycarbonyl(C_1 - C_6)alkoxy, (C_1 - C_6)alkoxy(C_1 - C_6)alkyl, halo(C_1 - C_6)alkoxy(C_1 - C_6)alkyl, hydroxy(C_1 - C_6)alkoxy, heteroaryl, oxo, amino(C_1 - C_6)alkyl, (C_1 - C_6)alkylamino(C_1 - C_6)alkyl, di(C_1 - C_6)alkylamino(C_1 - C_6)alkyl amino(C_2 - C_6)alkoxy, (C_1 - C_6)alkylamino(C_2 - C_6)alkoxy, di(C_1 - C_6)alkylamino(C_2 - C_6)alkoxy and (C_1 - C_6)alkylcarbonyl.

64. A compound of any one of Claims 1-5 wherein

R^3 is selected from (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, (C_1 - C_3)alkoxy(C_1 - C_3)alkoxy or (C_1 - C_3)alkoxy(C_1 - C_3)alkyl and is substituted with one to four groups independently selected from cyano, oxo, R^4O -, $(R^4)_2N$ -, R^4O_2C -, R^4S , $R^4S(=O)$ -, $R^4S(=O)_2$ -, $R^4C(=O)NR^4$ -, $(R^4)_2NC(=O)$ -, $(R^4)_2NC(=O)O$ -, $(R^4)_2NC(=O)NR^4$ -, $R^4OC(=O)NR^4$ -, $(R^4)_2NC(=NCN)NR^4$ -, $(R^4O)_2P(=O)O$ -, $(R^4O)_2P(=O)NR^4$ -, $R^4OS(=O)_2NR^4$ -, $(R^4)_2NS(=O)_2O$ -, $(R^4)_2NS(=O)_2NR^4$ -, $R^4S(=O)_2NR^4$ -, $R^4SO_2NR^4$ -, $R^4S(=O)_2NHC(=O)$ -, $R^4S(=O)_2NHC(=O)O$ -, $R^4S(=O)_2NHC(=O)NR^4$ -, $R^4OS(=O)_2NHC(=O)$ -, $R^4OS(=O)_2NHC(=O)O$ -, $R^4OS(=O)_2NHC(=O)NR^4$ -, $(R^4)_2NS(=O)_2NHC(=O)$ -, $(R^4)_2NS(=O)_2NHC(=O)O$ -, $(R^4)_2NS(=O)_2NHC(=O)NR^4$ -, $R^4C(=O)NHS(=O)_2$ -, $R^4C(=O)NHS(=O)_2O$ -, $R^4C(=O)NHS(=O)_2NR^4$ -, $R^4OC(=O)NHS(=O)_2$ -, $R^4OC(=O)NHS(=O)_2O$ -, $R^4OC(=O)NHS(=O)_2NR^4$ -, $(R^4)_2NC(=O)NHS(=O)_2$ -, $(R^4)_2NC(=O)NHS(=O)_2O$ - and $(R^4)_2NC(=O)NHS(=O)_2NR^4$ -;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.