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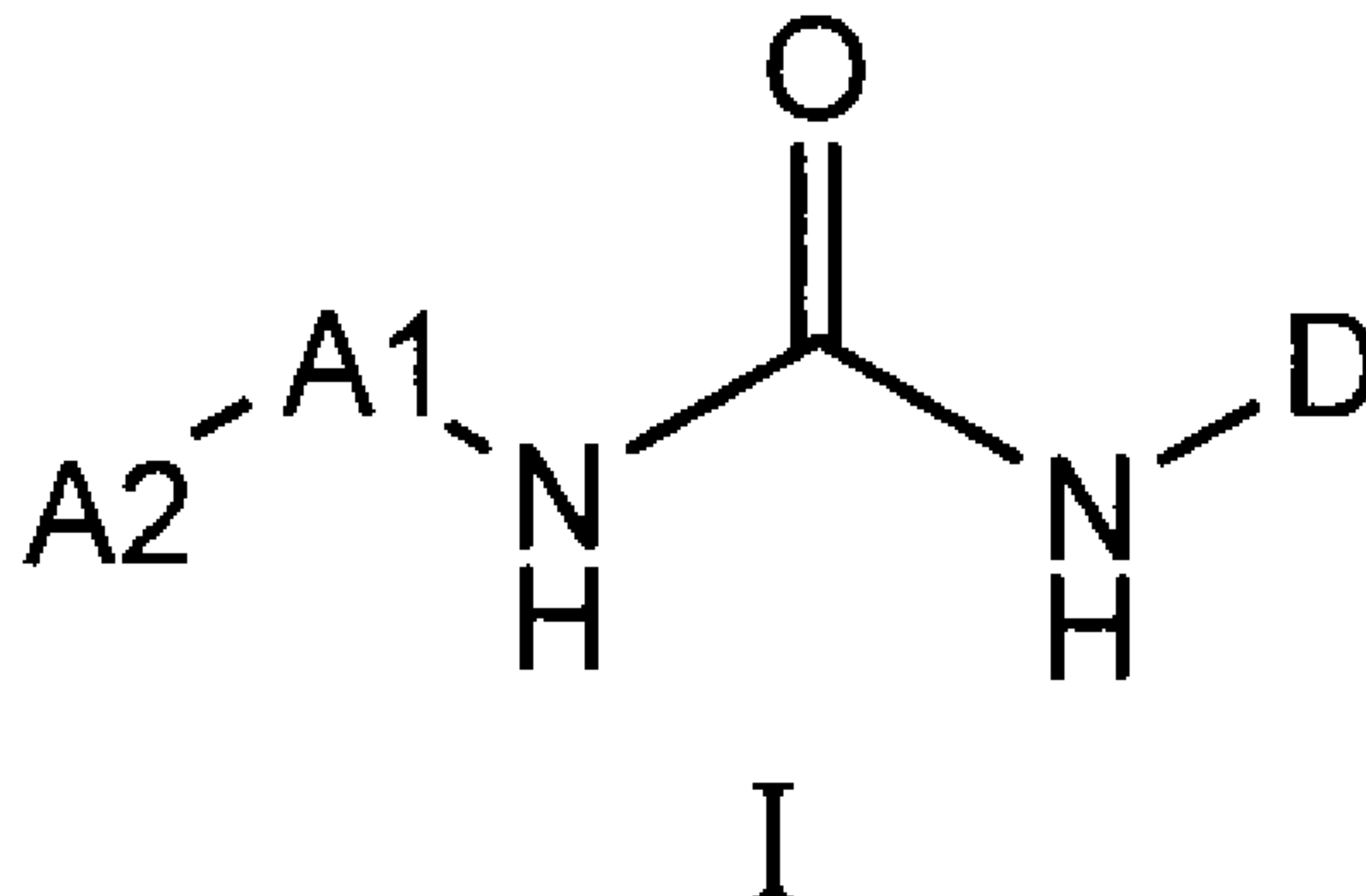
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(54) **Titre : DERIVES D'UREE EN TANT QUE MODULATEURS D'ENZYME**
(54) **Title: UREA DERIVATIVES AS ENZYME MODULATORS**



(57) **Abrégé/Abstract:**

Novel compounds and methods of using those compounds for the treatment of inflammatory conditions, hyperproliferative diseases, cancer, and diseases characterized by hypervascularization are provided. In a preferred embodiment, modulation of the activation state of p38 kinase protein ab1 kinase protein, bcr-ab1 kinase protein, braf kinase protein, VEGFR kinase protein, or PDGFR kinase protein comprises the step of contacting said kinase protein with the novel compounds.

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(54) Title: ENZYME MODULATORS AND TREATMENTS

(57) Abstract: Novel compounds and methods of using those compounds for the treatment of inflammatory conditions, hyperproliferative diseases, cancer, and diseases characterized by hypervascularization are provided. In a preferred embodiment, modulation of the activation state of p38 kinase protein ab1 kinase protein, bcr-ab1 kinase protein, braf kinase protein, VEGFR kinase protein, or PDGFR kinase protein comprises the step of contacting said kinase protein with the novel compounds.

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
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UREA DERIVATIVES AS ENZYME MODULATORS

Field of the Invention

The present invention relates to novel kinase inhibitors and modulator compounds useful for the treatment of various diseases. More particularly, the invention is concerned with such compounds, kinase/compound adducts, methods of treating diseases, and methods of synthesis of the compounds. Preferably, the compounds are useful for the modulation of kinase activity of C-Abl, c-Kit, VEGFR, PDGFR, Raf and P38 kinases and disease polymorphs thereof.

Background of the invention

Several members of the protein kinase family have been clearly implicated in the pathogenesis of various proliferative diseases and thus represent important targets for treatment of these diseases. Some of the proliferative diseases relevant to this invention include cancer, rheumatoid arthritis, atherosclerosis, and retinopathies. Important examples of kinases which have been shown to cause or contribute to the pathogenesis of these diseases include C-Abl kinase and the oncogenic fusion protein BCR-Abl kinase; PDGF receptor kinase; VEGF receptor kinases; MAP kinase p38 α ; and the RAF kinase family.

C-Abl kinase is an important non-receptor tyrosine kinase involved in cell signal transduction. This ubiquitously expressed kinase--- upon activation by upstream signaling factors including growth factors, oxidative stress, integrin stimulation, and ionizing radiation--localizes to the cell plasma membrane, the cell nucleus, and other cellular compartments including the actin cytoskeleton (Van Etten, *Trends Cell Biol.* (1999) 9: 179). There are two

normal isoforms of Abl kinase: Abl-1A and Abl-1B. The N-terminal half of c-Abl kinase is important for autoinhibition of the kinase domain catalytic activity (Pluk *et al*, *Cell* (2002) 108: 247). Details of the mechanistic aspects of this autoinhibition have recently been disclosed (Nagar *et al*, *Cell* (2003) 112: 859). The N-terminal myristoyl amino acid residue of Abl-1B has been shown to intramolecularly occupy a hydrophobic pocket formed from alpha-helices in the C-lobe of the kinase domain. Such intramolecular binding induces a novel binding area for intramolecular docking of the SH2 domain and the SH3 domain onto the kinase domain, thereby distorting and inhibiting the catalytic activity of the kinase. Thus, an intricate intramolecular negative regulation of the kinase activity is brought about by these N-terminal regions of c-Abl kinase. An aberrant dysregulated form of c-Abl is formed from a chromosomal translocation event, referred to as the Philadelphia chromosome (P.C. Nowell *et al*, *Science* (1960) 132: 1497; J.D. Rowley, *Nature* (1973) 243: 290). This abnormal chromosomal translocation leads aberrant gene fusion between the Abl kinase gene and the breakpoint cluster region (BCR) gene, thus encoding an aberrant protein called Bcr-Abl (G. Q. Daley *et al*, *Science* (1990) 247: 824; M. L. Gishizky *et al*, *Proc. Natl. Acad. Sci. USA* (1993) 90: 3755; S. Li *et al*, *J. Exp. Med.* (1999) 189: 1399). the Bcr-Abl fusion protein does not include the regulatory myristoylation site (B. Nagar *et al*, *Cell* (2003) 112: 859) and as a result functions as an oncoprotein which causes chronic myeloid leukemia (CML). CML is a malignancy of pluripotent hematopoietic stem cells. The p210 form of Bcr-Abl is seen in 95% of patients with CML, and in 20% of patients with acute lymphocytic leukemia. A p185 form has also been disclosed and has been linked to being causative of up to 10% of patients with acute lymphocytic leukemia .

Growth factor receptor kinases contribute to the growth and metastasis of tumors by stimulating the proliferation of endothelial cells, fibroblasts, smooth muscle cells, and matrix proteins. Conditions such as hypoxia can induce tumor cells to secrete growth factors which subsequently result in the growth of new blood vessels to support the tumor. These growth factors include platelet derived growth factor (PDGF) and transforming growth factor-beta (TGF-beta), which subsequently stimulate secretion of other growth factors including vascular endothelial growth factor (VEGF), fibroblast growth factor, and epidermal growth factor (EGF). The formation of new blood vessels, which is known as angiogenesis, also provides the tumor with a route to metastasize to remote secondary sites. Inhibiting angiogenic factors that support stromal growth has been proposed as a useful therapy for treating cancers (R.M. Shaheen *et al* , *Cancer Research* (1999) 59: 5412; R.M. Shaheen *et*

al, *Cancer Research* (2001) 61: 1464). Mutations of the PGDF receptor have also been identified which constitutively active in absence of growth factor. VEGF can also stimulate the formation of new lymphatic vessels through direct action on the so-called VEGF-3 receptor, providing yet another pathway for tumor metastasis. Among the three known VEGF receptors, in particular the so-called VEGFR2 (otherwise known as the kinase insert domain-containing receptor tyrosine kinase or KDR) has been demonstrated to be responsible for the role of VEGF in tumor angiogenesis.

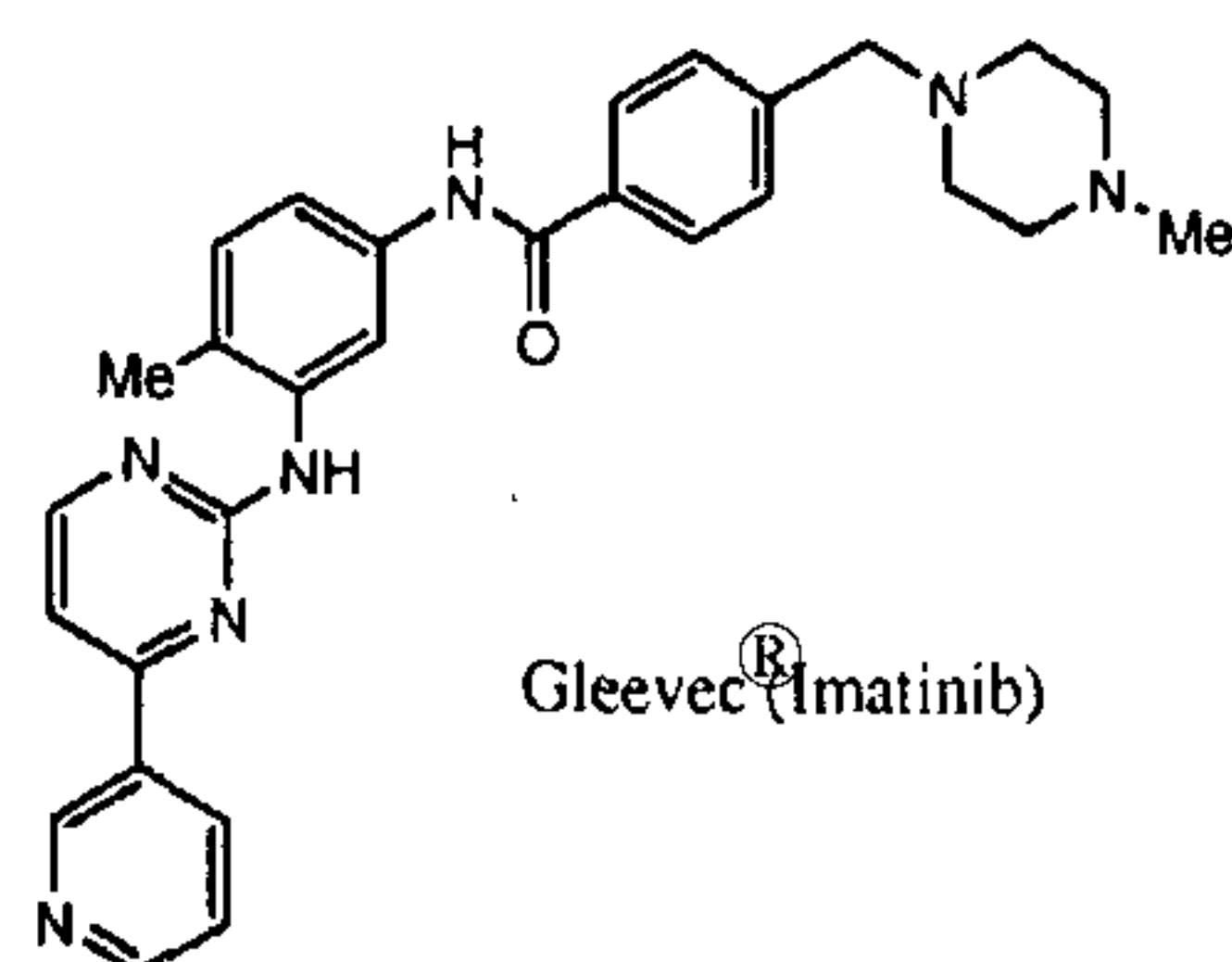
A major signaling pathway downstream of cell surface growth factor receptor activation is the Ras-RAF-MEK-ERK-MAP kinase pathway (Peyssonnaud, C. *et al*, *Biol. Cell* (2001) 93: 53-62, Cancers arise when mutations occur in one or more of the proteins involved in this signaling cascade. Cell proliferation and differentiation become dysregulated and cell survival mechanisms are activated which allow unregulated cancer cells to override protective programmed cell death surveillance. Mutations in the p21-Ras protein have been shown to be a major cause of dysregulation of this signaling pathway, leading to the development of human cancers. P21-Ras mutations have been identified in approximately 30% of human cancers (Bolton *et al*, *Ann. Rep. Med. Chem.* (1994) 29: 165-174). Cancer-causing mutations in the P21-Ras protein lead to a constitutively active signaling cascade, causing unregulated activation of the downstream components of the RAF-MEK-ERK-MAP kinase pathway (Magnuson *et al.*, *Semin.Cancer Biol.* (1994) 5: 247-253). The three RAF kinases which participate in this signaling cascade are known as ARAF, BRAF, and CRAF (Peyssonnaud, C. *et al*, *Biol. Cell* (2001) 93: 53-62; Avruch, J., *Recent Prog. Horm. Res.* (2001) 56: 127-155; Kolch, W., *Biochem. J.* (2000) 351: 289-305). These RAF kinase isoforms are all activated by Ras, and thus are activated in cancers that result from mutated and upregulated p21-Ras protein activity. In addition to activation of this signaling cascade at the initial p21-Ras protein level, mutations have also been found in BRAF kinase which results in activation of the cascade downstream from p21-Ras (Davies, H., *et al*, *Nature* (2002) 417: 949-954). A dominant single site mutation at position 599 in the BRAF kinase was shown to be particularly aggressive and linked to approximately 80% of the observed human malignant melanomas. This mutation substitutes the negatively charged amino acid glutamic acid for the normally occurring neutral amino acid valine. This single site mutation is sufficient to render the mutated BRAF kinase constitutively active, resulting in signaling pathway dysregulation and human cancer. Hence small molecule inhibitors of BRAF kinase

are a rational approach to the treatment of human malignancy, whether the signaling mutation is at the level of the upstream p21-Ras protein or at the level of BRAF kinase.

The MAP kinase p38 α has recently been identified as an important mechanistic target for the treatment of inflammatory diseases. Inhibition of the MAP kinase p38-*alpha* has been demonstrated to result in the suppression the production and release the proinflammatory mediators TNF- α , IL-1 β , IL-6, IL-8 and other proinflammatory cytokines (Chen, Z. *et al*, *Chem. Rev.* (2001) 101: 2449). Recently, p38-*alpha* kinase has been implicated in the regulation of tissue factor expression in monocytes, suggesting a role for inhibition of p38-*alpha* kinase in the treatment of thrombotic disorders and atherosclerosis (Chu, A.J., *et al*, *J. Surg. Res.* (2001) 101: 85-90; Eto, M., *et al*, *Circulation* (2002) 105: 1756-1759). The p38-*alpha* kinase has also been shown to be involved in thrombin-induced proinflammatory conditions (V. Marin, *et al*, *Blood*, August 1, 2001, 98: 667-673). Validation of this approach has been achieved by the successful application of various protein therapeutic agents for the treatment of severe chronic inflammatory disease. Monoclonal antibodies to TNF have shown effectiveness in the treatment of rheumatoid arthritis, ulcerative colitis, and Crohn's disease (Rankin, E.C.C., *et al*, *British J. Rheum.* (1997) 35: 334-342; Stack, W.A., *et al*, *Lancet* (1997) 349: 521-524). Enbrel[®] (etanercept), a soluble TNF receptor, has been developed by Immunex, Inc., and marketed currently by Amgen for the treatment of rheumatoid arthritis (Brower *et al*, *Nature Biotechnology* (1997) 15: 1240; Pugsley, M.K., *Curr. Opin. Invest. Drugs* (2001) 2: 1725). Ro 45-2081, a recombinant soluble TNF- α receptor chimeric protein, has also shown effectiveness in the treatment of the acute phase of lung injury and in animal models of allergic lung disease (Renzetti, *et al*, *Inflamm Res.* (1997) 46: S143). Remicade[®] (infliximab) is a monoclonal TNF- α antibody that has shown effectiveness in the treatment of rheumatoid arthritis and Crohn's disease (Bondeson, J. *et al*, *Int. J. Clin. Pract.* (2001) 55: 211).

Importantly, small molecule inhibitors of kinase activity have been shown to produce therapeutic benefit as anticipated. The most important example thus far is Gleevec[®] (Imatinib), which is an inhibitor of BCR-Abl kinase (J. Zimmermann *et al*, WO 99/03854; N. von Bubnoff *et al*, *Cancer Research* (2003) 63: 6395; B. J. Druker *et al*, *Nature Medicine* (1996) 2: 561; J. Zimmermann *et al*, *Bioorganic and Medicinal Chemistry Letters* (1997) 7: 187). Gleevec[®] has been shown to produce clinical remissions in CML patients. However,

resistance to the effects of Gleevec[®] have often been encountered (M. E. Gorre *et al*, *Science* (2001) 293: 876). Over 17 mutations of Bcr-Abl kinase have been associated with Gleevec[®] resistance (N. von Bubnoff *et al*, *Lancet* (2002) 359: 487; S. Branford *et al*, *Blood* (2002) 99: 3472; C. Roche-Lestienne *et al*, *Blood* (2002) 100: 1014; N.P. Shah *et al*, *Cancer Cell* (2002) 2: 117; A. Hochhaus *et al*, *Leukemia* (2002) 16: 2190; H.K. Al-Ali *et al*, *Hematology* (2004) 5: 55). These mutations are primarily found in the kinase active site domain of Bcr-Abl, and frequently occur in regions proximal to the ATP binding pocket.



The majority of small molecule kinase inhibitors that have been reported have been shown to bind in one of three ways. Most of the reported inhibitors interact with the ATP binding domain of the active site and exert their effects by competing with ATP for occupancy. Other inhibitors have been shown to bind to a separate hydrophobic region of the protein known as the “DFG-in-conformation” pocket, and still others have been shown to bind to both the ATP domain and the “DFG-in-conformation” pocket. Examples specific to inhibitors of RAF kinases can be found in Lowinger *et al*, *Current Pharmaceutical Design* (2002) 8: 2269-2278; Dumas, J. *et al.*, *Current Opinion in Drug Discovery & Development* (2004) 7: 600-616; Dumas, J. *et al*, WO 2003068223 A1 (2003); Dumas, J., *et al*, WO 9932455 A1 (1999), and Wan, P.T.C., *et al*, *Cell* (2004) 116: 855-867

Physiologically, kinases are regulated by a common activation/deactivation mechanism wherein a specific activation loop sequence of the kinase protein binds into a specific pocket on the same protein which is referred to as the switch control pocket. Such binding occurs when specific amino acid residues of the activation loop are modified for example by phosphorylation, oxidation, or nitrosylation. The binding of the activation loop into the switch pocket results in a conformational change of the protein into its active form (Huse, M. and Kuriyan, J. *Cell* (109) 275-282.)

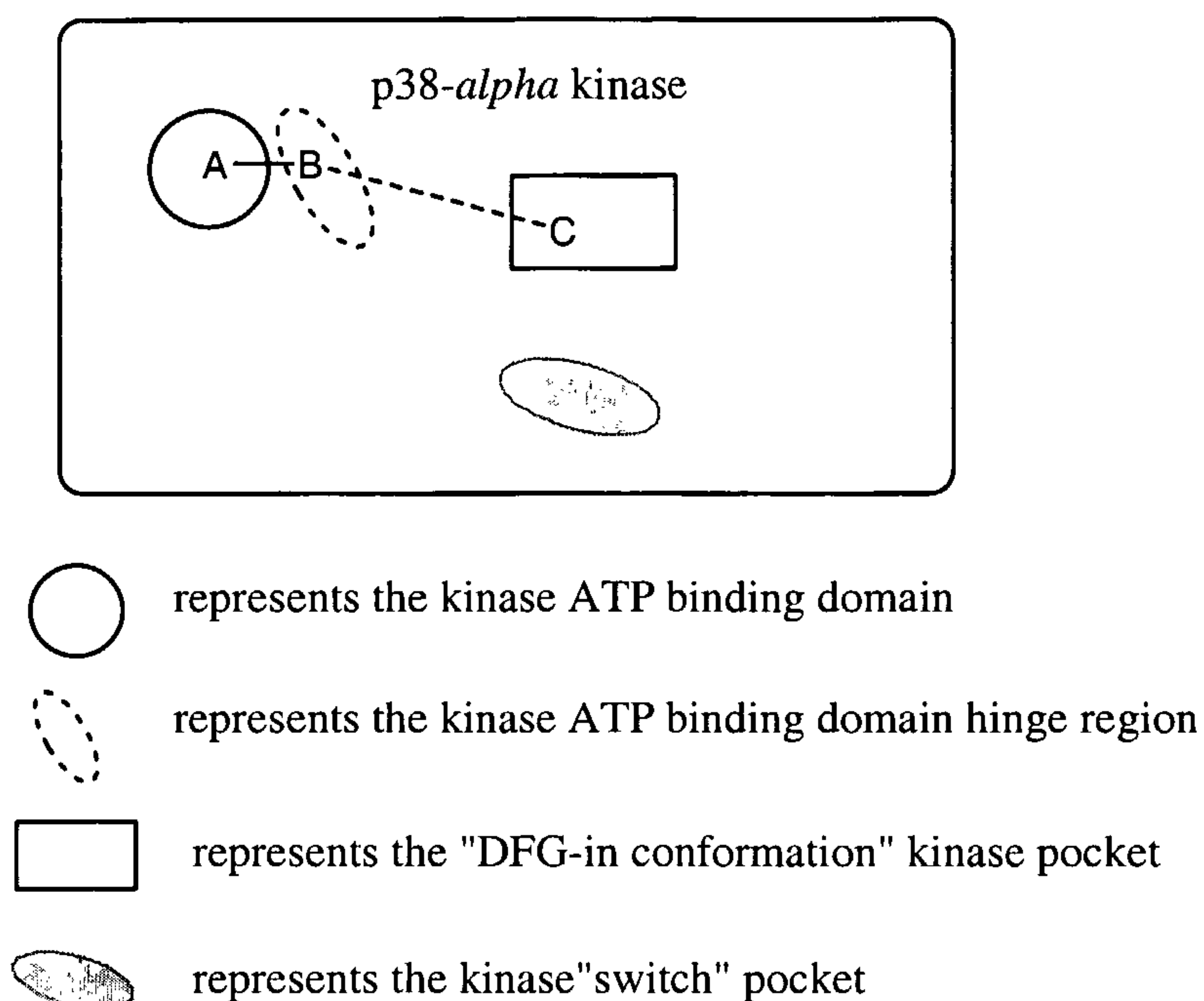
Summary of the Invention

The present invention describes novel potent and selective inhibitors of CAbl kinase, VEGFR2/KDR kinase, and BRAF kinase. The compounds of this invention inhibit kinase

activity in a novel way by binding into the “switch pocket” remote from the ATP-cofactor pocket with or without concomitant binding into the “DFG-in-conformation” pocket. X-ray structures determined from small molecule/BRAF co-crystals have confirmed this novel mode of binding to the kinase by the compounds of this present invention, and illustrate the novel features of this binding mode when compared to inhibitors which anchor or bind into the ATP pocket of BRAF kinase. The novel inhibitors of the present invention in some cases also exhibit a preference for inhibiting the oncogenic mutant form of a kinase (V599E-BRAF) and a sparing of normal wild-type kinase that lack the cancer-causing mutation, wherein the oncogenic mutation is a modification of a critical binding amino acid residue of the switch control pocket. An example of this profile has been identified for BRAF, wherein mutation of the valine 599 residue to a glutamic acid residue results in an oncogenic form of BRAF and for which it has been found that compounds of this invention inhibit the oncogenic mutant form of BRAF but not the wild type BRAF. This desirable feature of inhibitor selectivity enables the use of a BRAF inhibitor to treat mammalian cancer caused by mutant V559E BRAF kinase, while sparing the normal wildtype BRAF kinase present in non-cancerous cells. Enhanced safety and selectivity realized from this “wild-type kinase-sparing” provides safer inhibitors that target the cancer-causing forms of BRAF kinase.

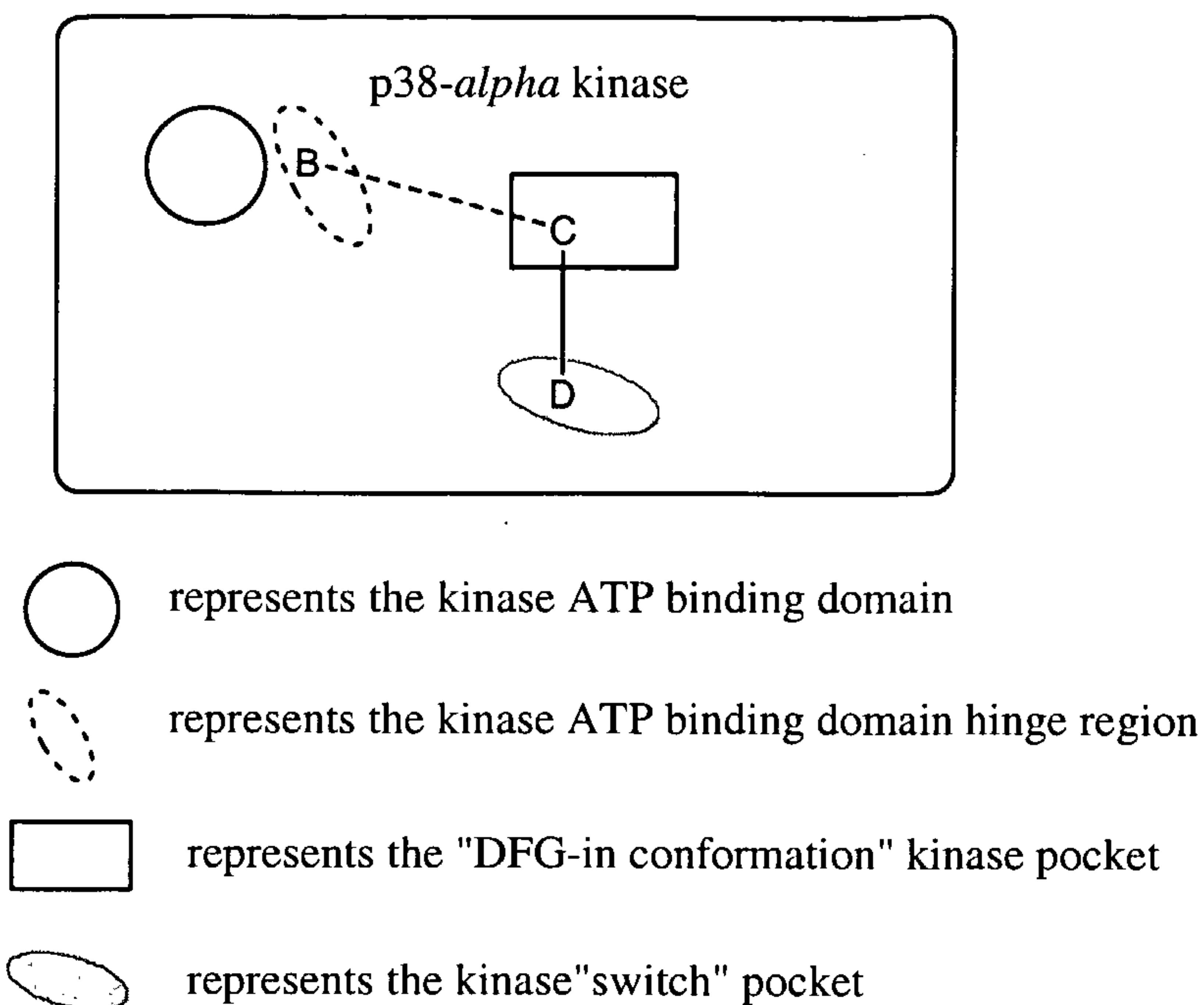
Figures 1 and 2 further illustrates the novel binding interaction for the compounds of this invention with kinases. In Figure 1, the known interactions of kinase inhibitors reported previously are defined as directed to a combination of the ATP binding domain, an adjacent binding area known as the ATP binding domain hinge region, and in some cases a third domain known as the “DFG-in conformation” kinase pocket.

Figure 1. Illustration of the kinase binding domains of known kinase inhibitors



The binding modality of the compounds of this invention is illustrated in Figure 2. The unique feature is the necessary engagement of another binding domain within the kinase referred to as the switch pocket. Compounds of this invention uniquely and necessarily bind within the switch pocket, and optionally the "DFG-in conformation" domain, and optionally to the ATP binding domain hinge region. This unique binding modality confers upon compounds of this invention a novel mechanism to modulate kinase activity as well as significant advantages over previously described kinase inhibitors in achieving a therapeutically important degree of selectivity for the preferred target over inhibitors which occupy the ATP binding domain. The novel binding modality of the compounds of this invention also avoids mutations within the ATP binding domain which commonly confer resistance to inhibition by compounds which require interaction with the ATP binding domain.

Figure 2. Illustration of the binding modality for compounds of this invention to kinases



Compounds of the present invention find utility in the treatment of mammalian cancers and especially human cancers including but not limited to malignant melanoma, colorectal cancer, ovarian cancer, papillary thyroid carcinoma, non small cell lung cancer, and mesothelioma. Compounds of the present invention also find utility in the treatment of rheumatoid arthritis and retinopathies including diabetic retinal neuropathy and macular degeneration.

Description of the Preferred Embodiments

The following descriptions refer to various compounds and moieties thereof. Generally, the following definitions apply to these descriptions, with the understanding that in some instances the descriptions are further limited. However, as broadly defined, the following definitions apply.

Carbocyclyl refers to monocyclic saturated carbon rings taken from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl;

Aryl refers to monocyclic or fused bicyclic ring systems characterized by delocalized π electrons (aromaticity) shared among the ring carbon atoms of at least one carbocyclic ring; preferred aryl rings are taken from phenyl, naphthyl, tetrahydronaphthyl, indenyl, and indanyl;

Heteroaryl refers to monocyclic or fused bicyclic ring systems characterized by delocalized π electrons (aromaticity) shared among the ring carbon or heteroatoms including nitrogen, oxygen, or sulfur of at least one carbocyclic or heterocyclic ring; heteroaryl rings are taken from, but not limited to, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, indolyl, isoindolyl, isoindolinyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl, phthalazinyl, benzodioxyl, indolinyl, benzisothiazoline-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzoxapinyl, or benzoxazepinyl;

Heterocyclyl refers to monocyclic rings containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur and wherein there is not delocalized π electrons (aromaticity) shared among the ring carbon or heteroatoms; heterocyclyl rings include, but are not limited

to, oxetanyl, azetadiny, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, homotropanyl;

Poly-aryl refers to two or more monocyclic or fused bicyclic ring systems characterized by delocalized π electrons (aromaticity) shared among the ring carbon atoms of at least one carbocyclic ring wherein the rings contained therein are optionally linked together.

Poly-heteroaryl refers to two or more monocyclic or fused bicyclic systems characterized by delocalized π electrons (aromaticity) shared among the ring carbon or heteroatoms including nitrogen, oxygen, or sulfur of at least one carbocyclic or heterocyclic ring wherein the rings contained therein are optionally linked together, wherein at least one of the monocyclic or fused bicyclic rings of the poly-heteroaryl system is taken from heteroaryl as defined broadly above and the other rings are taken from either aryl, heteroaryl, or heterocyclyl as defined broadly above;

Poly-heterocyclyl refers to two or more monocyclic or fused bicyclic ring systems containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur and wherein there is not delocalized π electrons (aromaticity) shared among the ring carbon or heteroatoms wherein the rings contained therein are optionally linked, wherein at least one of the monocyclic or fused bicyclic rings of the poly-heteroaryl system is taken from heterocyclyl as defined broadly above and the other rings are taken from either aryl, heteroaryl, or heterocyclyl as defined broadly above;

Lower alkyl refers to straight or branched chain C1-C6alkyls;

Substituted in connection with a moiety refers to the fact that a further substituent may be attached to the moiety to any acceptable location on the moiety.

The term salts embraces pharmaceutically acceptable salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid.

Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclyl, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, (3-hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts and organic salts. More preferred metallic salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metals. Such salts can be made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine.

The term prodrug refers to derivatives of active compounds which revert *in vivo* into the active form. For example, a carboxylic acid form of an active drug may be esterified to create a prodrug, and the ester is subsequently converted *in vivo* to revert to the carboxylic acid form. See Ettmayer et. al, *J. Med. Chem*, 2004, 47(10), 2393-2404 and Lorenzi et. al, *J. Pharm. Exp. Therapeutics*, 2005, 883-8900 for reviews.

Protein definitions

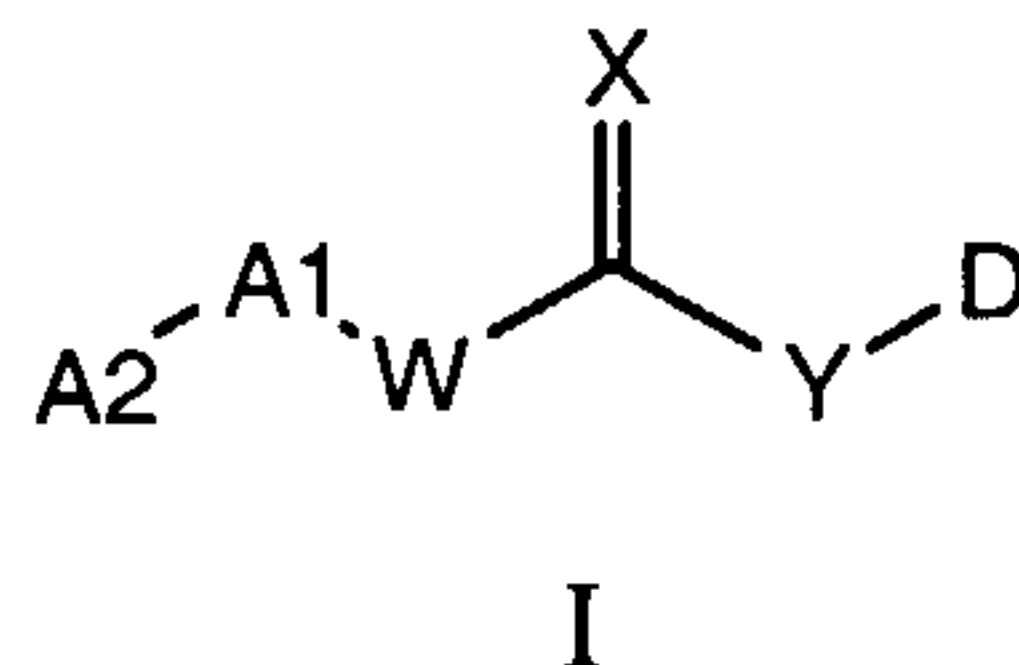
PGDF refers to platelet-derived growth factor; PGDFR refers to platelet-derived growth factor receptor; VEGF refers to vascular endothelial growth factor; VEGFR refers to vascular endothelial growth factor receptor; MAP kinase refers to mitogen-activated protein kinase; BCR refers to breakpoint cluster region; CML refers to chronic myeloid leukemia; TGF-beta refers to transforming growth factor beta; EGF refers to epidermal growth factor; KDR refers to kinase insert domain-containing receptor; TNF refers to tumor necrosis factor; ATP refers to adenosine triphosphate; DFG-in-conformation refers to the tripeptide sequence aspartylphenylalanylglycyl in the kinase protein sequence; V599E refers to the mutational

replacement of valine 599 of BRAF kinase by glutamic acid; FGFR refers to fibroblast growth factor receptor; TrkA refers to tyrosine receptor kinase type A and neurotrophic tyrosine kinase type 1 (NTRK1); TrkB refers to tyrosine receptor kinase type B and neurotrophic tyrosine kinase type 2 (NTRK2); EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHA9, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4, EPHB5, EPHB6, EPHB7, and EPHB8 refers to members of the ephrin receptor subfamily of the receptor tyrosine kinases.

1. *First aspect of the invention – C-Abl Kinase Modulator Compounds, Methods, Preparations and Adducts*

1.1 *Generally – A2 Bicyclic Compounds*

The invention includes compounds of the formula



wherein A2 is selected from the group consisting of bicyclic fused aryl, bicyclic fused heteroaryl, and bicyclic fused heterocyclyl rings, each A2 moiety presenting a proximal ring bonded with A1 and a distal ring attached to the proximal ring, and either the distal ring has a heteroatom in the ring structure thereof and/or the distal ring has Z2 or Z3 substituents;

A1 is selected from the group consisting of R2' and R7-substituted phenyl, pyridyl, or pyrimidinyl, R2-substituted monocyclic 5-membered ring heteroaryl, and R2'-substituted monocyclic heterocyclyl moieties;

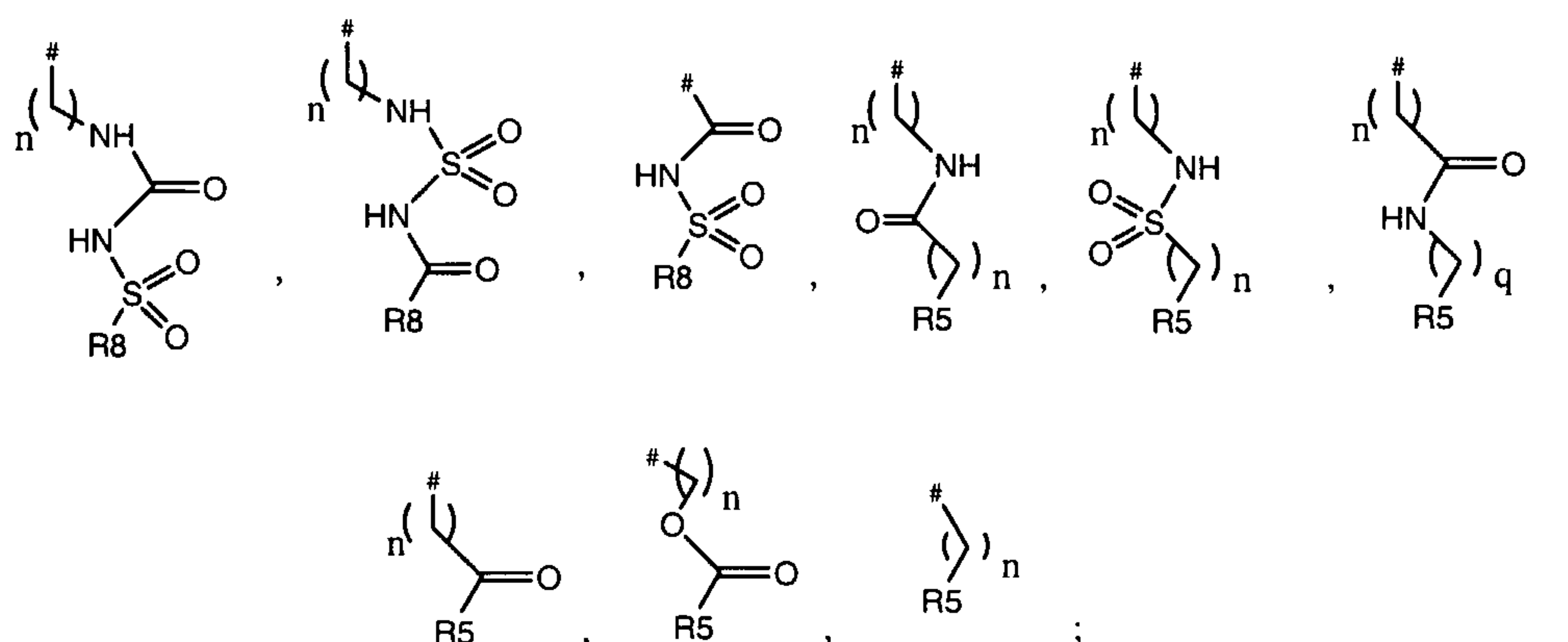
W and Y are CHR4, NR3, or O and wherein W and Y are not simultaneously O;

X is O, S, or NR3;

D comprises a member of the group consisting of Z5- or Z6-substituted mono- and poly-aryl, of Z5- or Z6-substituted mono- and poly-heteroaryl, of Z5- or Z6-substituted mono- and poly-heterocyclyl, of Z5- or Z6-substituted mono- and poly-arylalkyl, of Z5- or Z6-substituted mono- and poly-aryl branched alkyl, of Z5- or Z6-substituted mono- and poly-heteroarylalkyl, of Z5- or Z6-substituted mono- and poly-heteroaryl branched alkyl, of Z5- or

Z6-substituted mono- and poly-heterocyclalkyl, of Z5- or Z6-substituted mono- and poly-heterocyclalkyl branched alkyl, alkyl, and carbocyclalkyl moieties;

each Z2 is independently and individually selected from the group consisting of hydroxyl, hydroxylC1-C6alkyl, cyano, (R3)₂N-, (R4)₂N-, (R4)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, (R3)₂N-C(=O)-, (R4)₂N-C(=O)-, (R4)₂N-CO-C1-C6alkyl, carboxyl, carboxylC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)₂NSO₂, (R4)₂NSO₂, -SO₂R5-, -(CH₂)_nN(R4)C(O)R8, =O, =NOH, =N(OR6), heteroarylC1-C6alkyl, heterocyclalkylC1-C6alkyl, heteroaryloxyC1-C6alkyl, heterocyclalkyloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocyclalkylaminoC1-C6alkyl, or moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z2 moiety to the A2 ring of formula I;

in the event that Z2 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z2 may cyclize to form a C3-C7 heterocyclalkyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z2 may cyclize to form a C3-C7 heterocyclalkyl ring;

$\begin{array}{c} \# \\ | \\ \text{O}=\text{S}=\text{O} \\ | \\ \text{R5} \end{array}, \quad \begin{array}{c} \# \\ | \\ \text{N}=\text{S}(\text{R6})(\text{R8}) \\ || \\ \text{O} \end{array}, \quad \begin{array}{c} \# \\ | \\ \text{O}=\text{S}=\text{NR3} \\ | \\ \text{R6} \end{array}, \quad \begin{array}{c} \# \\ | \\ (\text{---})_n\text{NH}-\text{C}(=\text{O})\text{---} \\ | \\ \text{HN}-\text{S}(=\text{O})_2\text{---R8} \end{array}, \quad \begin{array}{c} \# \\ | \\ (\text{---})_n\text{NH}-\text{S}(=\text{O})_2\text{---} \\ | \\ \text{HN}-\text{C}(=\text{O})\text{---R8} \end{array}, \quad \begin{array}{c} \# \\ | \\ \text{HN}-\text{C}(=\text{O})\text{---} \\ | \\ \text{S}(=\text{O})_2\text{---R8} \end{array}$

$\begin{array}{c} \# \\ | \\ \text{HN}-\text{S}(=\text{O})_2\text{---} \\ | \\ \text{C}(=\text{O})\text{---R8} \end{array}, \quad \begin{array}{c} \# \\ | \\ (\text{---})_n\text{NH}-\text{C}(=\text{O})\text{---} \\ | \\ \text{O}-\text{C}(=\text{O})\text{---}(\text{---})_n\text{---R5} \end{array}, \quad \begin{array}{c} \# \\ | \\ (\text{---})_n\text{NH}-\text{S}(=\text{O})_2\text{---}(\text{---})_n\text{---R5} \end{array}, \quad \begin{array}{c} \# \\ | \\ (\text{---})_n\text{C}(=\text{O})\text{---} \\ | \\ \text{HN}-\text{C}(=\text{O})\text{---}(\text{---})_q\text{---R5} \end{array}, \quad \begin{array}{c} \# \\ | \\ (\text{---})_n\text{C}(=\text{O})\text{---R5} \end{array}, \quad \begin{array}{c} \# \\ | \\ (\text{---})_n\text{O}-\text{C}(=\text{O})\text{---R5} \end{array},$

$\begin{array}{c} \# \\ | \\ (\text{---})_n\text{S}(=\text{O})_2\text{---} \\ | \\ \text{HN}-\text{C}(=\text{O})\text{---}(\text{---})_q\text{---R5} \end{array}, \quad \begin{array}{c} \# \\ | \\ (\text{---})_p\text{C}(\text{OH})(\text{---})\text{---R5} \end{array}, \quad \begin{array}{c} \# \\ | \\ \text{HO}-\text{C}(\text{---})\text{---R4} \\ | \\ \text{HO}-\text{C}(\text{---})\text{---R4} \end{array}, \quad \begin{array}{c} \# \\ | \\ (\text{---})_n\text{---R5} \end{array}, \quad \begin{array}{c} \# \\ | \\ \text{R5}-\text{C}(\text{---})=\text{NH} \end{array}, \quad \begin{array}{c} \# \\ | \\ \text{R4}-\text{N}(\text{---})\text{---R4} \\ | \\ \text{C}(\text{---})=\text{NH} \end{array},$

$\begin{array}{c} \# \\ | \\ \text{R5}-\text{C}(\text{---})=\text{NOR3} \end{array}, \quad \begin{array}{c} \# \\ | \\ \text{R4}-\text{N}(\text{---})\text{---R4} \\ | \\ \text{C}(\text{---})=\text{NOR3} \end{array}, \quad \begin{array}{c} \# \\ | \\ \text{HN}-\text{C}(\text{---})=\text{NH} \\ | \\ \text{R8} \end{array};$

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

each Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocycliloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

each R2' is selected from the group consisting of halogen and R2;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

Chemical structures 1-15 are shown below:

- Structure 1: A five-membered ring with a nitrogen atom (N) and a substituent ##.
- Structure 2: A six-membered ring with a nitrogen atom (N) and a substituent ##.
- Structure 3: A six-membered ring with a nitrogen atom (N), an oxygen atom (O), and a substituent ##.
- Structure 4: A six-membered ring with a nitrogen atom (N), a sulfur atom (S), and a substituent ##.
- Structure 5: A six-membered ring with a nitrogen atom (N), a sulfone group (SO₂), and a substituent ##.
- Structure 6: A six-membered ring with a nitrogen atom (N), a hydroxyl group (OH), and a substituent ##.
- Structure 7: A six-membered ring with a nitrogen atom (N) and a substituent R₄.
- Structure 8: A six-membered ring with a nitrogen atom (N) and a substituent R₄.
- Structure 9: A six-membered ring with a nitrogen atom (N) and a substituent R₄.
- Structure 10: A six-membered ring with a nitrogen atom (N) and a substituent R₄.
- Structure 11: A six-membered ring with a nitrogen atom (N) and a substituent R₄.
- Structure 12: A six-membered ring with a nitrogen atom (N) and a substituent R₄.
- Structure 13: A six-membered ring with a nitrogen atom (N) and a substituent R₄.
- Structure 14: A six-membered ring with a nitrogen atom (N) and a substituent R₄.
- Structure 15: A six-membered ring with a nitrogen atom (N) and a substituent R₄.

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wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

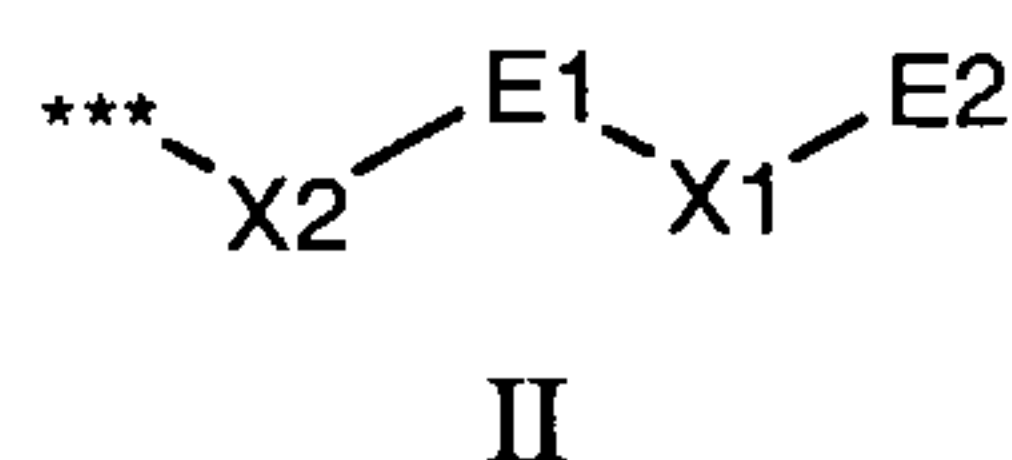
and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

1.1.1 Preferred D Moieties

1.1.1a

Preferrably, the compounds of formula I above contain D moieties of the formula



wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

wherein the symbol (***) is the point of attachment to the Y group of formula I;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, (CH₂)_p-, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, -(CH₂)_p-, C2-C5alkenyl, and C2-C5alkynyl of X2 can be further substituted by one or more C1-C6alkyl;

and E2 is selected from the group comprising cyclopentyl, cyclohexyl, phenyl, naphthyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl,

triazinyl, fused bicyclic rings selected from the group comprising indolyl, isoindolyl, isoindolinyl, isoindolonyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, imidazopyrimidinyl, imidazolopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, furylopyrimidinyl, thienopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnoliny, quinoxaliny, quinazoliny, quinoliny, isoquinoliny, phthalaziny, benzodioxyl, indoliny, benzisothiazoline-1,1,3-trionyl, dihydroquinoliny, tetrahydroquinoliny, dihydroisoquinolyl, tetrahydroisoquinoliny, benzoazepiny, benzodiazepiny, benzoxapiny, benzoxazepiny, non-fused bicyclic rings comprising pyridylpyridiminy, pyrimidinylpyrimidinyl, oxazolylpyrimidinyl, thiazolylpyrimidinyl, imidazolylpyrimidinyl, isoxazolylpyrimidinyl, isothiazolylpyrimidinyl, pyrazolylpyrimidinyl, triazolylpyrimidinyl, oxadiazoylpyrimidinyl, thiadiazoylpyrimidinyl, morpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, and heterocyclyls selected from the group comprising oxetanyl, azetadiny, tetrahydrofuranyl, pyrrolidinyl, oxazoliny, oxazolidiny, imidazolonyl, pyranly, thiopyranly, tetrahydropyranly, dioxaliny, piperidinyl, morpholinyl, thiomorpholinyl, dioxothiomorpholinyl, piperaziny, azepiny, oxepiny, diazepiny, tropanyl, and homotropanyl;

and n is 0-4; p is 1-4; q is 2-6.

1.1.1b

Additional preferred D moieties comprise carbocyclyls and a moiety of the formula



X₂ is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E₂ is directly linked to the Y group of formula I.

1.1.1c

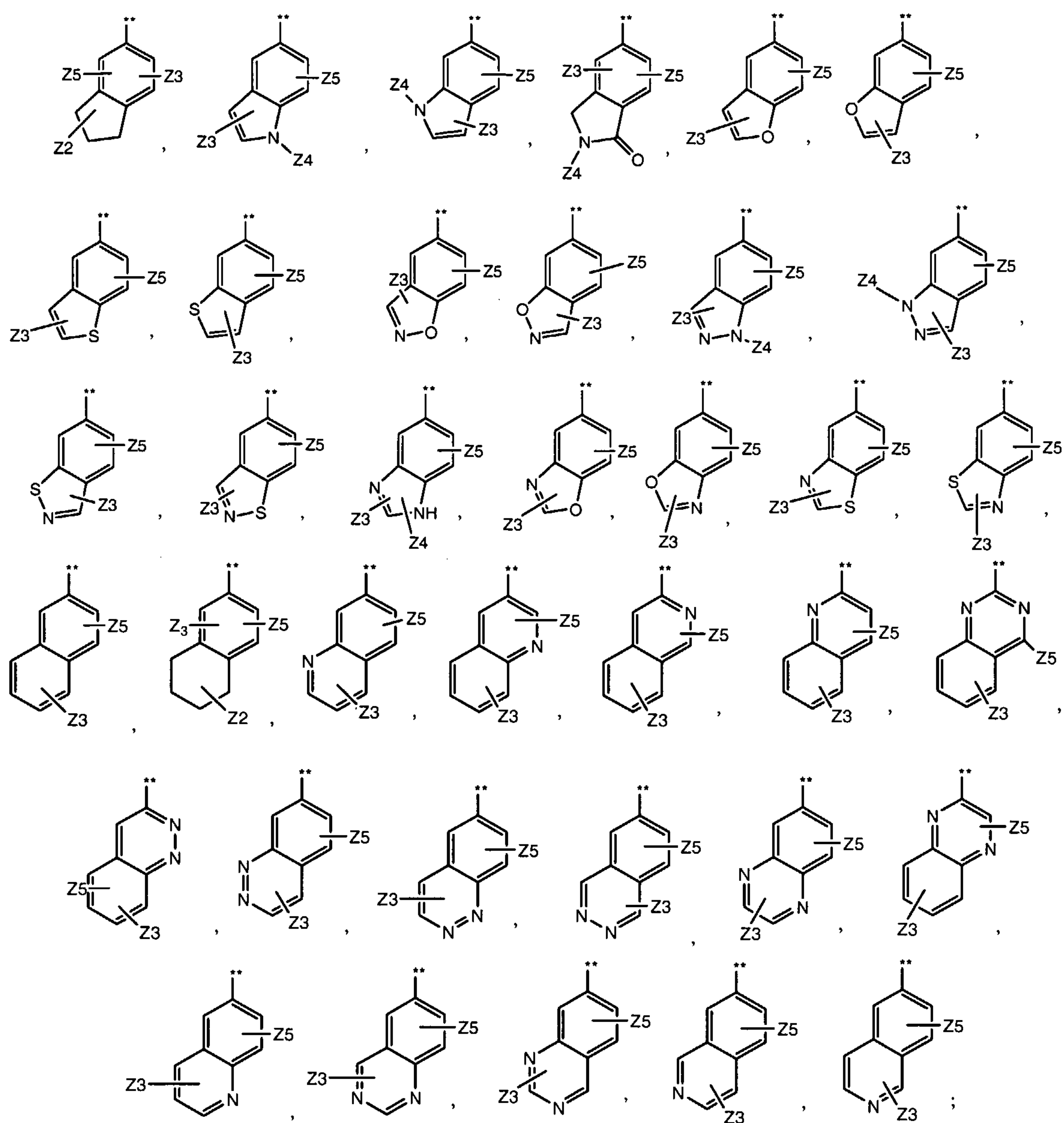
More preferred D moieties from 1.1.1b comprise the compounds of Formula III wherein the E₂ ring is selected from the group comprising cyclopentyl, cyclohexyl, phenyl, naphthyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl,

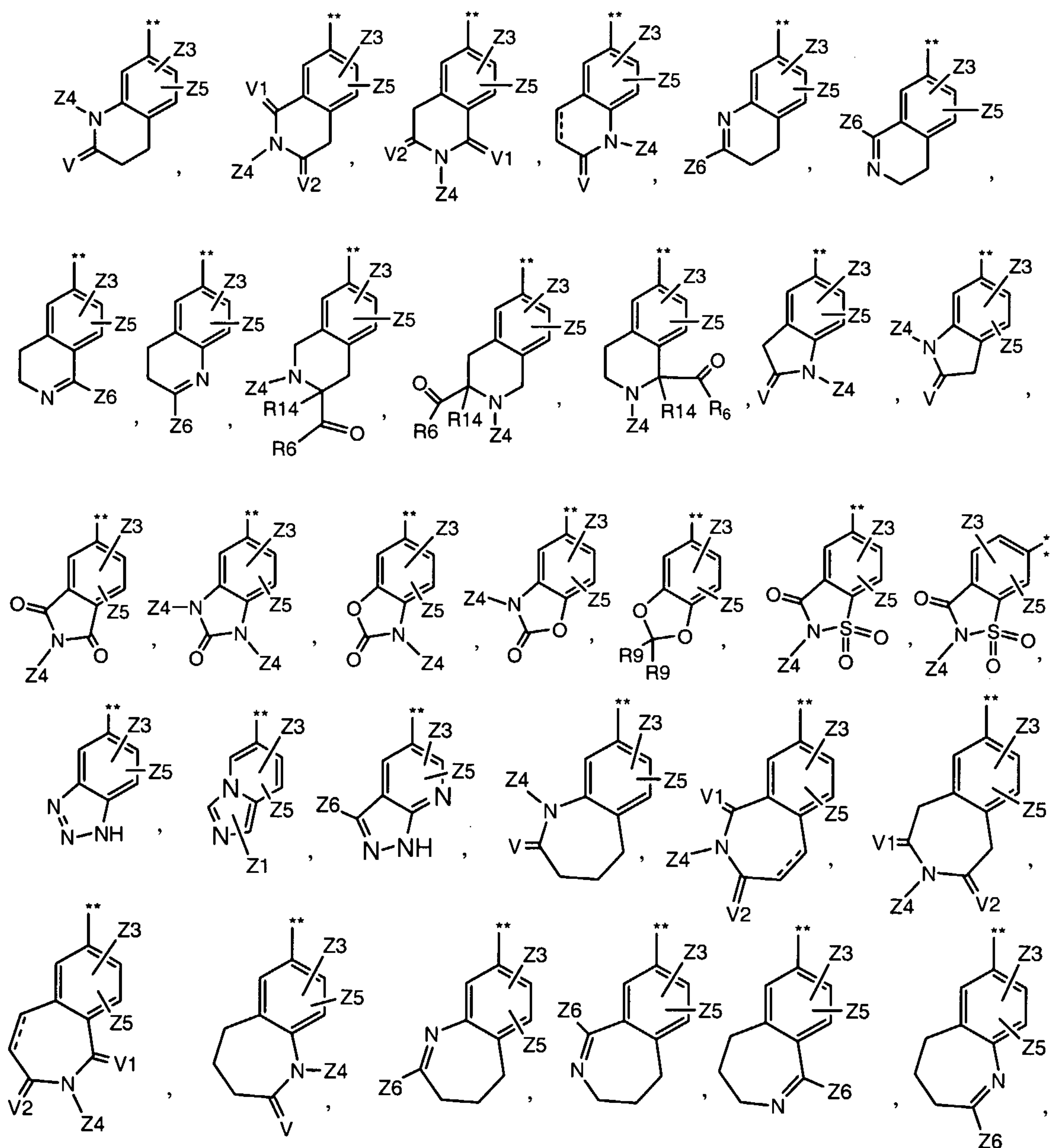
triazinyl, fused bicyclic rings selected from the group comprising indolyl, isoindolyl, isoindolinyl, isoindolonyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, imidazopyrimidinyl, imidazolopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, furylopyrimidinyl, thienopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnoliny, quinoxaliny, quinazoliny, quinoliny, isoquinoliny, phthalazinyl, benzodioxyl, indoliny, benzisothiazoline-1,1,3-trionyl, dihydroquinoliny, tetrahydroquinoliny, dihydroisoquinolyl, tetrahydroisoquinoliny, benzoazepiny, benzodiazepiny, benzoxapiny, benzoxazepiny, non-fused bicyclic rings comprising pyridylpyridiminy, pyrimidinylpyrimidinyl, oxazolylpyrimidinyl, thiazolylpyrimidinyl, imidazolylpyrimidinyl, isoxazolylpyrimidinyl, isothiazolylpyrimidinyl, pyrazolylpyrimidinyl, triazolylpyrimidinyl, oxadiazoylpyrimidinyl, thiadiazoylpyrimidinyl, morpholiny, dioxothiomorpholiny, thiomorpholiny, and heterocyclyls selected from the group comprising oxetany, azetadiny, tetrahydrofurany, pyrrolidinyl, oxazoliny, oxazolidiny, imidazolonyl, pyranly, thiopyranly, tetrahydropyranly, dioxaliny, piperidinyl, morpholiny, thiomorpholiny, dioxothiomorpholiny, piperazinyl, azepiny, oxepiny, diazepiny, tropany, and homotropany.

1.1.2 Preferred A2 Moieties

1.1.2a

Preferred A2 moieties of Formula I are selected from the group consisting of





and wherein the symbol (**) is the point of attachment to the A1 ring of formula I;

and wherein ----- indicates either a saturated or an unsaturated bond;

wherein each Z3 and Z5 may be independently attached to either of the rings making up the foregoing bicyclic structures;

each R9 is independently and individually selected from the group consisting of H, F, C1-C6alkyl, branched C4-C7alkyl, carbocyclyl, phenyl, phenyl C1-C6alkyl, heterocyclyl and heterocyclylC1-C6alkyl;

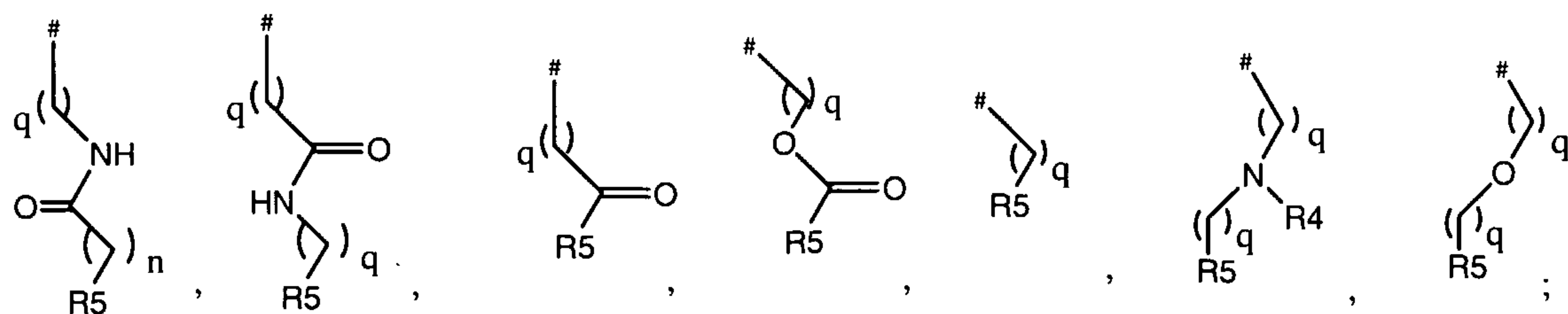
each R13 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, hydroxyC2-C7alkyl, C1-C6alkoxyC2-C7alkyl, (R4)₂N-CO, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_q, R5-C2-C6alkylN(R4)-(CH₂)_q, (R4)₂N-C2-C6alkylO-(CH₂)_q, R5-C2-C6alkyl-O-(CH₂)_q, -(CH₂)_qN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC2-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, and heterocyclylaminoC2-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R13 may cyclize to form a C3-C7 heterocyclyl ring;

each R14 is independently and respectively selected from the group consisting of H and C1-C6alkyl;

V, V1, and V2 are each independently and respectively selected from the group consisting of O and H₂;

each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

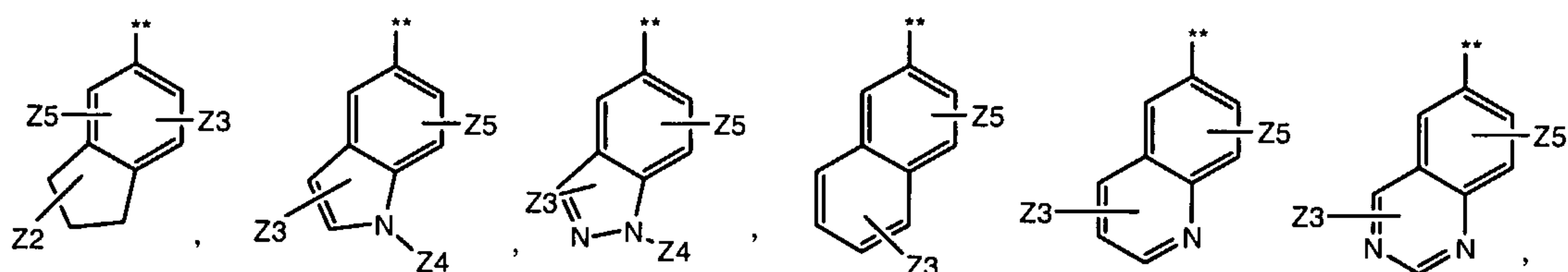
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

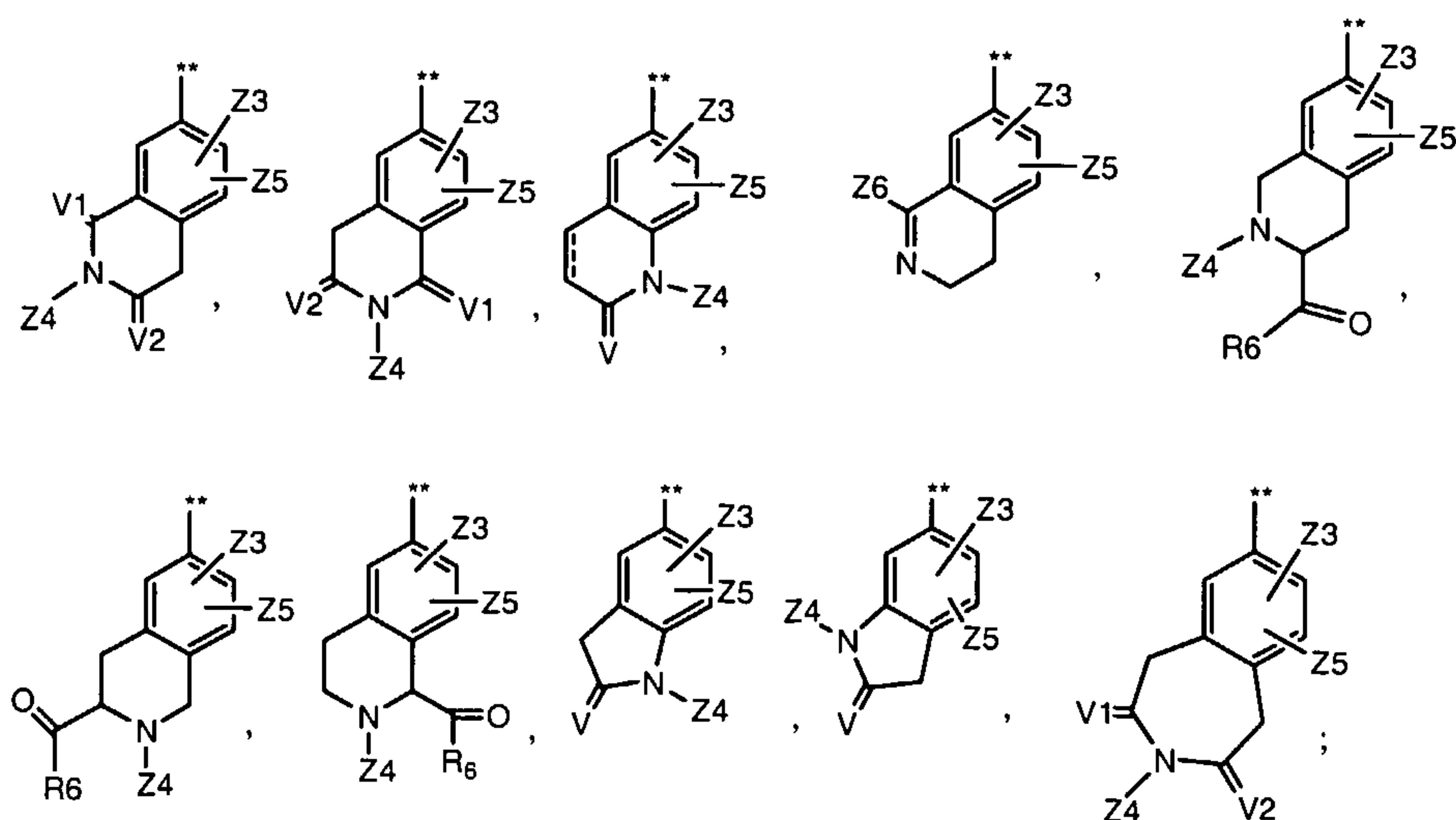
wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2.

1.1.2b

More preferred A2 moieties are selected from the group consisting of



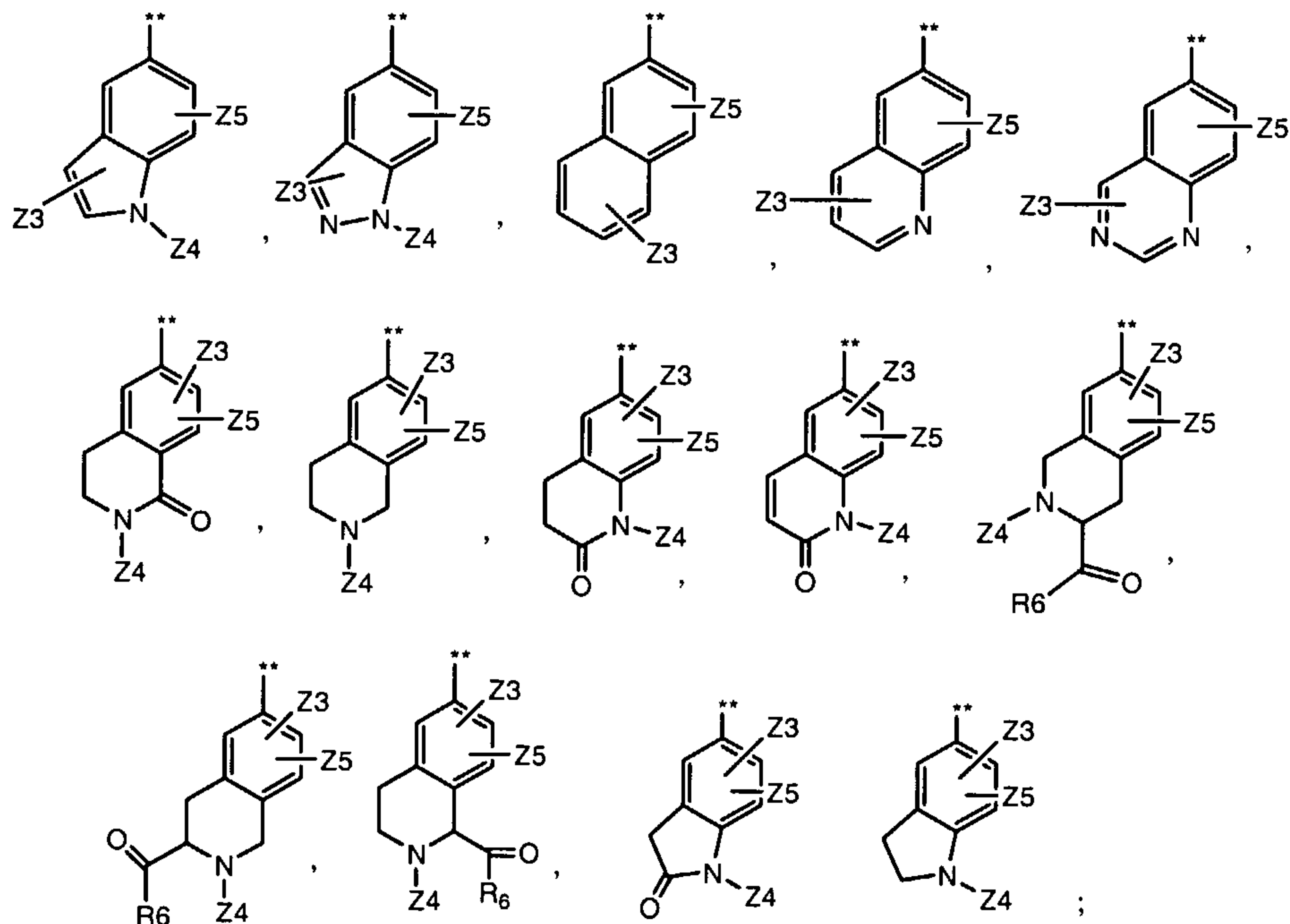


and wherein the symbol (**) is the point of attachment to the A1 ring for formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring.

1.1.2c

Still more preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring.

1.1.3 Preferred Classes of Compounds

1.1.3a

Compounds as defined in *1.1.1a* wherein the A2 group is defined in *1.1.2a*.

1.1.3b

Compounds as defined in *1.1.3a* wherein the A2 group is defined in *1.1.2b*.

1.1.3c

Compounds as defined in *1.1.3a* wherein the A2 group is defined in *1.1.2c*.

1.1.3d

Compounds as defined in *1.1.1b* wherein the A2 group is defined in *1.1.2a*.

1.1.3e

Compounds as defined in *1.1.3c* wherein the A2 group is defined in *1.1.2b*.

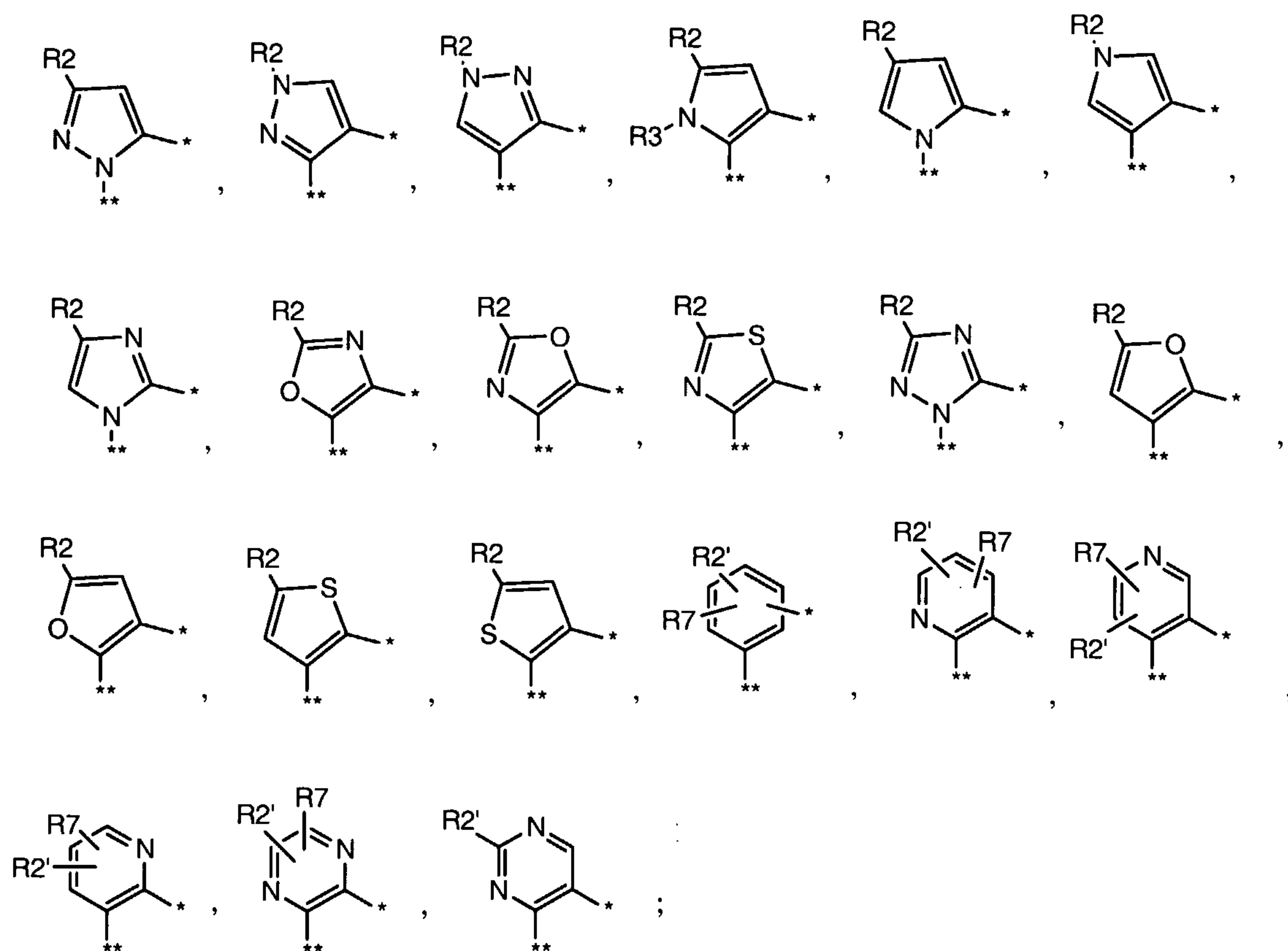
1.1.3f

Compounds as defined in *1.1.3c* wherein the A2 group is defined in *1.1.2c*.

1.1.4 Preferred A1 Moieties

1.1.4a

A1 moieties are selected from the group consisting of

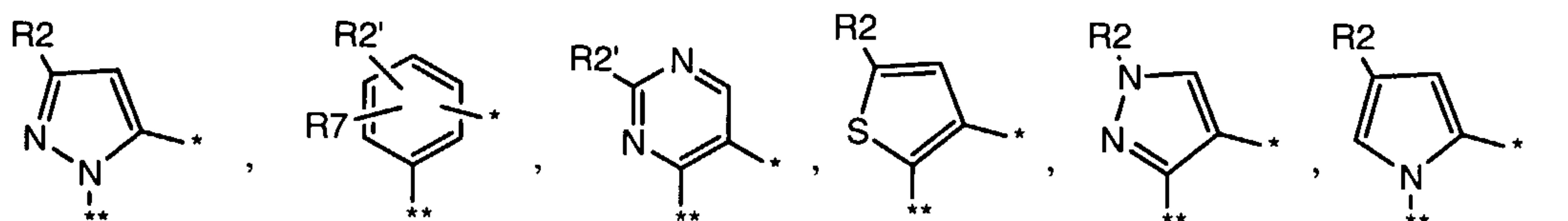


wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

each R7 is selected from the group consisting of halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy.

1.1.4b

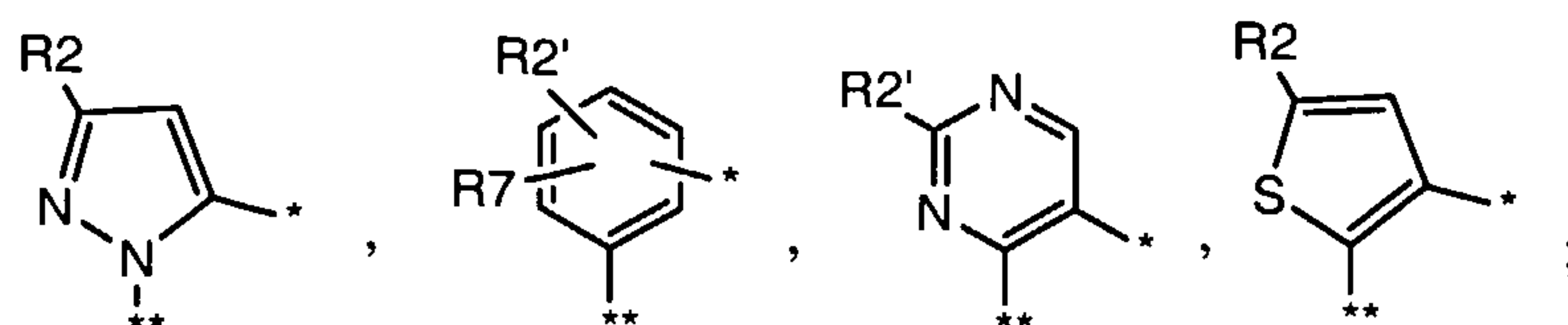
Preferred A1 moieties are selected from the group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I.

1.1.4c

Still more preferred A1 moieties are selected from the group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I.

1.1.5 Preferred W and Y Moieties

1.1.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR₄ and X=O; or (3) W=CHR₄, Y=NH, and X=O.

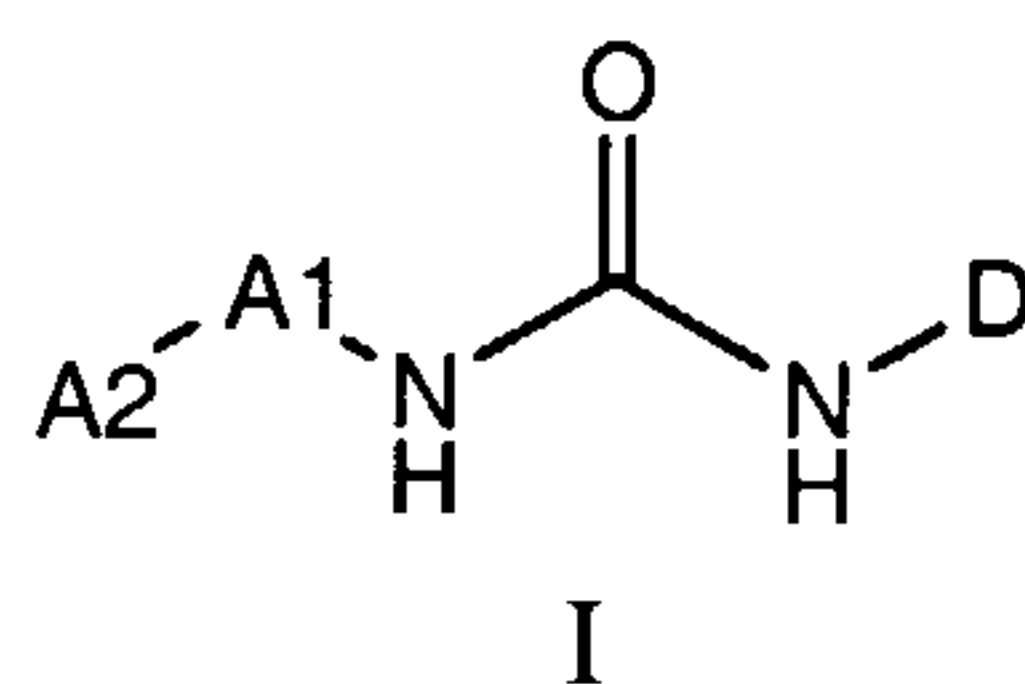
1.1.5b

W and Y are each NH and X=O.

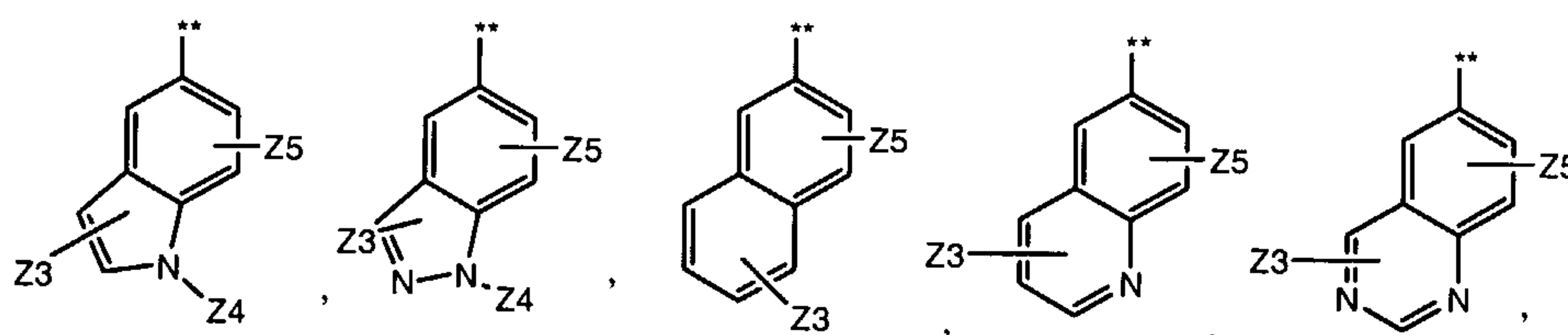
1.1.6 Further Preferred Compounds

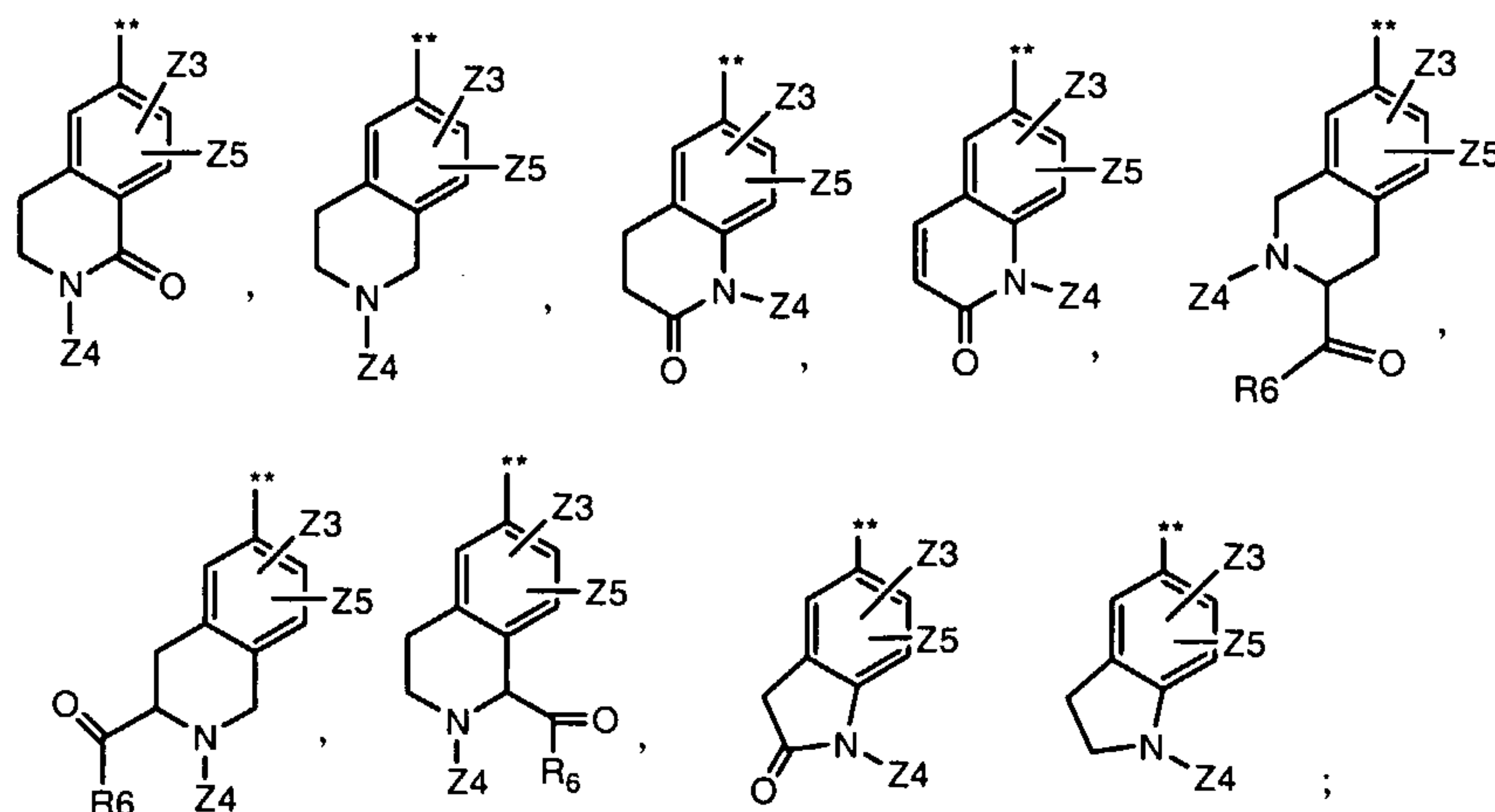
1.1.6a

Further preferred compounds are of the formula



wherein A2 is selected from the group consisting of

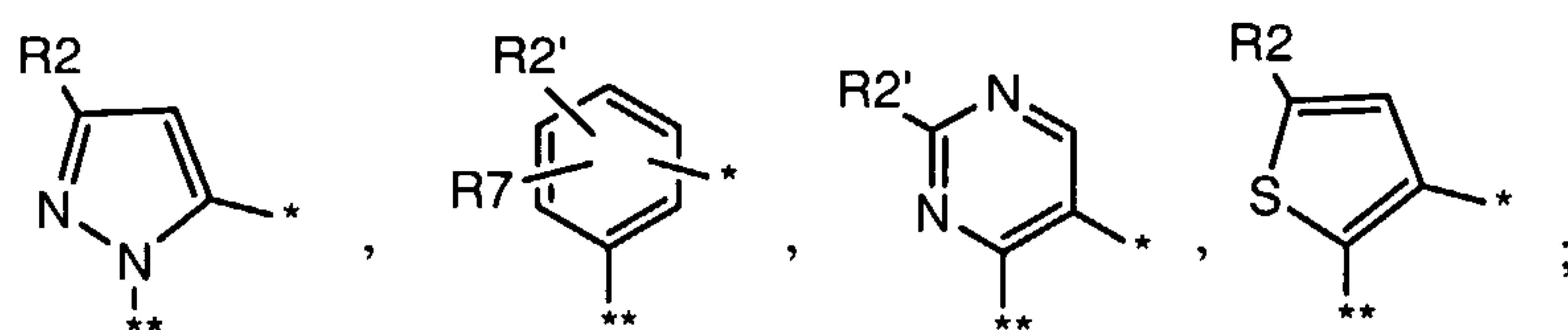




wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring;

wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

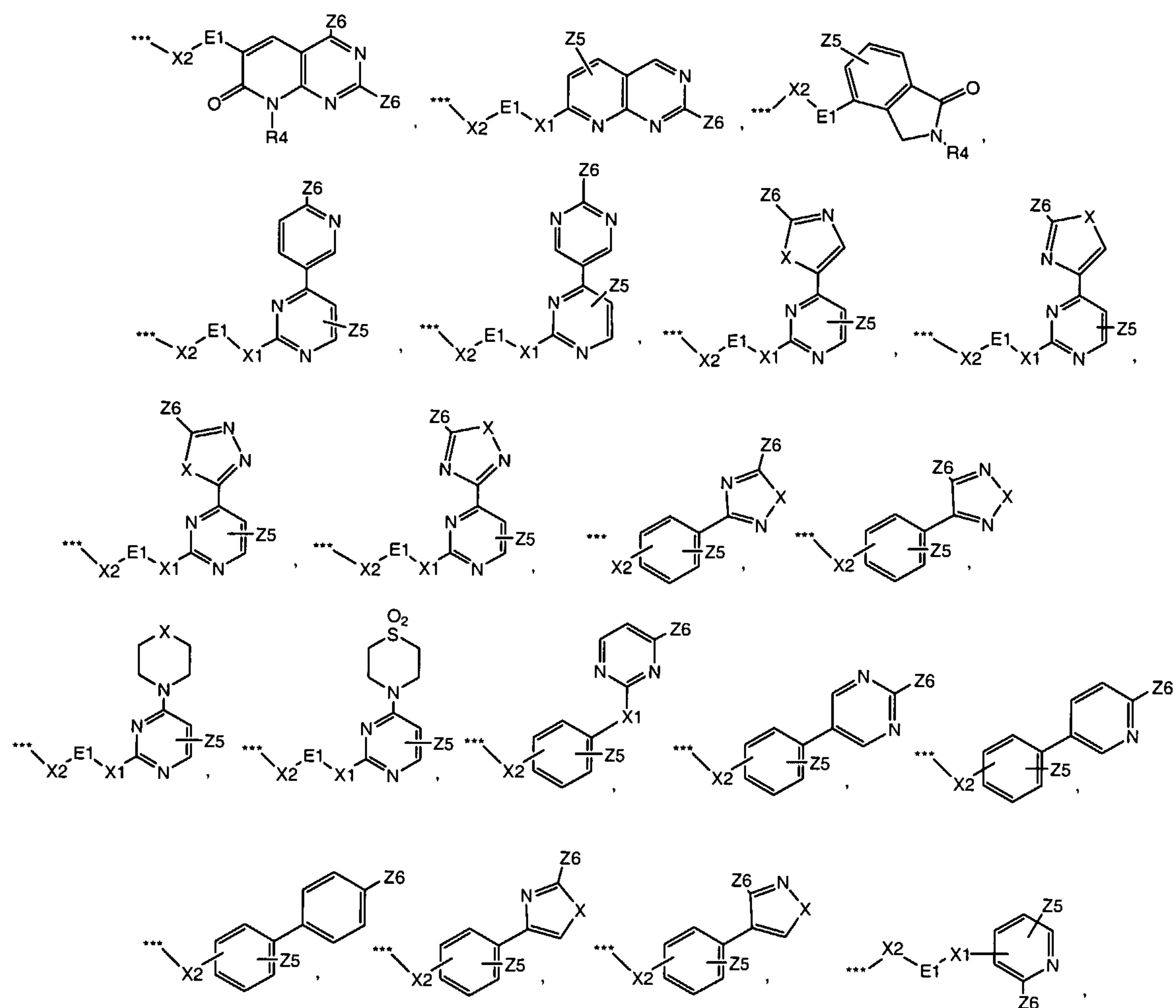
A1 is selected from the group consisting of

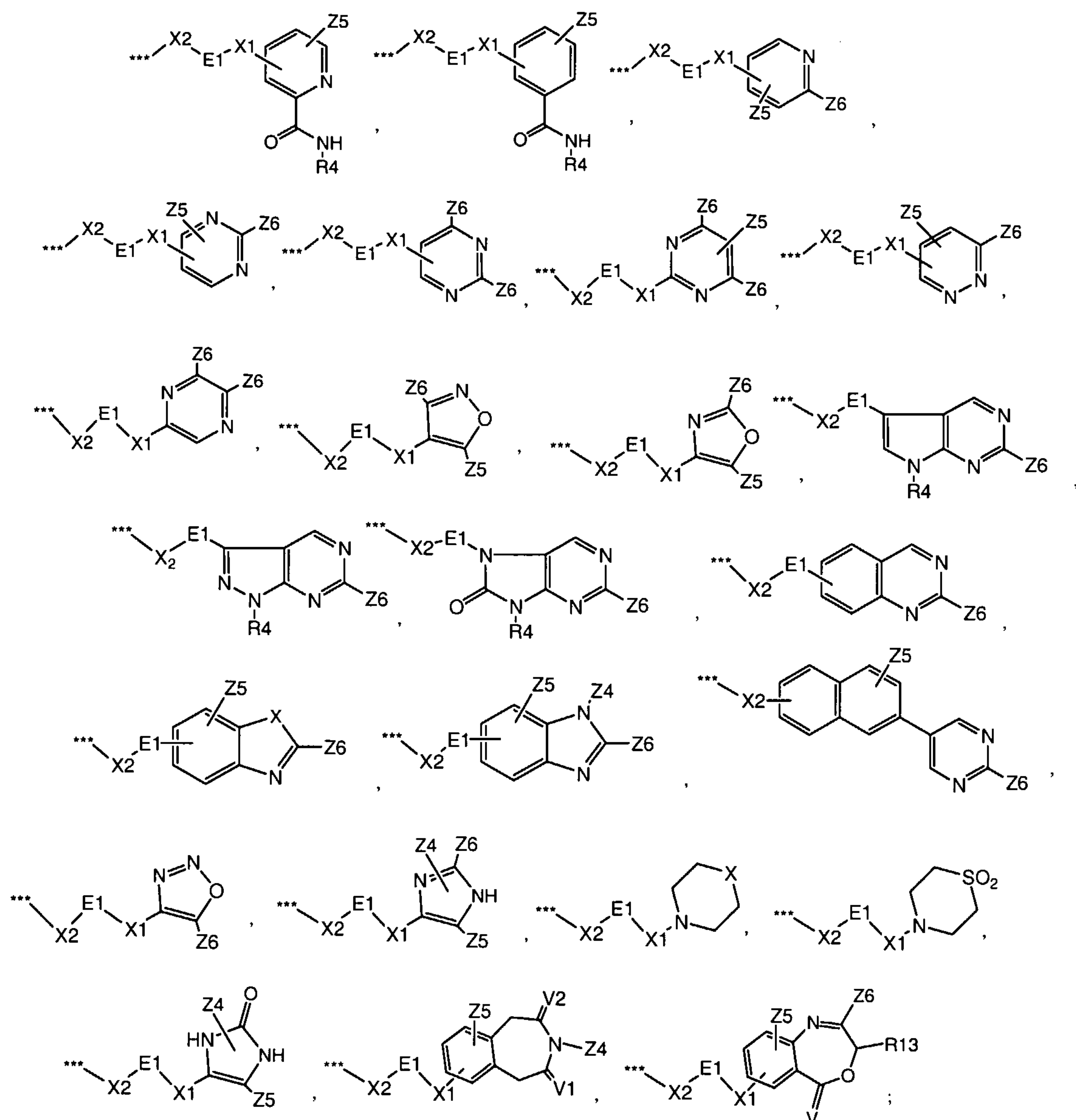


wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR3;

D is selected from the group consisting of 2,3-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-cyanophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 3,4,5-trifluorophenyl, 4-cyanophenyl, 3-fluoro-5-cyanophenyl, 3-(R8SO₂)-phenyl, 3-(hydroxyC1-C3alkyl)-phenyl, 3-(R3O-N=C(R6))-phenyl, 3-phenoxyphenyl, 4 phenoxyphenyl,





wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C₂-C₅alkenyl, C₂-

C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of $-(CH_2)_n-$, $-(CH_2)_q-$, $(CH_2)_p$, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

and wherein the carbon atoms of $-(CH_2)_n-$, $-(CH_2)_q-$, $-(CH_2)_p-$, C2-C5alkenyl, and C2-C5alkynyl of X2 can be further substituted by one or more C1-C6alkyl;

each R2 is selected from the group consisting of alkyl, branched alkyl, fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and C1-C6alkyl;

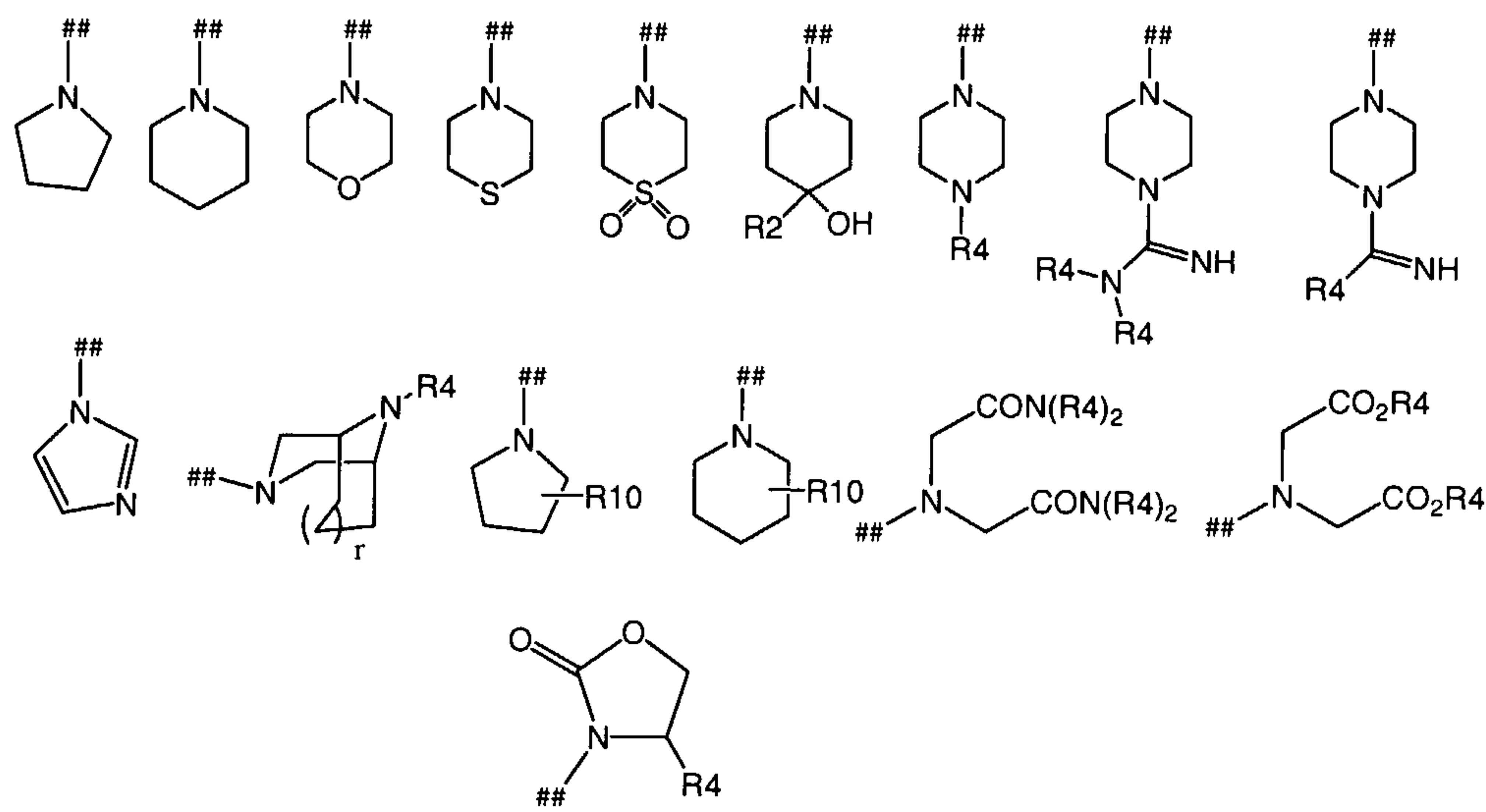
each R2' is selected from the group consisting of halogen and R2;

each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

each R5 is independently and individually selected from the group consisting of



wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

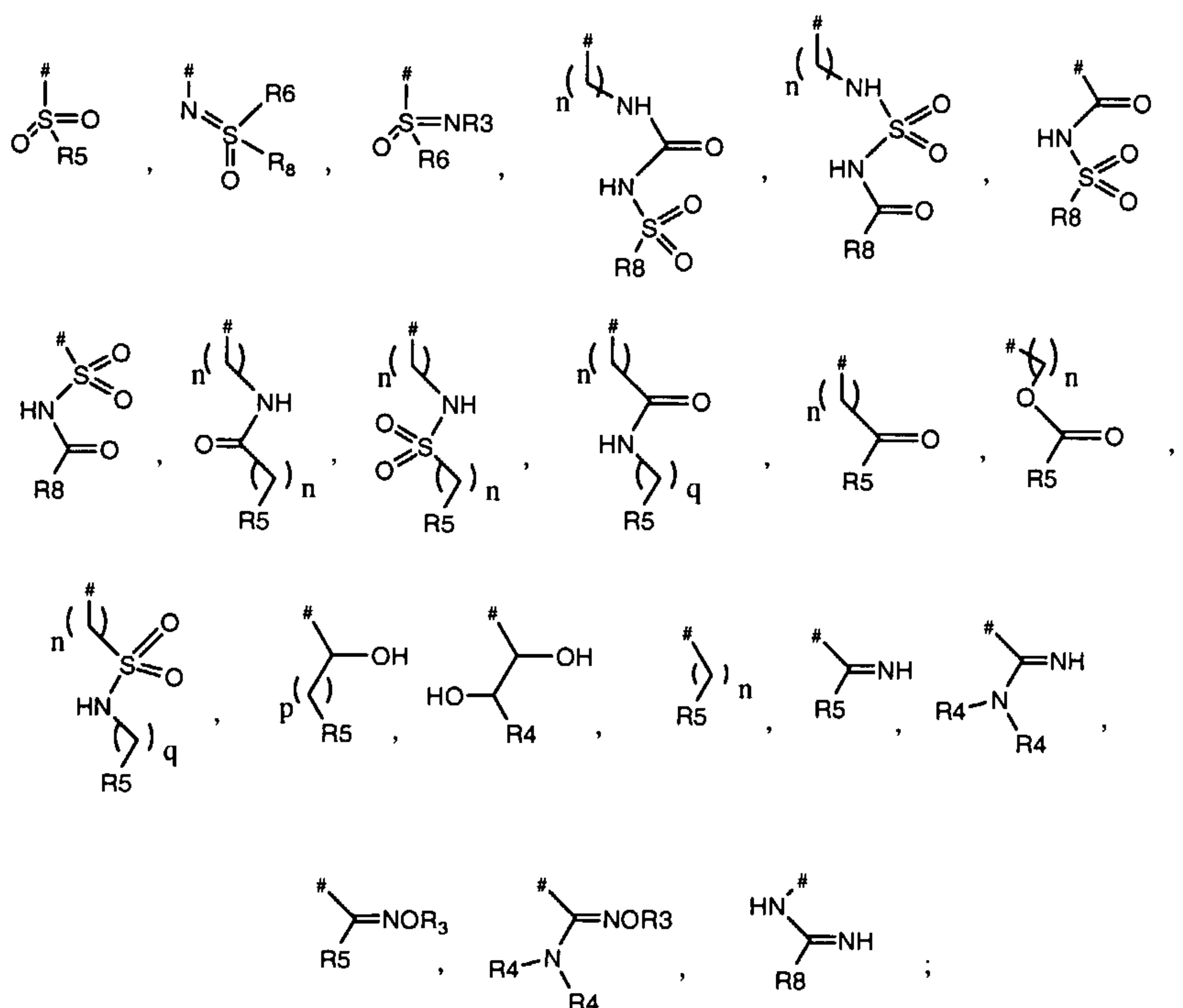
each R13 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, hydroxyC2-C7alkyl, C1-C6alkoxyC2-C7alkyl, (R4)₂N-CO, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_q, R5-C2-C6alkylN(R4)-(CH₂)_q, (R4)₂N-C2-C6alkylO-(CH₂)_q, R5-C2-C6alkyl-O-(CH₂)_q, -(CH₂)_qN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC2-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, and heterocyclylaminoC2-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R13 may cyclize to form a C3-C7 heterocyclyl ring;

each R14 is independently and respectively selected from the group consisting of H and C1-C6alkyl;

V, V1, and V2 are each independently and respectively selected from the group consisting of O and H₂;

each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyl, hydroxyC1-C6alkyl, cyano, C1-C6alkoxy, C1-C6alkoxyC1-C6alkyl, halogen, CF₃, (R₃)₂N-, (R₄)₂N-, (R₄)₂NC1-C6alkyl, (R₄)₂NC2-C6alkylN(R₄)-(CH₂)_n, (R₄)₂NC2-C6alkylO-(CH₂)_n, R₈CO-, (R₄)₂N-CO-C1-C6alkyl, carboxyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R₃)₂NSO₂, -SO₂R₃, SOR₃, (R₄)₂NSO₂, -SO₂R₄, -SOR₄, -(CH₂)_nN(R₄)C(O)R₈, -C=(NOH)R₆, -C=(NOR₃)R₆, heteroaryl, heterocyclyl, heteroarylC1-C6alkyl, heterocyclylC1-C6alkyl, heteroaryloxy, heterocycliloxy, heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylamino, heteroarylamino, heterocyclylamino, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocyclylaminoC1-C6alkyl, or moieties of the formulae



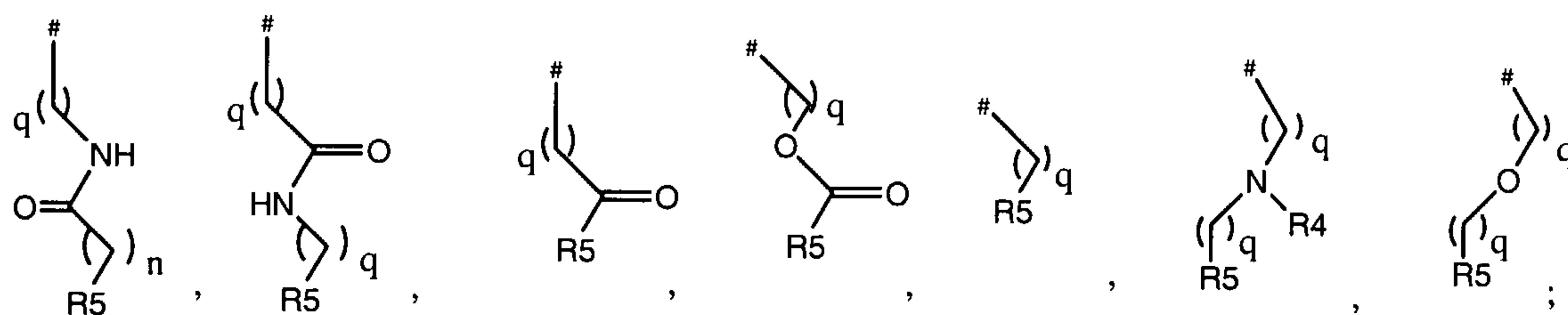
wherein the symbol (#) indicates the point of attachment of the Z3 moiety to the A2 ring of formula I;

in the event that Z3 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

1.1.6b

The following specific compounds are most preferred:

1-(3-t-butyl-1-(1-(methanesulfonylureidoamidomethyl)naphthalen-3-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(4-(2-aminoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, (3S)-6-(3-t-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 6-(3-t-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3,4-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-((1-amino-1-oxo-methylamino)methyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-((1-amino-1-oxo-methylamino)methyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3,5-difluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3,5-difluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,5-difluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(1,3-dihydroxypropan-2-ylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,5-difluorophenyl)urea, 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-cyanophenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-cyanophenyl)urea, 1-(3-t-

butyl-1-(1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(5-chloropyridin-3-yloxy)phenyl)urea, 6-(3-t-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1-(3-t-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(3-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(2-(2-aminoethylamino)quinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-(dimethylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-((R)-3-(dimethylamino)pyrrolidin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(2-aminoquinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-(methylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(1-oxoisindolin-4-yl)phenyl)urea, 1-(3-t-

butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(4-(1-oxoisindolin-4-yl)phenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(4-(1-oxoisindolin-4-yl)phenyl)urea, 6-(3-t-butyl-5-(3-(4-(1-oxoisindolin-4-yl)phenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea, 1-(3-t-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea

1.1.7 Methods

1.1.7a Methods of Protein Modulation

The invention includes methods of modulating kinase activity of a variety of kinases, e.g. C-Abl kinase, BCR-Abl kinase. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 1.1 and 1.1.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

The methods of the invention may also involve the step of inducing, synergizing, or promoting the binding of a second modulator compound of said kinase, especially C-Abl kinase or BCR-Abl kinase, to form a ternary adduct, such co-incident binding resulting in enhanced biological modulation of the kinase when compared to the biological modulation of the protein affected by either of said compounds alone. The second compound may interact at a substrate, co-factor or regulatory site on the kinase, with the second site being distinct from the site of interaction of the first compound. For example, the second site may be an ATP co-factor site. The second compounds may be taken from the group consisting of N-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide(Gleevec®); N-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825); 6-(2,6-dichlorophenyl)-2-(3-(hydroxymethyl)phenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 166326); 6-(2,6-dichlorophenyl)-8-methyl-2-(3-(methylthio)phenylamino)pyrido[2,3-d]pyrimidin-7(8H)-one (PD 173955); 6-(2,6-dichlorophenyl)-2-(4-fluoro-3-methylphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD180970); 6-(2,6-dichlorophenyl)-2-(4-ethoxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 173958); 6-(2,6-dichlorophenyl)-2-(4-fluorophenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 173956); 6-(2,6-dichlorophenyl)-2-(4-(2-(diethylamino)ethoxy)phenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 166285); 2-(4-(2-aminoethoxy)phenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one; N-(3-(6-(2,6-dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)phenyl)acetamide (SKI DV-MO16); 2-(4-aminophenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 1-10); 6-(2,6-dichlorophenyl)-2-(3-hydroxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV2-89); 2-(3-aminophenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 2-43); N-(4-(6-(2,6-dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)phenyl)acetamide (SKI DV-M017); 6-(2,6-dichlorophenyl)-2-(4-hydroxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV-M017); 6-(2,6-dichlorophenyl)-2-(3-ethylphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 2 87).

1.1.7b Treatment Methods

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer and hyperproliferative diseases. These methods

comprise administering to such individuals compounds of the invention, and especially those of section 1.1 and 1.1.6a. Exemplary conditions include chronic myelogenous leukemia, acute lymphocytic leukemia, gastrointestinal stromal tumors, and hypereosinophilic syndrome. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

1.1.8 *Pharmaceutical Preparations*

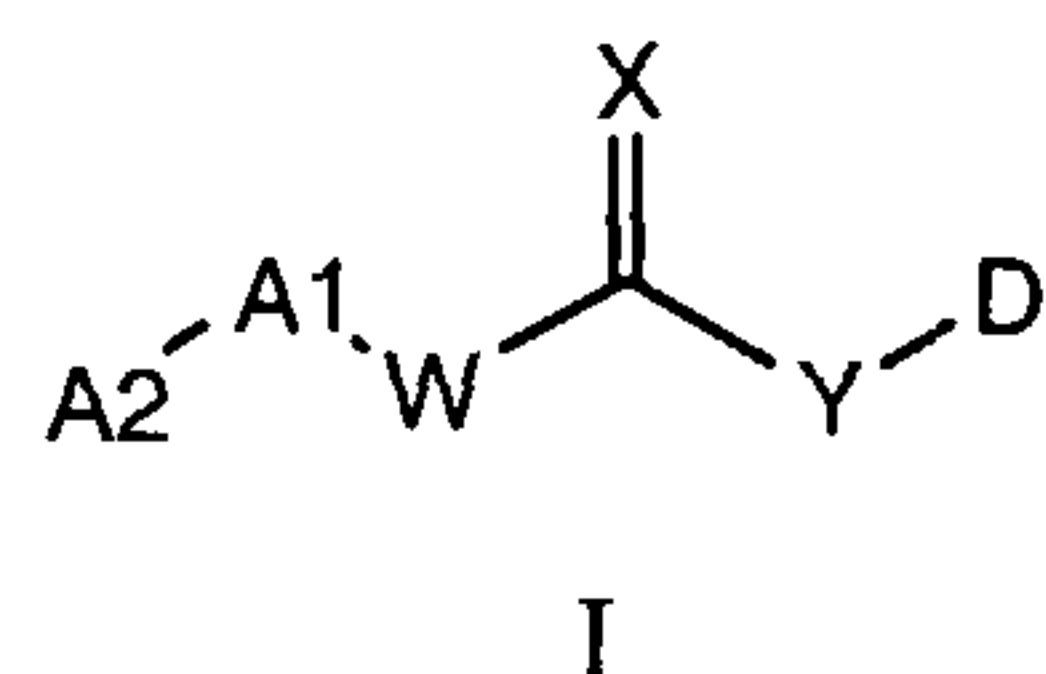
The compounds of the invention, especially those of 1.1 and 1.1.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

1.1.9 *Kinase/Compound Adducts*

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 1.1 and 1.1.6a.

1.2 *Generally – Monocyclic A2 Compounds with Polycyclic E2 Rings*

The invention includes compounds of the formula



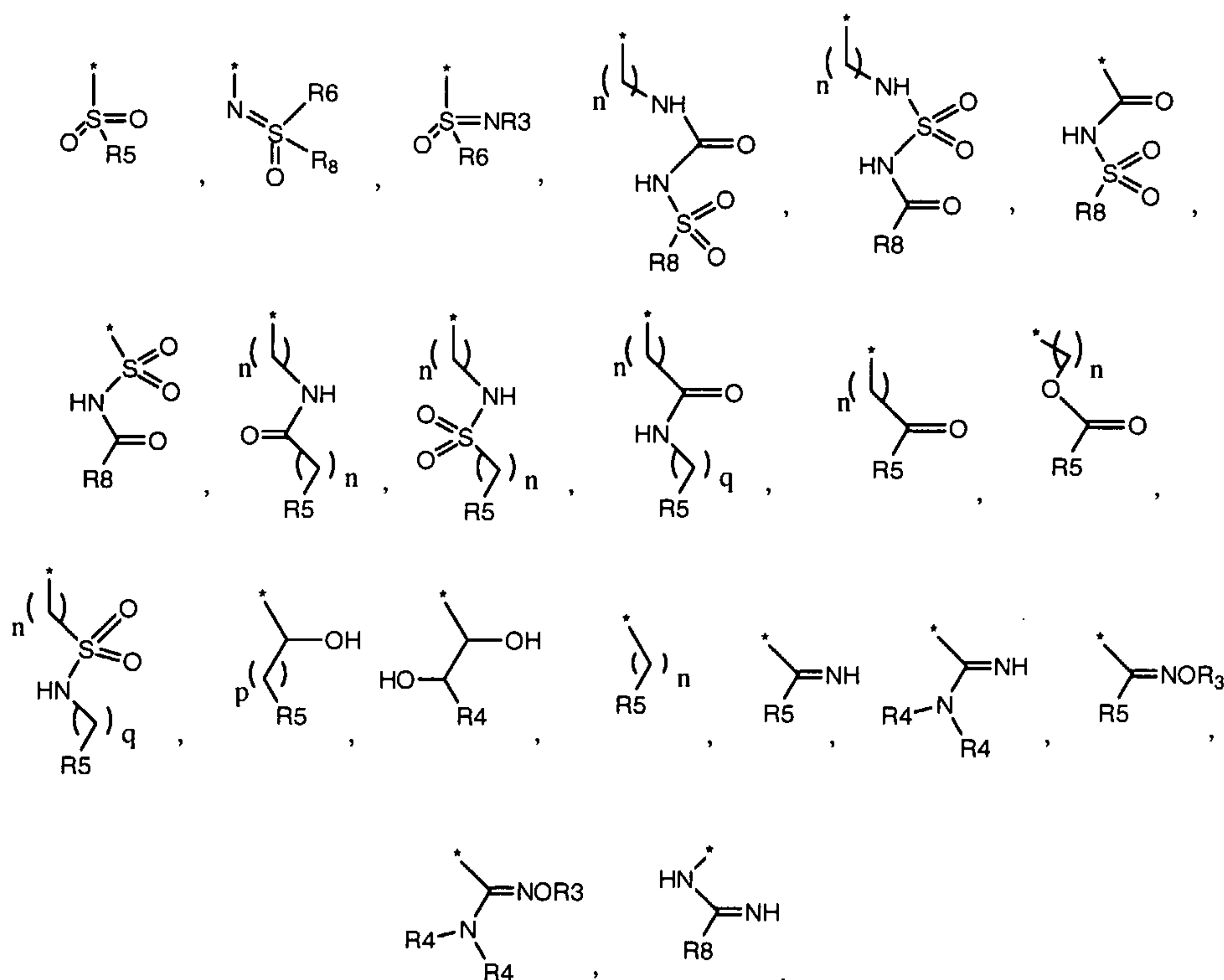
wherein A2 is selected from the group consisting of a Z1-substituted phenyl, Z1-substituted pyridyl, Z1-substituted pyrimidinyl, Z1-substituted thienyl, Z1 or Z4'-substituted monocyclic heterocyclyl rings, and other monocyclic heteroaryls, excluding tetrazolyl, 1,2,4-oxadiazolonyl, 1,2,4-triazolonyl, and alkyl-substituted pyrrolyl wherein the pyrrolyl nitrogen is the site of attachment to the A1 ring;

A1 is selected from the group consisting of R2' and R7-substituted phenyl, pyridyl, or pyrimidinyl, R2-substituted monocyclic 5-membered ring heteroaryl, and R2'-substituted monocyclic heterocyclyl moieties;

W and Y are CHR₄, NR₃, or O and wherein W and Y are not simultaneously O;

X is O, S, or NR₃;

each Z₁ is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC₁-C₆alkyl, C₂-C₆alkoxy, C₁-C₆alkoxyC₁-C₆alkyl, (R₄)₂NC₁-C₆alkyl, (R₄)₂NC₂-C₆alkylN(R₄)-(CH₂)_n, (R₄)₂NC₂-C₆alkylO-(CH₂)_n, (R₃)₂N-C(=O)-, (R₄)₂N-C(=O)-, (R₄)₂N-CO-C₁-C₆alkyl, C₁-C₆alkoxycarbonyl, carboxyC₁-C₆alkyl, C₁-C₆alkoxycarbonylC₁-C₆alkyl, (R₃)₂NSO₂, SO₂R₃, (R₄)₂NSO₂, -SO₂R₃', -SO₂R₄, -C(=O)R₆, -C(=NOH)R₆, -C(=NOR₃)R₆, -(CH₂)_nN(R₄)C(O)R₈, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC₁-C₆alkyl, monocyclic heterocyclylC₁-C₆alkyl, monocyclic heteroaryloxy, monocyclic heterocyclioxy, monocyclic heteroaryloxyC₁-C₆alkyl, monocyclic heterocyclioxyC₁-C₆alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC₁-C₆alkyl, monocyclic heteroarylaminoC₁-C₆alkyl, monocyclic heterocyclylaminoC₁-C₆alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A₂ ring is meta to the point of attachment to the A₁ ring and wherein A₂ is phenyl, and cyano wherein the site of attachment is to a substitutable position when A₂ is pyridyl, pyrimidinyl or a five-membered ring;

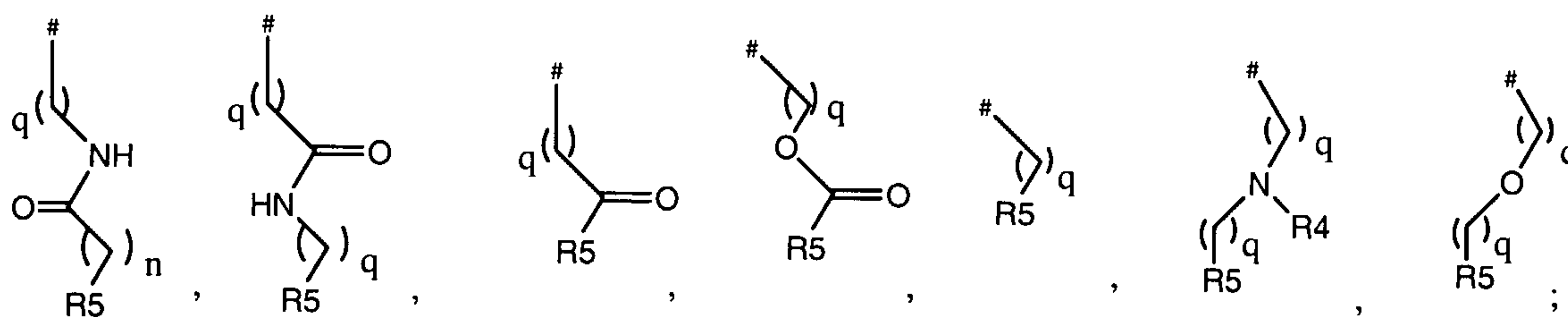
wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

each Z4' is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4' moiety to the A1 ring of formula I;

in the event that Z4' contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4' may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4' may cyclize to form a C3-C7 heterocyclyl ring;

each R2 is selected from the group consisting of alkyl, branched alkyl, fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and C1-C6alkyl;

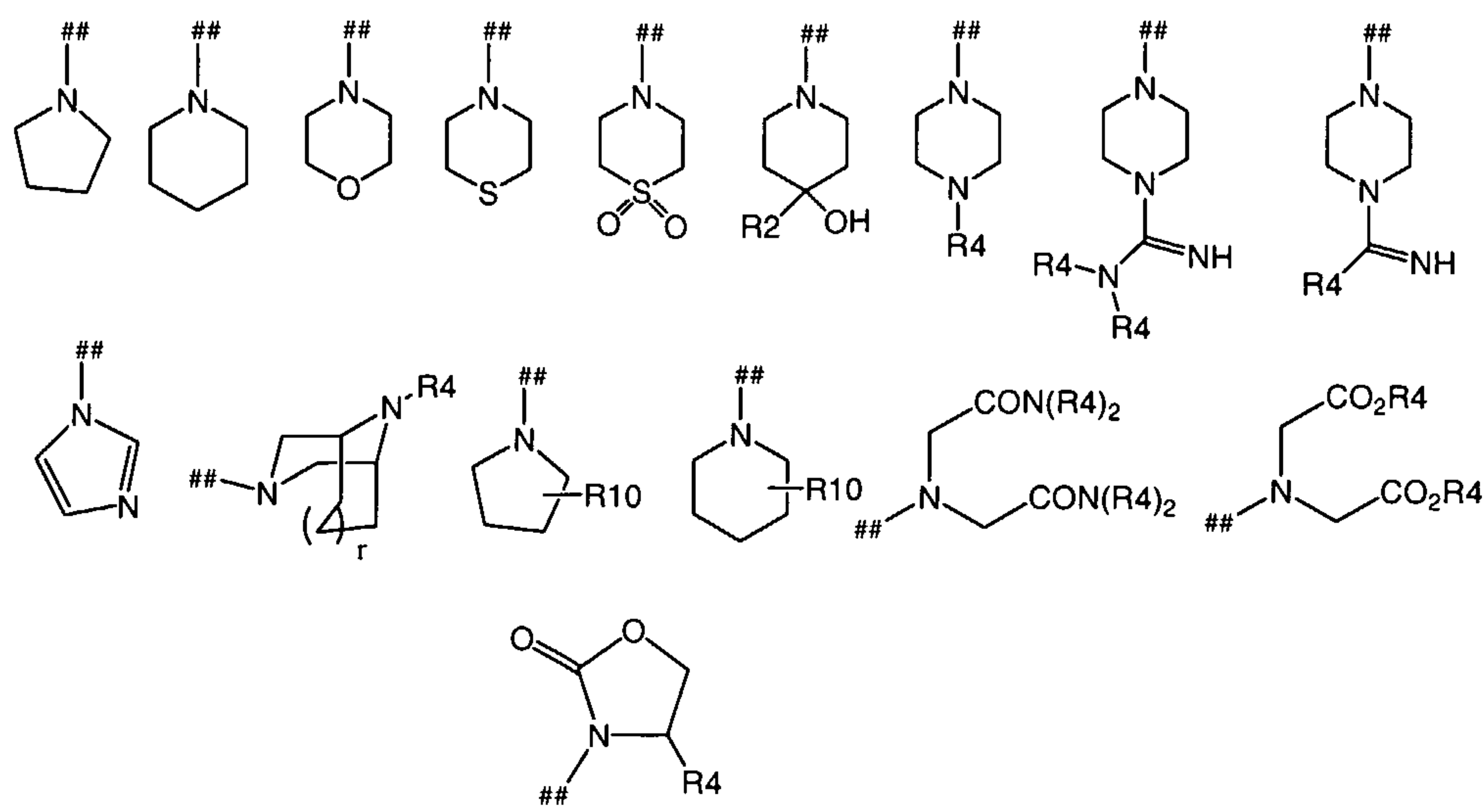
each R2' is selected from the group consisting of halogen and R2;

each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7cycloalkyl, or phenyl;

each R3' is independently and individually selected from the group consisting of C2-C6alkyl, branched C3-C7alkyl, C3-C7cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

each R5 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R8, R10, Z1, Z4', Z5, Z6 or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

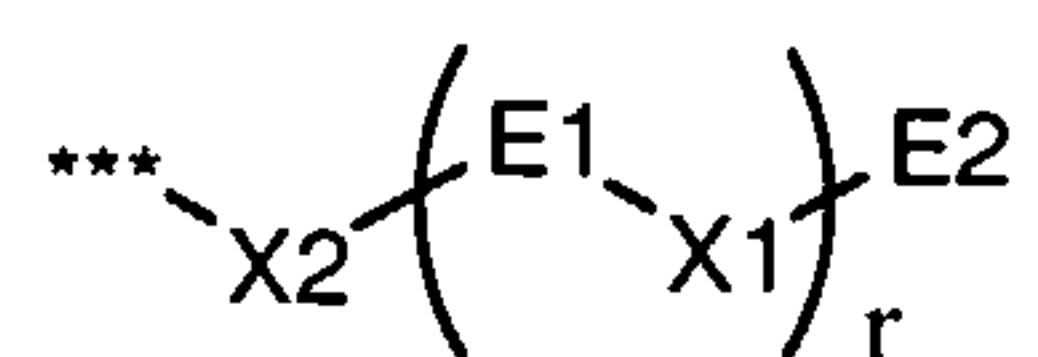
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

D comprises a moiety taken from group consisting of moieties of the formula



wherein the symbol (***) is the point of attachment to the Y group of formula I;

wherein E2 is taken from the group consisting of poly-aryl, poly-heteroaryl, mono- and poly heterocyclyl, and carbocyclyl;

wherein E1 is taken from the group consisting of mono- and poly-aryl, mono- and poly-heteroaryl, mono- and poly heterocyclyl and carbocyclyl;

X1 is selected from the group consisting of O, S, NR3, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR3-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR3-, -N(R3)-(CH₂)_q-N(R3)-, -(CH₂)_n-N(R4)-C(=O)-, -(CH₂)_n-N(R4)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R4)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, (CH₂)_p-, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein either E1 or E2 is directly linked to the Y group of formula I;

and n is 0-4; p is 1-4; q is 2-6, r is 0 or 1;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs, and salts of any of the foregoing.

1.2.1 Preferred D Moieties

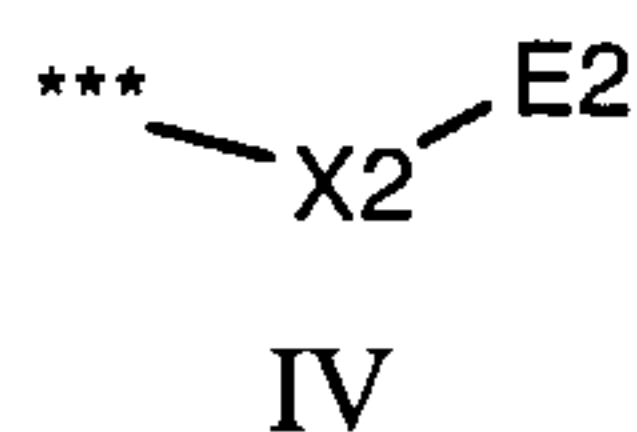
1.2.1a

Preferably, the compounds of formula I in 1.2 contain D moieties wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

wherein E2 comprises the group consisting of cyclopentyl, cyclohexyl, non-fused bicyclic rings comprising pyridylpyridiminy, pyrimidinylpyrimidinyl, oxazolylpyrimidinyl, thiazolylpyrimidinyl, imidazolylpyrimidinyl, isoxazolylpyrimidinyl, isothiazolylpyrimidinyl, pyrazolylpyrimidinyl, triazolylpyrimidinyl, oxadiazoylpyrimidinyl, thiadiazoylpyrimidinyl, morpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, and heterocyclyls selected from the group comprising oxetanyl, azetadiny, tetrahydrofuranyl, pyrrolidinyl, oxazoliny, oxazolidiny, imidazolony, pyranyl, thiopyranyl, tetrahydropyranyl, dioxaliny, piperidinyl, morpholinyl, thiomorpholinyl, dioxothiomorpholinyl, piperaziny, azepiny, oxepiny, diazepiny, tropanyl, and homotropanyl.

1.2.1b

Additionally preferred D moieties of formula I in 1.2 comprise a formula



wherein X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E2 is directly linked to the Y group of formula I.

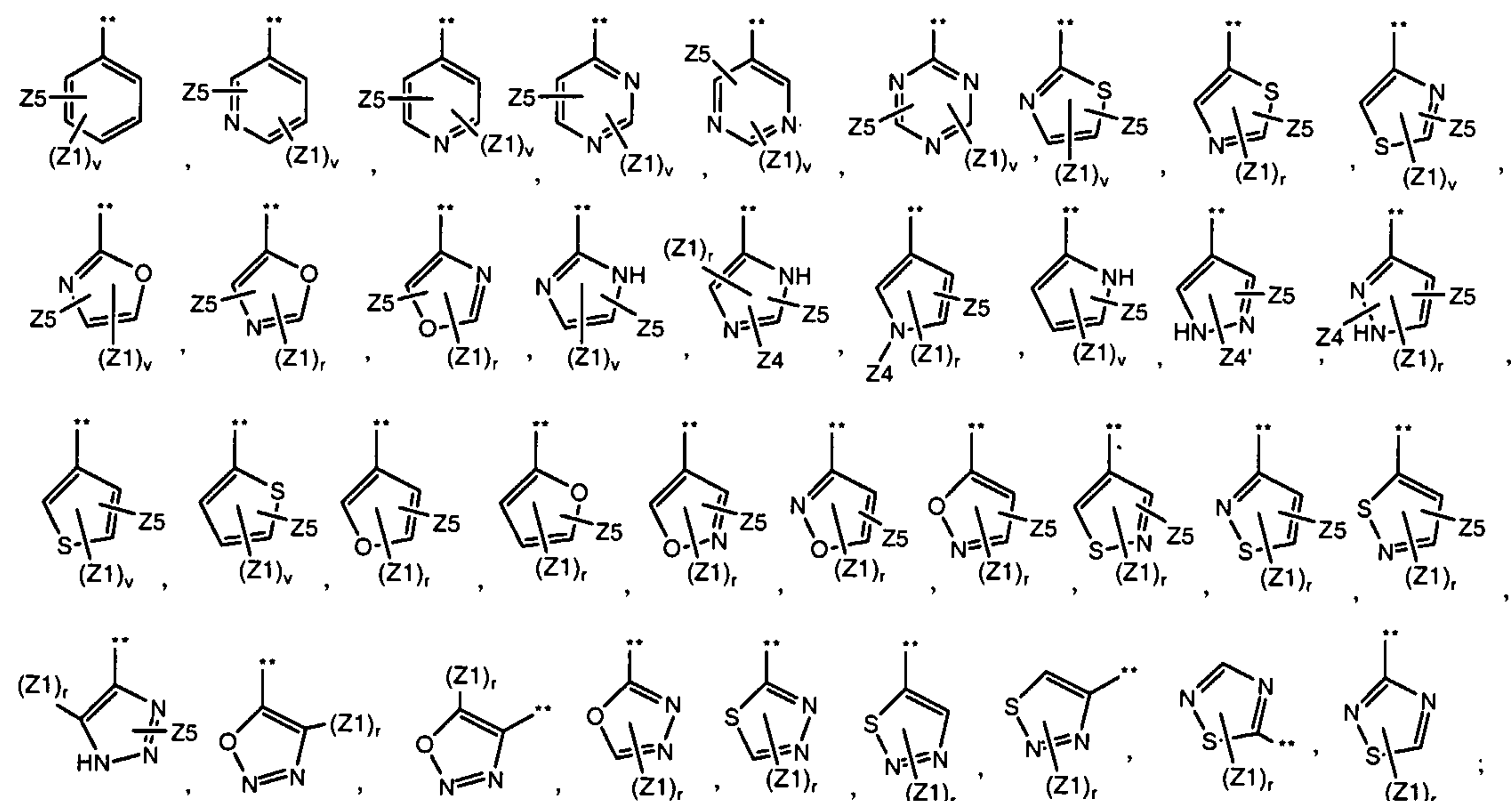
1.2.1c

More preferred D moieties of 1.2.1b are wherein E2 is cyclopentyl, cyclohexyl, non-fused bicyclic rings comprising pyridylpyridiminy, pyrimidinylpyrimidinyl, oxazolylpyrimidinyl, thiazolylpyrimidinyl, imidazolylpyrimidinyl, isoxazolylpyrimidinyl, isothiazolylpyrimidinyl,

pyrazolylpyrimidinyl, triazolylpyrimidinyl, oxadiazoylpyrimidinyl, thiadiazoylpyrimidinyl, morpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, and heterocyclyls selected from the group comprising oxetanyl, azetadiny, tetrahydrofuranyl, pyrrolidinyl, oxazoliny, oxazolidiny, imidazolonyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxaliny, piperidinyl, morpholinyl, thiomorpholinyl, dioxothiomorpholinyl, piperazinyl, azepiny, oxepiny, diazepiny, tropanyl, and homotropanyl.

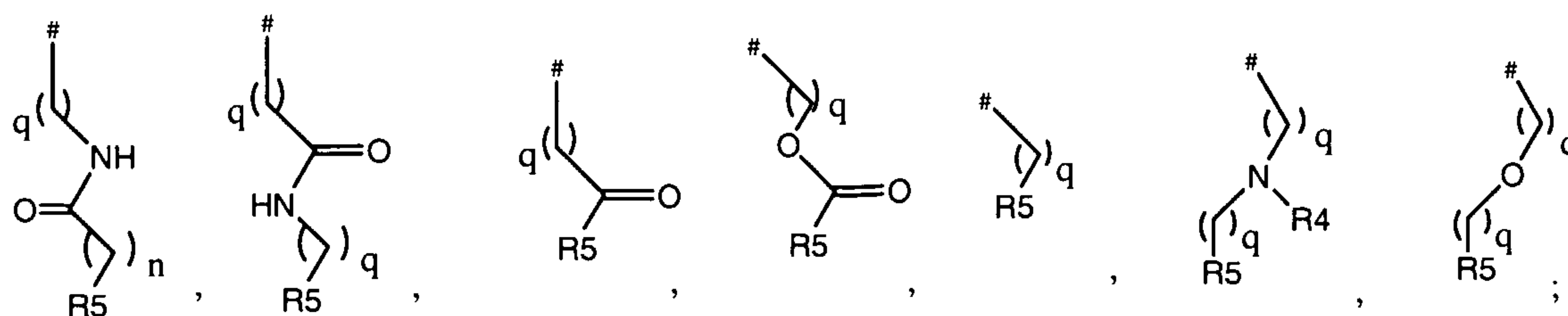
1.2.2 Preferred A2 Moieties

1.2.2a



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I;

each Z4 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

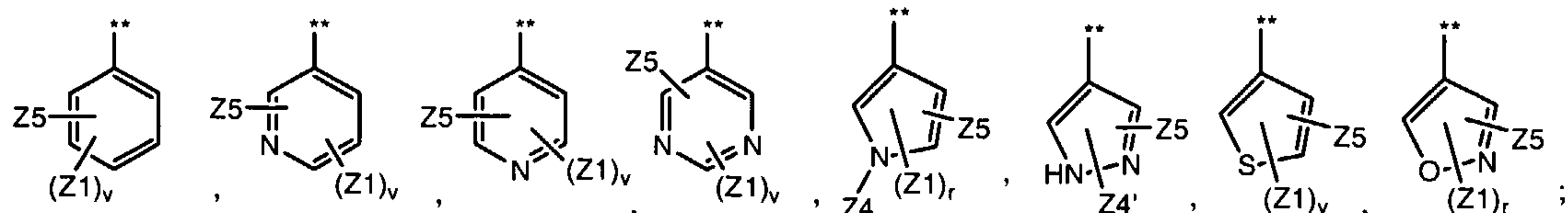
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2.

1.2.2b

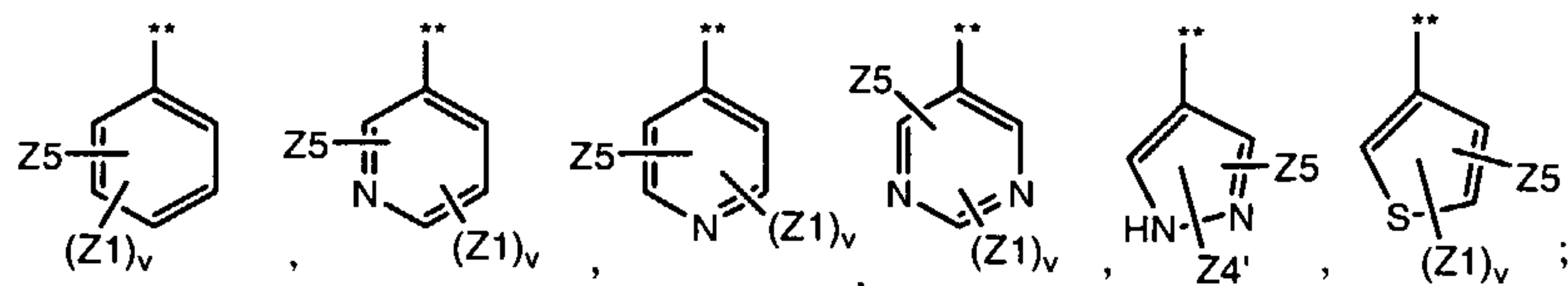
More preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring for formula I.

1.2.2c

Even more preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I.

*1.2.3 Preferred Classes of Compounds**1.2.3a*

Compounds as defined in *1.2.1a* wherein the A2 group is defined in *1.2.2a*.

1.2.3b

Compounds as defined in *1.2.3a* wherein the A2 group is defined in *1.2.2b*.

1.2.3c

Compounds as defined in *1.2.3a* wherein the A2 group is defined in *1.2.2c*.

1.2.3d

Compounds as defined in *1.2.1b* wherein the A2 group is defined in *1.2.2a*.

1.2.3e

Compounds as defined in *1.2.3c* wherein the A2 group is defined in *1.2.2b*.

1.2.3f

Compounds as defined in *1.2.3c* wherein the A2 group is defined in *1.2.2c*.

*1.2.4 Preferred A1 Moieties**1.2.4a*

These preferred A1 moieties are defined in *1.1.4a*.

1.2.4b

These more preferred A1 moieties are defined in *1.1.4b*.

1.2.4c

These even more preferred A1 moieties are defined in 1.1.4c.

1.2.5 Preferred W and Y Moieties

1.2.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR⁴ and X=O; or (3) W=CHR⁴, Y=NH, and X=O.

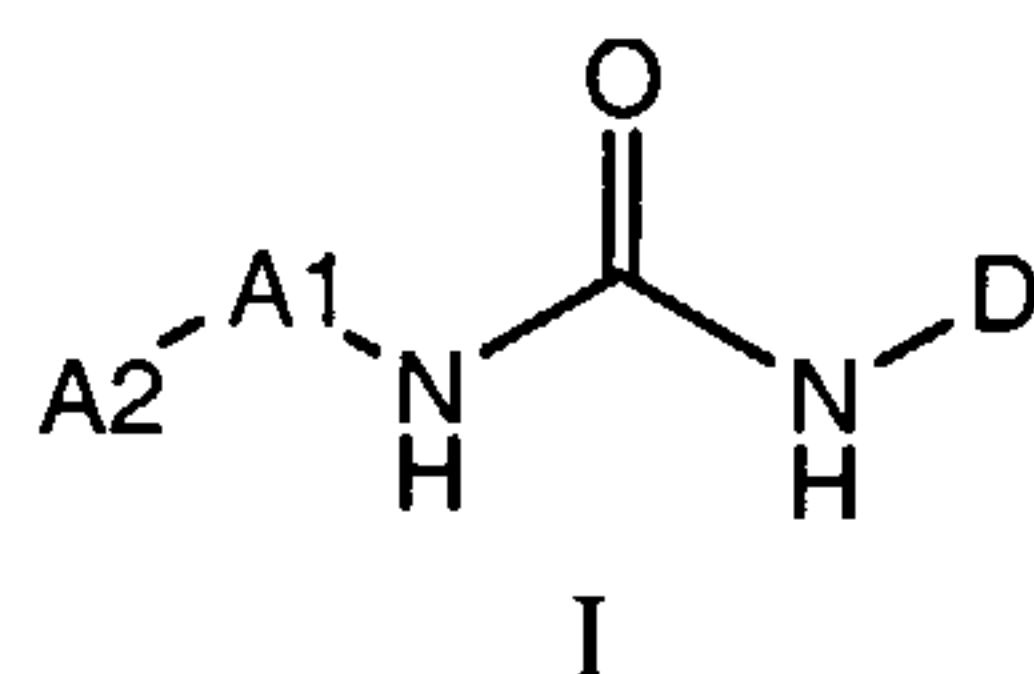
1.2.5b

W and Y are each NH and X=O.

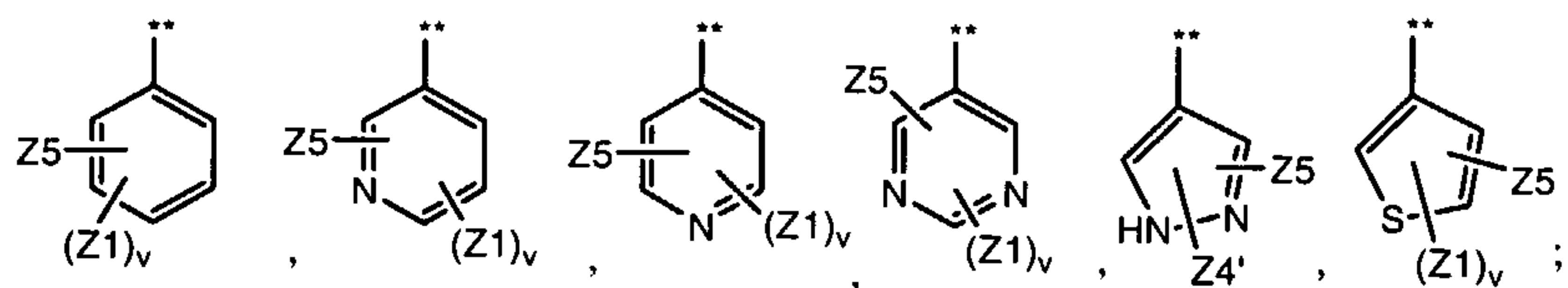
1.2.6 Further Preferred Compounds

1.2.6a

The invention includes compounds of the formula

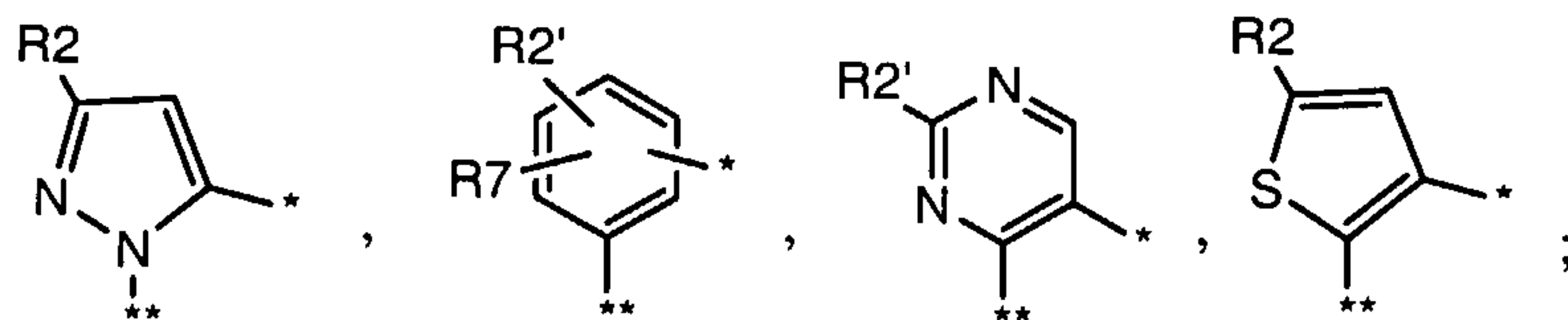


wherein A2 is selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I.

A1 is selected from the group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

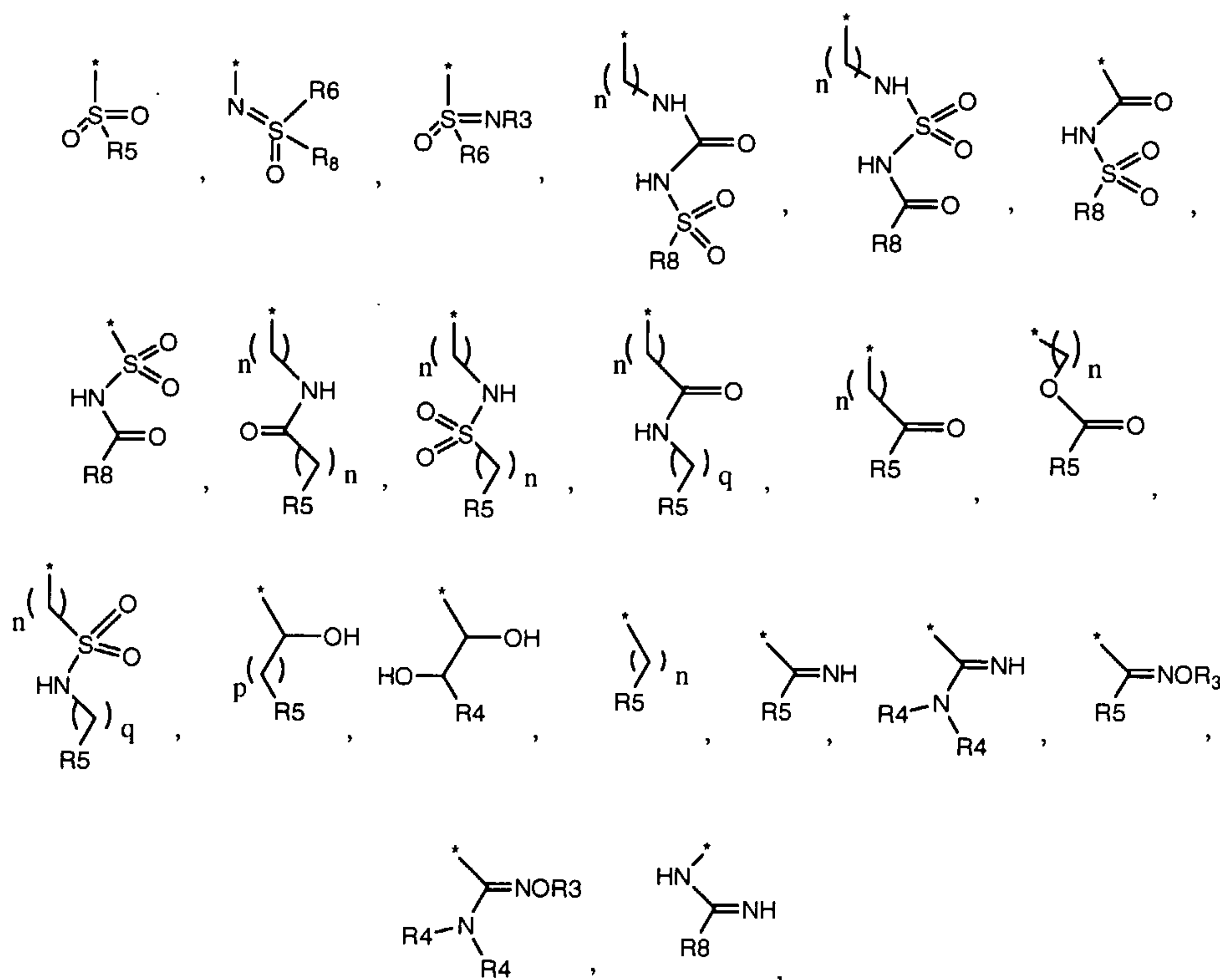
X is O, S, or NR³;

D comprises a member of

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

each Z1 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC1-C6alkyl, C2-C6alkoxy, C1-C6alkoxyC1-

C6alkyl, (R4)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, (R3)₂N-C(=O)-, (R4)₂N-C(=O)-, (R4)₂N-CO-C1-C6alkyl, C1-C6alkoxycarbonyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)₂NSO₂, SOR3, (R4)₂NSO₂, -SO₂R3', -SOR4, -C(=O)R6, -C(=NOH)R6, -C(=NOR3)R6, -(CH₂)_nN(R4)C(O)R8, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocycliloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocycliloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

In the foregoing definition of Z1, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

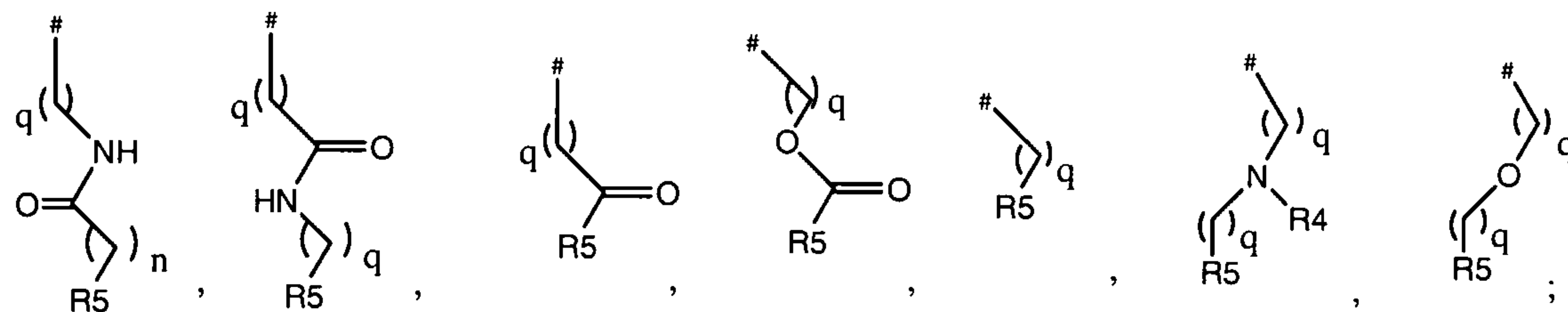
Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



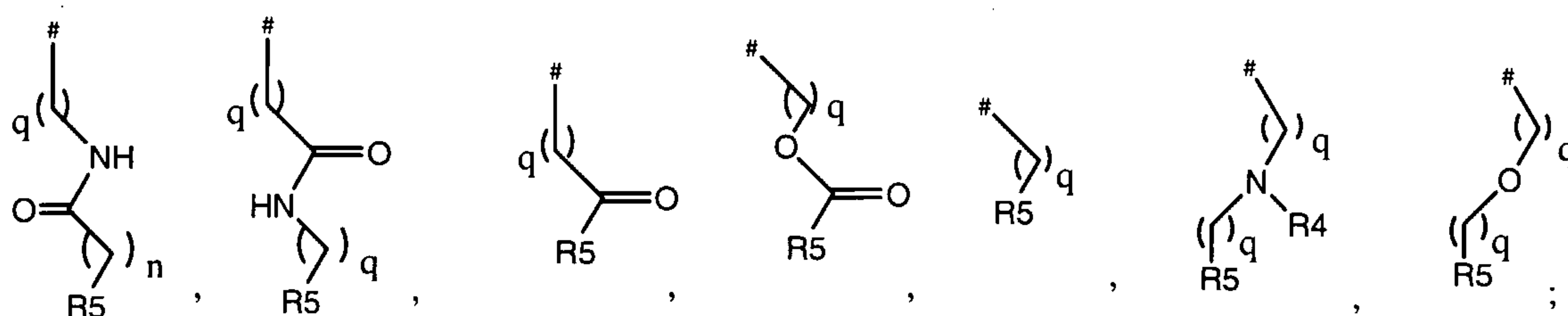
wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

each Z4' is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclioxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoc2-C6alkyl, heterocyclylaminoc2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4' moiety to the A1 ring of formula I;

in the event that Z4' contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4' may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4' may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-

N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

each R2 is selected from the group consisting of alkyl, branched alkyl, fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and C1-C6alkyl;

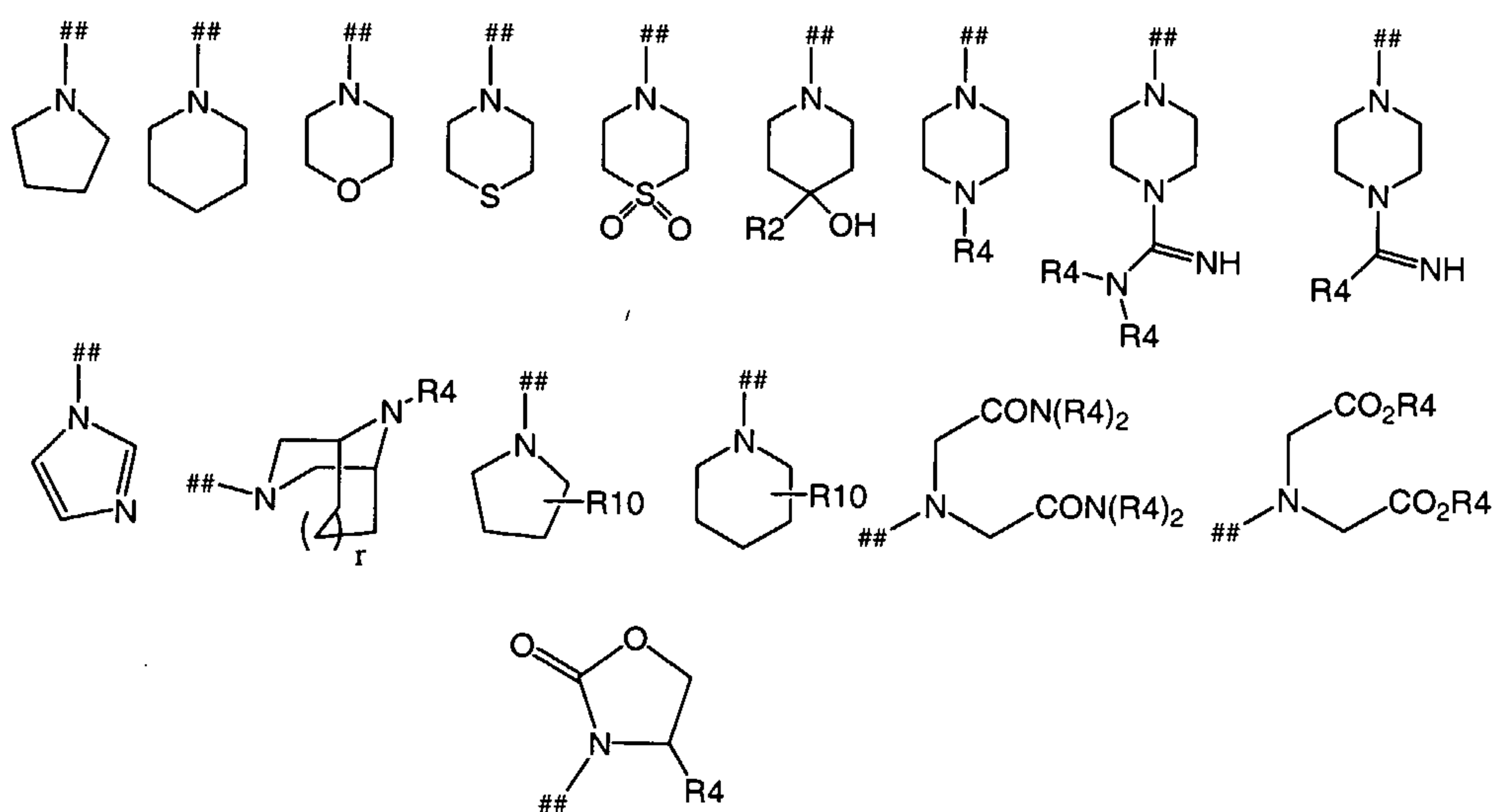
each R2' is selected from the group consisting of halogen and R2;

each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7cycloalkyl, or phenyl;

each R3' is independently and individually selected from the group consisting of C2-C6alkyl, branched C3-C7alkyl, C3-C7cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

each R5 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R8, R10, Z1, Z4', Z5, Z6 or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branchedC4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

1.2.6b

The following specific compounds are most preferred: 1-(3-t-butyl-1-(3-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea, 1-(2-(3-(2-

amino-2-oxoethyl)phenyl)-5-t-butylthiophen-3-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea, 1-(1-(3-(1H-pyrazol-4-yl)phenyl)-3-cyclopentyl-1H-pyrazol-5-yl)-3-(4-(6-(thiazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-cyclopentyl-1H-pyrazol-5-yl)-3-(3-(4-(pyridin-3-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-cyclopentyl-1H-pyrazol-5-yl)-3-(3-(4-(isoxazol-4-yl)pyrimidin-2-ylamino)phenyl)urea, 1-(1-(3-(1H-pyrazol-4-yl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea

1.2.7 Methods

1.2.7a Methods of Protein Modulation

The invention includes methods of modulating kinase activity of a variety of kinases, e.g. C-Abl kinase, BCR-Abl kinase. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 1.2 and 1.2.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

The methods of the invention may also involve the step of inducing, synergizing, or promoting the binding of a second modulator compound of said kinase, especially C-Abl kinase or BCR-Abl kinase, to form a ternary adduct, such co-incident binding resulting in enhanced biological modulation of the kinase when compared to the biological modulation of the protein affected by either of said compounds alone. The second compound may interact at a substrate, co-factor or regulatory site on the kinase, with the second site being distinct from the site of interaction of the first compound. For example, the second site may be an ATP co-factor site. The second compounds may be taken from the group consisting of N-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide(Gleevec®); N-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825); 6-(2,6-dichlorophenyl)-2-(3-(hydroxymethyl)phenylamino)-8-methylpyrido[2,3-

d]pyrimidin-7(8H)-one (PD 166326); 6-(2,6-dichlorophenyl)-8-methyl-2-(3-(methylthio)phenylamino)pyrido[2,3-d]pyrimidin-7(8H)-one (PD 173955); 6-(2,6-dichlorophenyl)-2-(4-fluoro-3-methylphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD180970); 6-(2,6-dichlorophenyl)-2-(4-ethoxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 173958); 6-(2,6-dichlorophenyl)-2-(4-fluorophenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 173956); 6-(2,6-dichlorophenyl)-2-(4-(2-(diethylamino)ethoxy)phenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 166285); 2-(4-(2-aminoethoxy)phenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one; N-(3-(6-(2,6-dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)phenyl)acetamide (SKI DV-MO16); 2-(4-aminophenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 1-10); 6-(2,6-dichlorophenyl)-2-(3-hydroxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV2-89); 2-(3-aminophenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 2-43); N-(4-(6-(2,6-dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)phenyl)acetamide (SKI DV-M017); 6-(2,6-dichlorophenyl)-2-(4-hydroxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV-M017); 6-(2,6-dichlorophenyl)-2-(3-ethylphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 2 87).

1.2.7b Treatment Methods

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer and hyperproliferative diseases. These methods comprise administering to such individuals compounds of the invention, and especially those of section 1.2 and 1.2.6a. Exemplary conditions include chronic myelogenous leukemia, acute lymphocytic leukemia, gastrointestinal stromal tumors, and hypereosinophilic syndrome. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

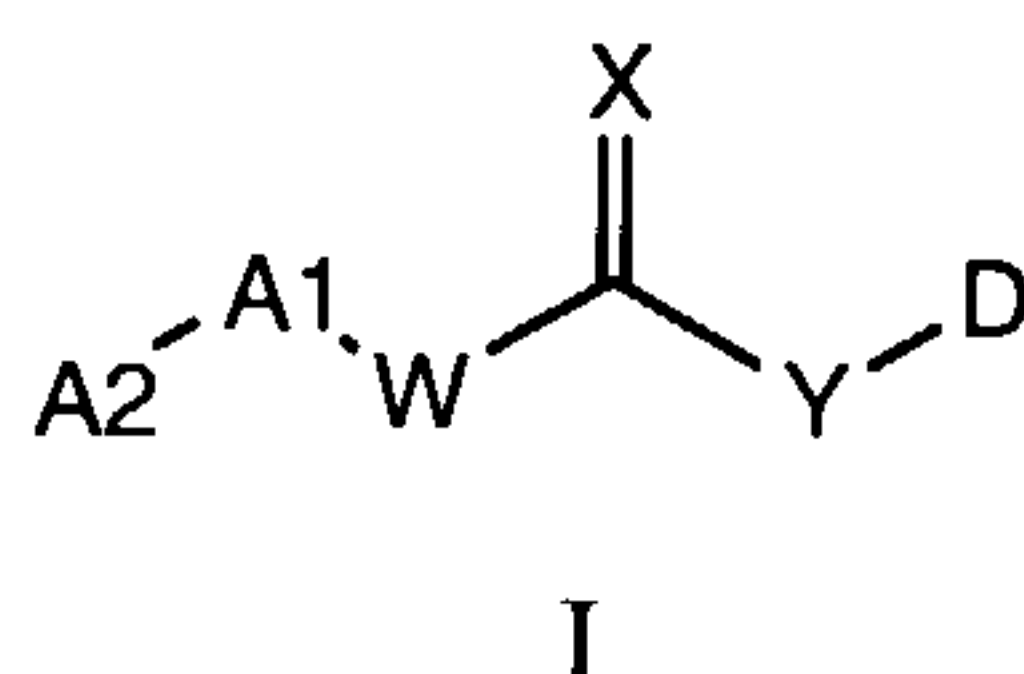
1.2.8 Pharmaceutical Preparations

The compounds of the invention, especially those of 1.2 and 1.2.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

1.2.9 Kinase/Compound Adducts

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 1.2 and 1.2.6a.

1.3 Generally – Monocyclic A2 Compounds with Monocyclic E2 Rings



wherein A2 is selected from the group consisting of a Z7-substituted phenyl, Z7-substituted pyridyl, Z7-substituted pyrimidinyl, Z1-substituted thienyl, Z1 or Z4'-substituted monocyclic heterocyclyl rings and other monocyclic heteroaryls, excluding tetrazolyl, 1,2,4-oxadiazolonyl, 1,2,4-triazolonyl, and alkyl-substituted pyrrolyl wherein the pyrrolyl nitrogen is the site of attachment to the A1 ring;

A1 is selected from the group consisting of R2' and R7-substituted phenyl, pyridyl, or pyrimidinyl, R2-substituted monocyclic 5-membered ring heteroaryl, and R2'-substituted monocyclic heterocyclyl moieties;

W and Y are CHR4, NR3, or O and wherein W and Y are not simultaneously O;

X is O, S, or NR3;

each R2 is selected from the group consisting of alkyl, branched alkyl, fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and C1-C6alkyl;

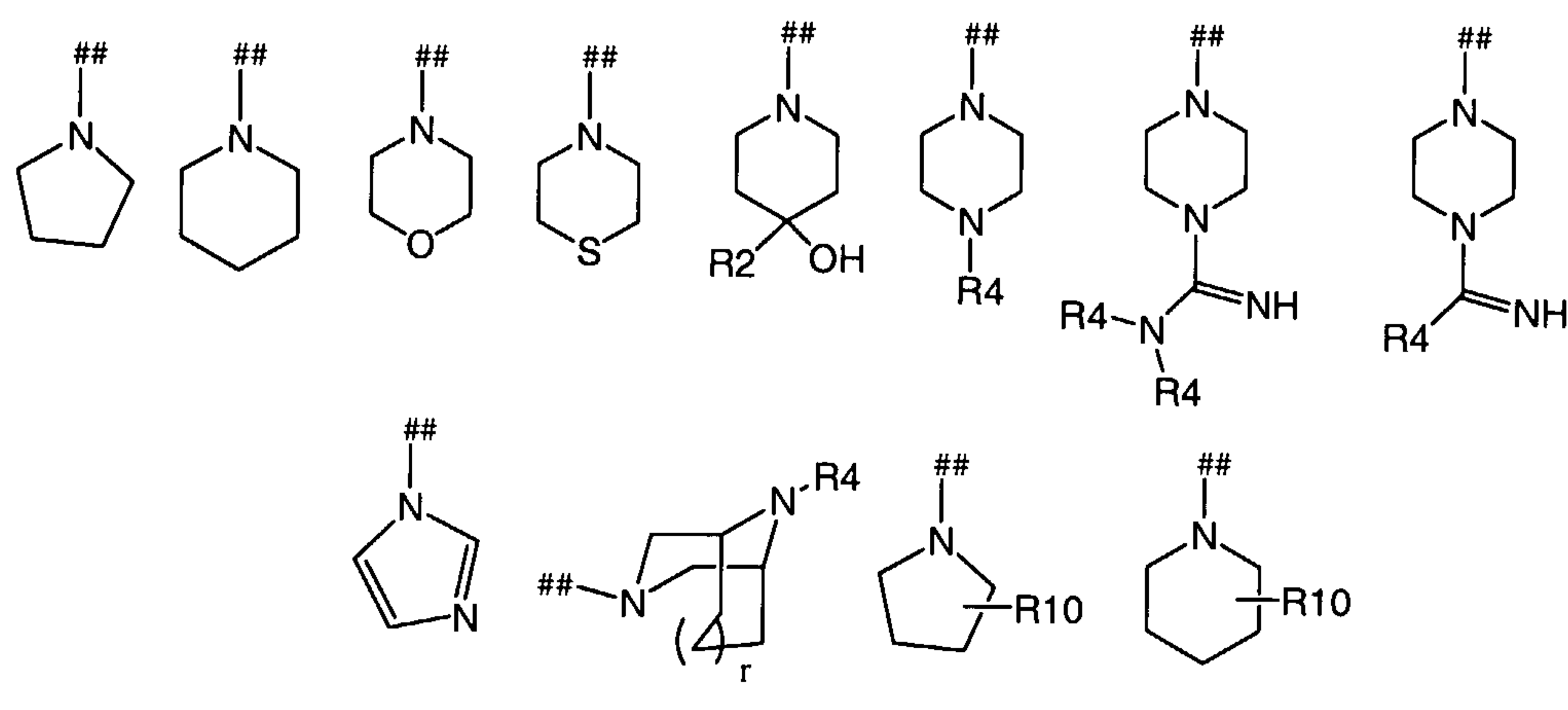
each R2' is selected from the group consisting of halogen and R2;

each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7cycloalkyl, or phenyl;

each R3' is independently and individually selected from the group consisting of C2-C6alkyl, branched C3-C7alkyl, C3-C7cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

each R5 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R8, R10, Z1, Z4', Z5, Z6 and Z7 moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

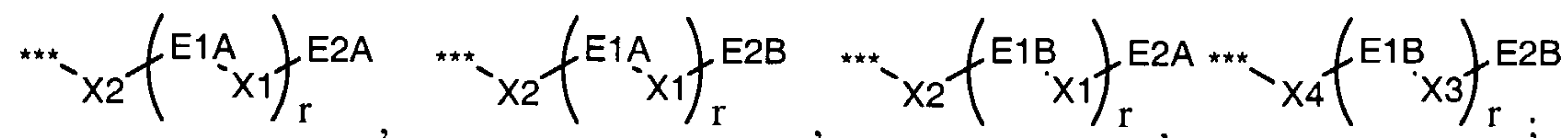
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

D comprises a moiety taken from group consisting of



wherein the symbol (***) is the point of attachment to the Y group of formula I;

wherein E1A is taken from the groups consisting of carbocyclyl, mono- and poly-heterocyclyl and mono- and poly- heteroaryl;

wherein E1B is taken from the groups consisting of phenyl and naphthyl;

wherein E2A is taken from the group consisting of naphthyl, a 5-membered ring heteroaryl, or a fused bicyclic heteroaryl;

wherein E2B is taken from the group consisting of phenyl, pyridyl, and pyrimidyl;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1A or E1B ring and the E2A or E2B ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, (CH₂)_p, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1A or E1B or E2A or E2B are directly linked to the Y group of formula I;

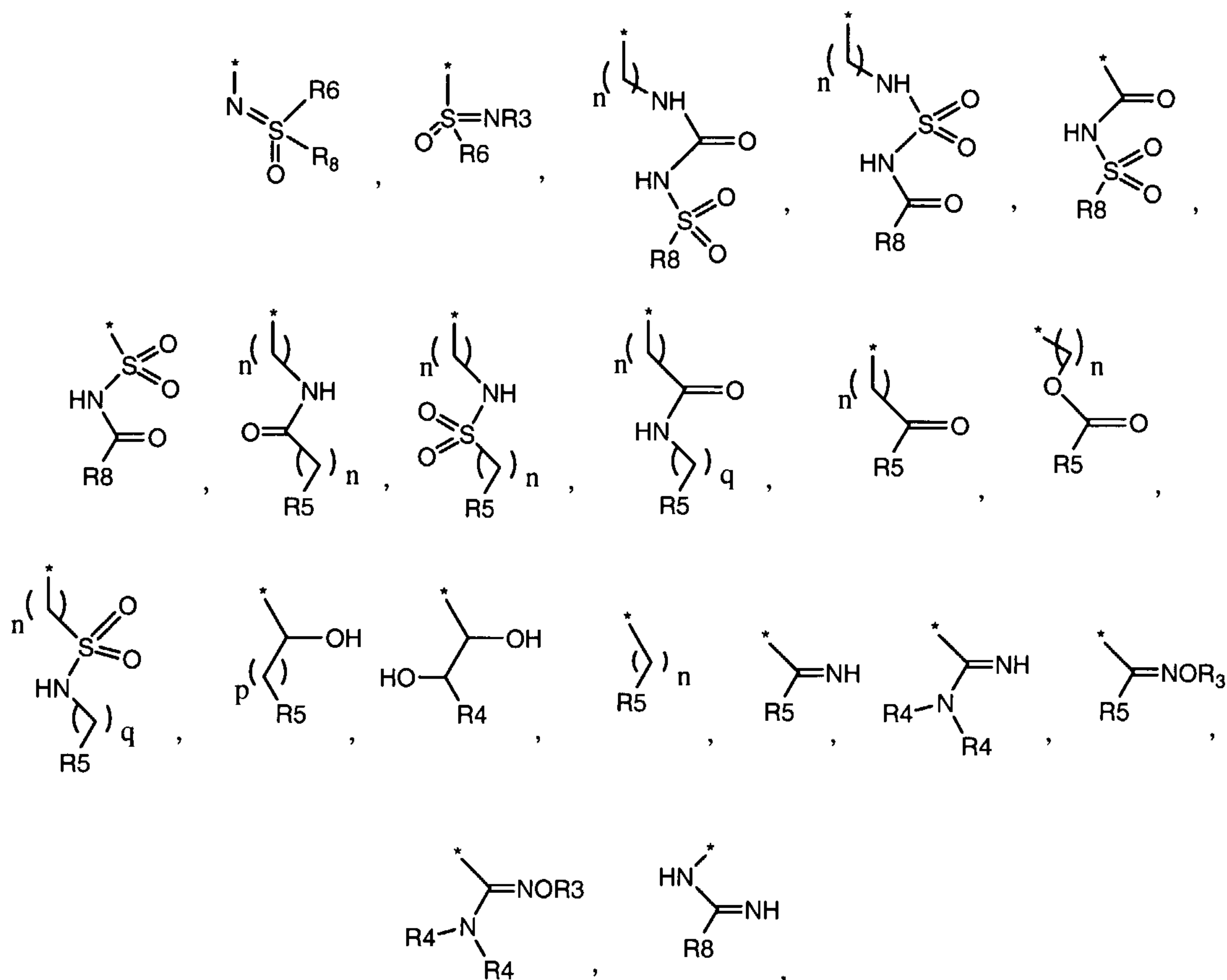
X3 is selected from the group consisting of NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_q-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the either the E1B ring or E2B ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_q-, C2-C5alkenyl, and C2-C5alkynyl moieties of X3 may be further substituted by one or more C1-C6alkyl;

X4 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl;

each Z1 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC1-C6alkyl, C2-C6alkoxy, C1-C6alkoxyC1-C6alkyl, (R₄)₂NC1-C6alkyl, (R₄)₂NC2-C6alkylN(R₄)-(CH₂)_n, (R₄)₂NC2-C6alkylO-(CH₂)_n, (R₃)₂N-C(=O)-, (R₄)₂N-C(=O)-, (R₄)₂N-CO-C1-C6alkyl, C1-C6alkoxycarbonyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, (R₃)₂NSO₂, SO₂R₃, (R₄)₂NSO₂, -SO₂R₃', -SO₂R₄, -C(=O)R₆, -C(=NOH)R₆, -C(=NOR₃)R₆, -(CH₂)_nN(R₄)C(O)R₈, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocyclyloxy, monocyclic

heteroaryloxyC1-C6alkyl, monocyclic heterocyclyloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



and cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

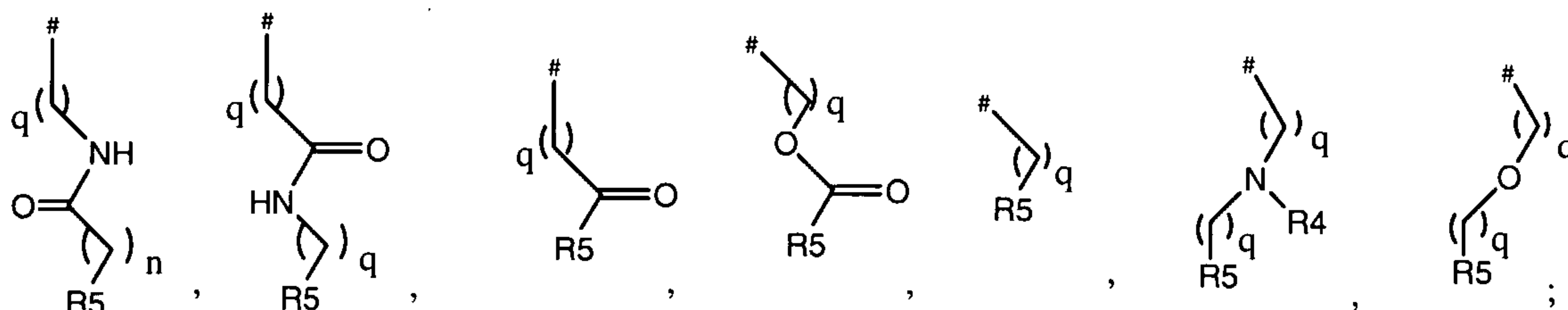
Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

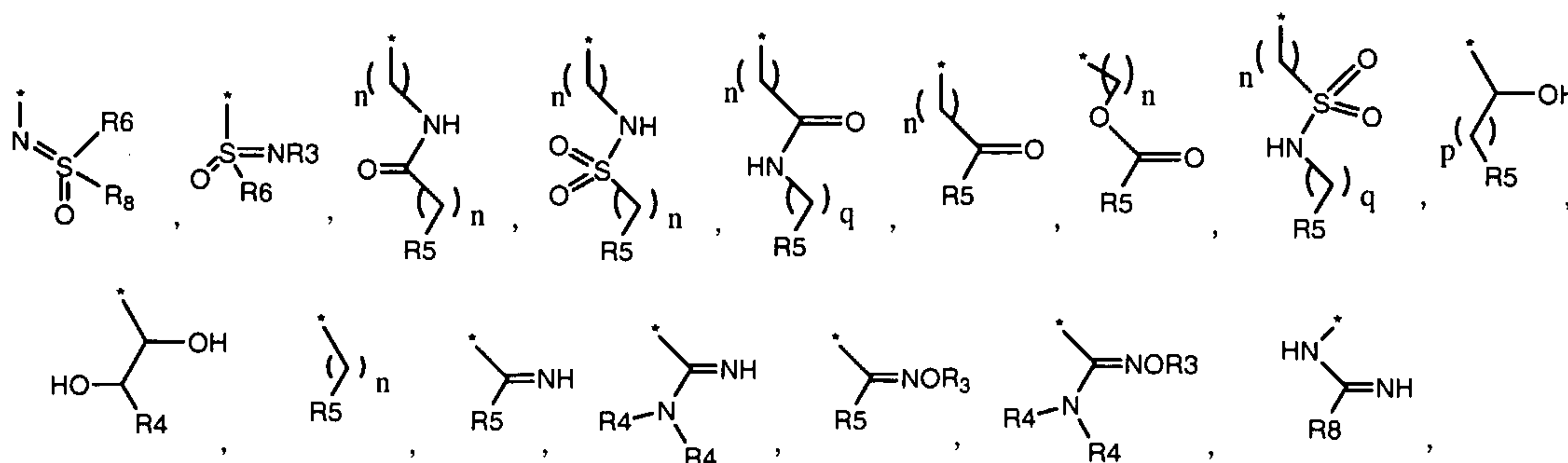
each Z4' is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyoxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4' moiety to the A1 ring of formula I;

in the event that Z4' contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

each Z7 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R6)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, (R3)₂N-CO, (R4)₂N-CO, -SO₂R3', SOR3, -SOR4, -C(=O)R6, -C(=NOH)R6, -C(=NOR3)R6, (CH₂)_nN(R4)C(O)N(R4)₂, (CH₂)_nN(R4)C(O)R5, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocyclyoxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocyclyoxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

In the foregoing definition of Z7, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z7 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z7 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z7 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6, r is 0 or 1;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs, and salts of any of the foregoing.

1.3.1 Preferred D Moieties

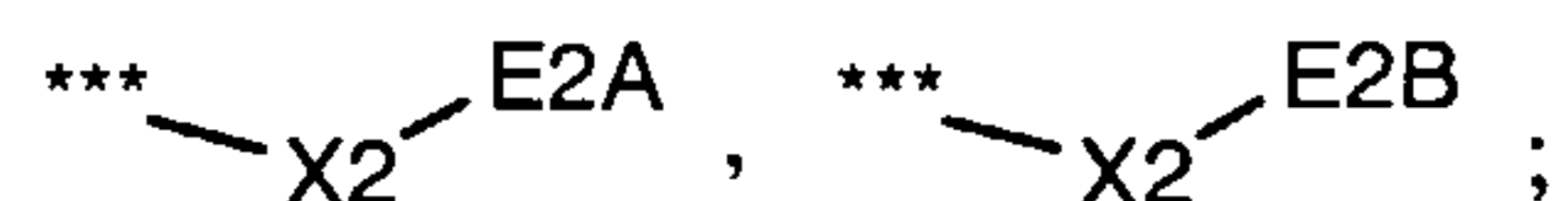
1.3.1a

Preferably, the compounds of formula I in 1.3 contain D moieties wherein E1A is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

wherein E2A is comprises the group consisting of cyclopentyl, cyclohexyl, non-fused bicyclic rings comprising pyridylpyridiminy, pyrimidinylpyrimidinyl, oxazolylpyrimidinyl, thiazolylpyrimidinyl, imidazolylpyrimidinyl, isoxazolylpyrimidinyl, isothiazolylpyrimidinyl, pyrazolylpyrimidinyl, triazolylpyrimidinyl, oxadiazoylpyrimidinyl, thiadiazoylpyrimidinyl, morpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, and heterocyclyls selected from the group comprising oxetanyl, azetadiny, tetrahydrofuranyl, pyrrolidinyl, oxazoliny, oxazolidiny, imidazolony, pyranyl, thiopyranyl, tetrahydropyranyl, dioxaliny, piperidinyl, morpholinyl, thiomorpholinyl, dioxothiomorpholinyl, piperazinyl, azepiny, oxepiny, diazepiny, tropanyl, and homotropanyl.

1.3.1b

Additionally preferred D moieties of formula I in 1.3 comprise a formula



X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E2A or E2B is directly linked to the Y group of formula I.

1.3.1c

More preferred D moieties of 1.3.1b are wherein the E2A ring is selected from the group comprising naphthyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, triazinyl and fused bicyclic rings selected from the group comprising indolyl, isoindolyl, isoindolinyl, isoindolonyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, imidazopyrimidinyl, imidazolopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, furylopyrimidinyl, thienopyrimidinyl, phthalimidyl, phthalimidiny, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnoliny, quinoxaliny, quinazoliny, quinoliny, isoquinoliny,

1.3.2a

1.3.2b

The figure shows eight chemical structures representing different heterocyclic compounds. Each structure has a double bond between two adjacent atoms in the ring, which are labeled with a double asterisk (**). The first structure is a benzene ring with a substituent Z5 at position 1 and a substituent (Z1)_v at position 4. The second structure is a pyridine ring with a substituent Z5 at position 1 and a substituent (Z1)_v at position 4. The third structure is a pyrimidine ring with a substituent Z5 at position 1 and a substituent (Z1)_v at position 4. The fourth structure is a purine ring with a substituent Z5 at position 1 and a substituent (Z1)_r at position 9. The fifth structure is a pyrrole ring with a substituent Z5 at position 1 and a substituent (Z1)_r at position 4. The sixth structure is a thiazole ring with a substituent Z5 at position 1 and a substituent (Z1)_v at position 4. The seventh structure is an oxazole ring with a substituent Z5 at position 1 and a substituent (Z1)_r at position 4. The eighth structure is a selenazole ring with a substituent Z5 at position 1 and a substituent (Z1)_r at position 4.

1.3.2c

1.3.3 Preferred Classes of Compounds

1.3.3a

1.3.3b

1.3.3c

1.3.3d

1.3.3e

1.3.3f

Compounds as defined in 1.3.3c wherein the A2 group is defined in 1.3.2c.

*1.3.4 Preferred A1 Moieties**1.3.4a*

These preferred A1 moieties are defined in *1.1.4a*.

1.3.4b

These more preferred A1 moieties are defined in *1.1.4b*.

1.3.4c

These even more preferred A1 moieties are defined in *1.1.4c*.

*1.3.5 Preferred W and Y Moieties**1.3.5a*

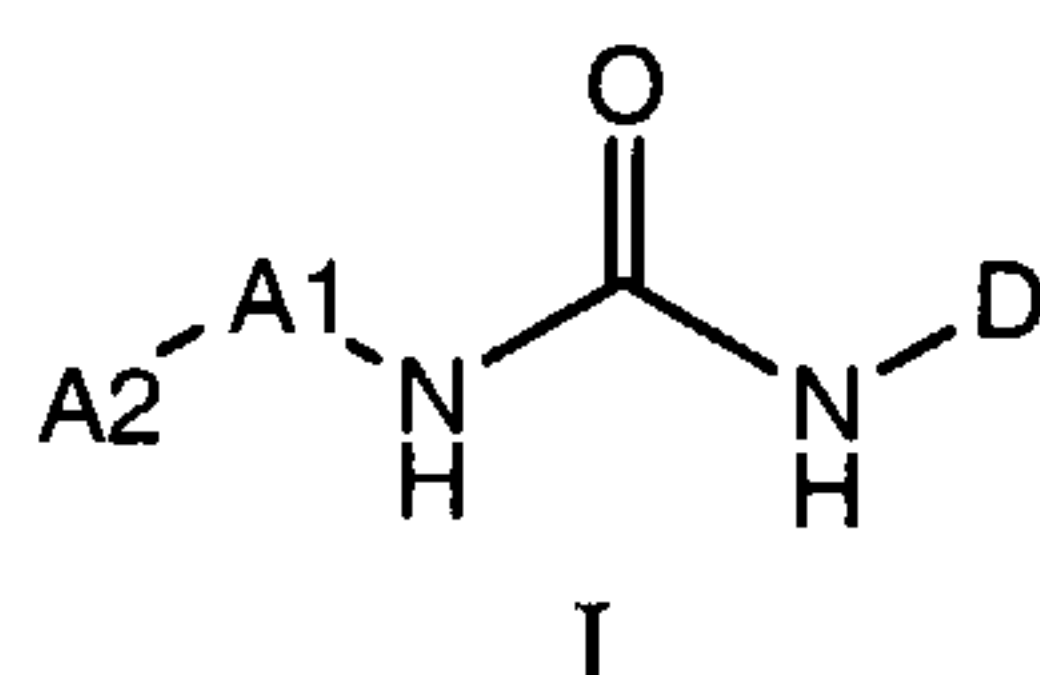
(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR⁴ and X=O; or (3) W=CHR⁴, Y=NH, and X=O.

1.3.5b

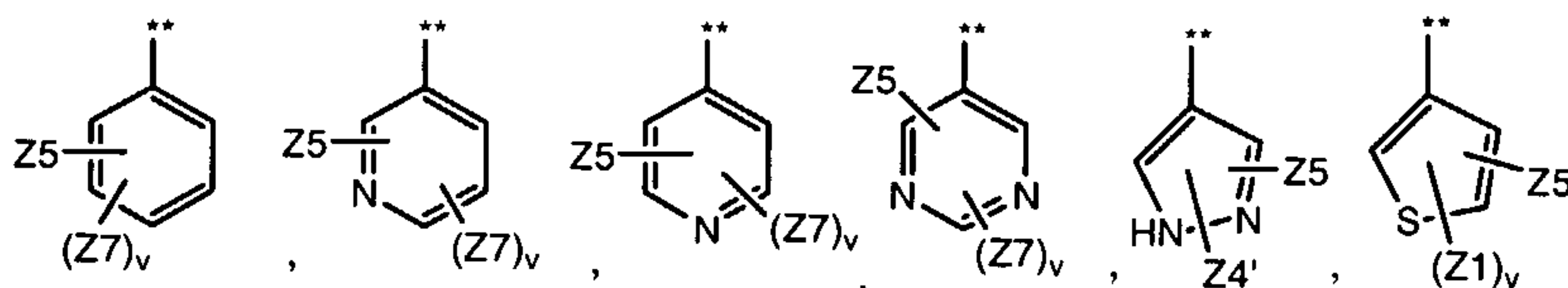
W and Y are each NH and X=O.

*1.3.6 Further Preferred Compounds**1.3.6a*

The invention includes compounds of the formula

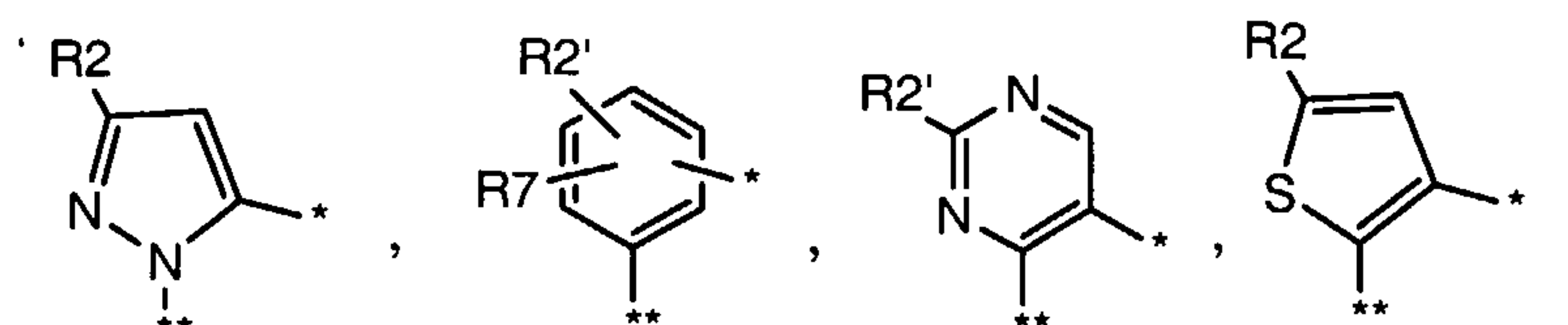


wherein A2 is selected from the group consisting of



wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

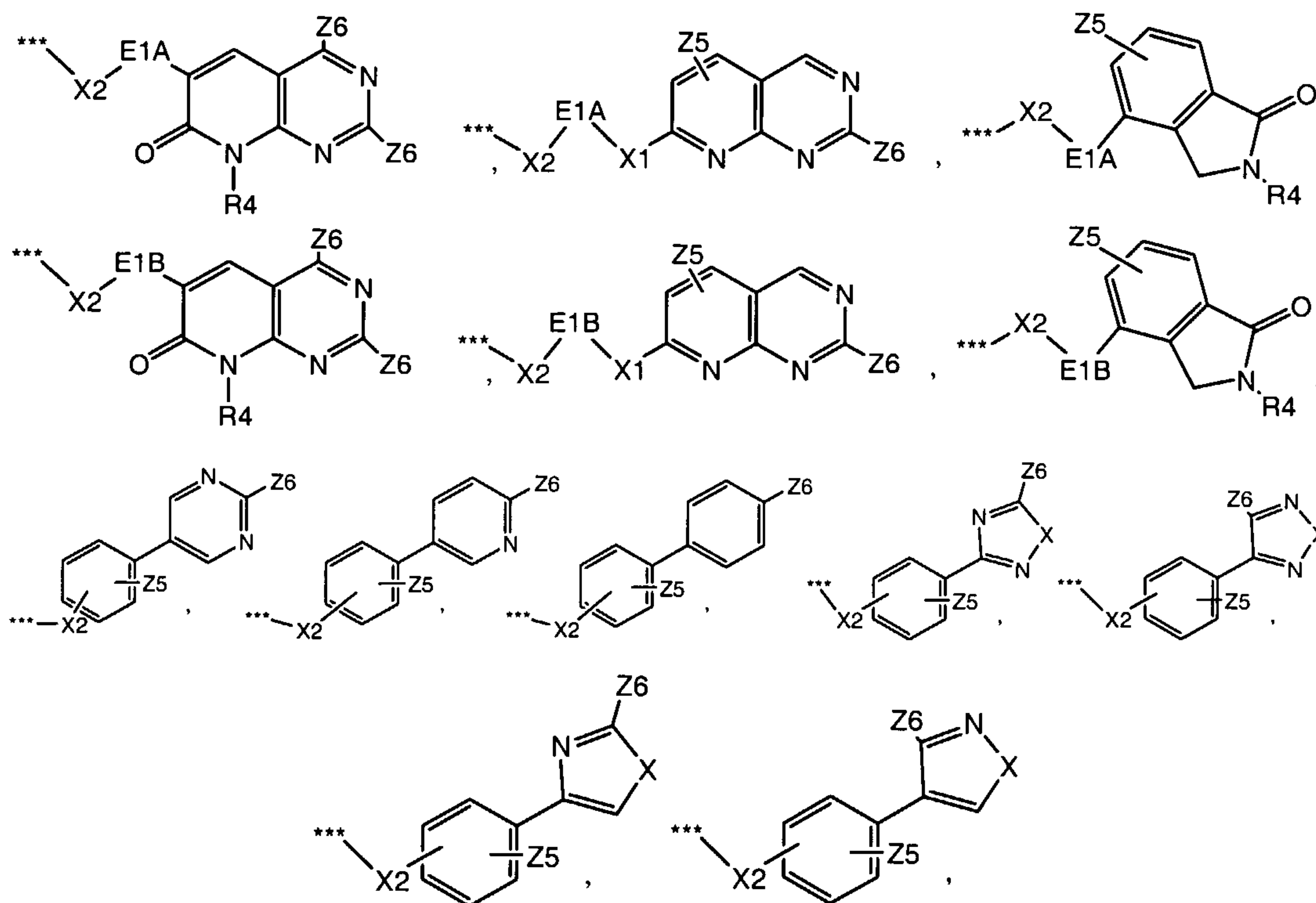
A1 is selected from the group consisting of

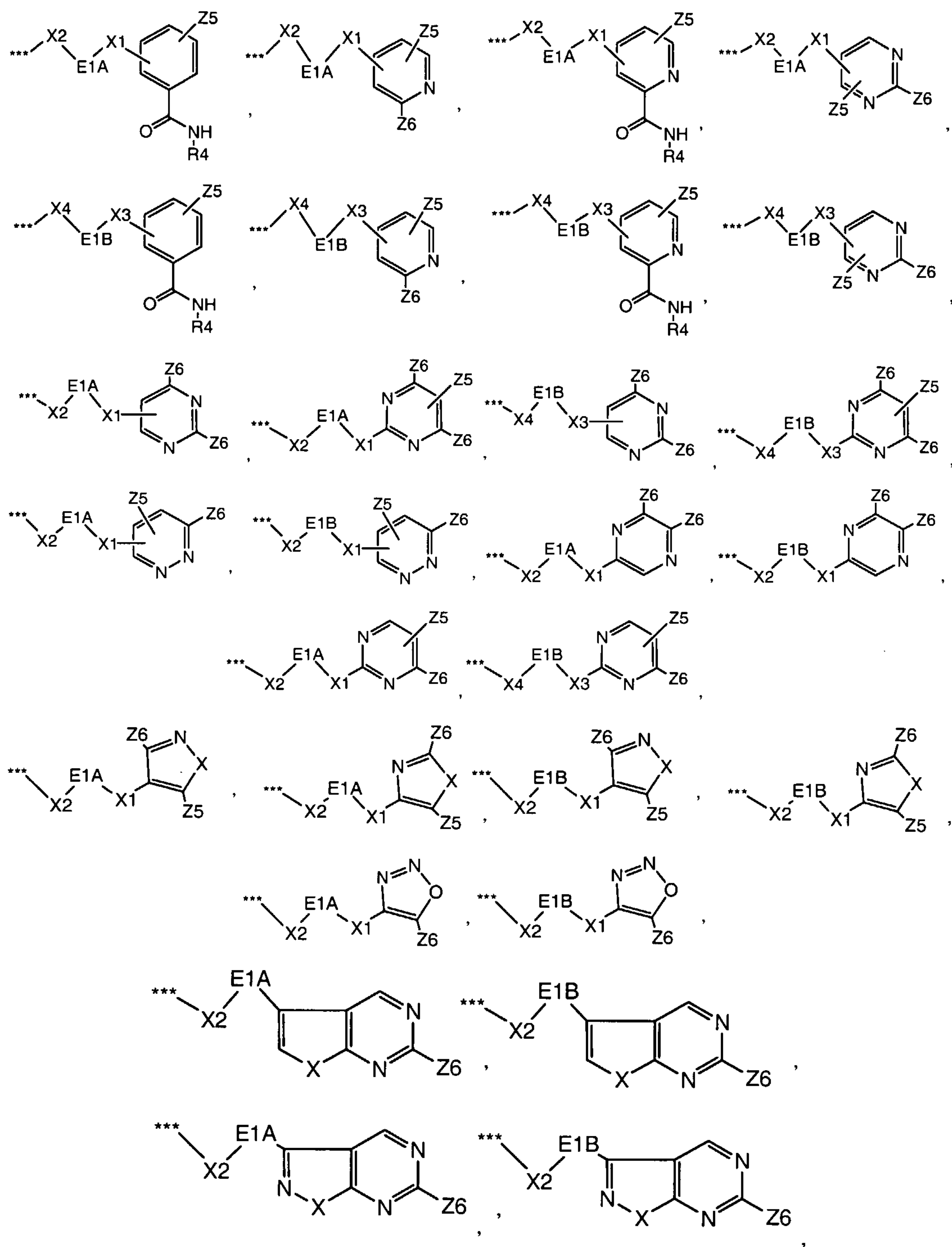


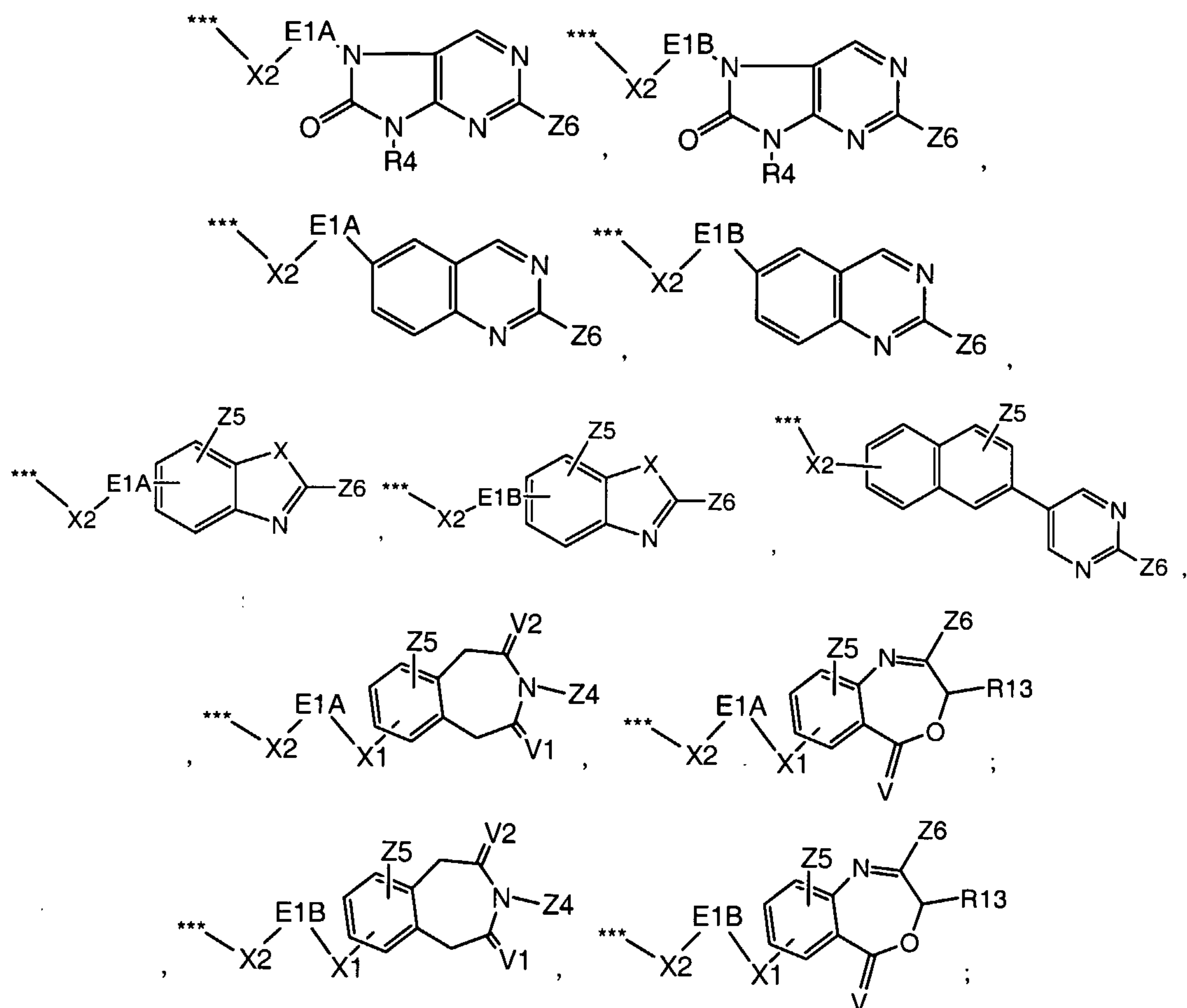
wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR₃;

D comprises a member of 2,3-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-cyanophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 3,4,5-trifluorophenyl, 4-cyanophenyl, 3-fluoro-5-cyanophenyl, 3-(R₈SO₂)-phenyl, 3-(hydroxyC₁-C₃alkyl)-phenyl, 3-(R₃O-N=C(R₆))-phenyl, 3-phenoxyphenyl, 4-phenoxyphenyl,







wherein E1A is taken from the groups consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, and pyrimidinyl;

wherein E1B is taken from the groups consisting of phenyl and naphthyl;

wherein E2A is taken from the group comprising naphthyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, triazinyl and fused bicyclic rings selected from the group consisting of indolyl, isoindolyl, isoindolinyl, isoindolonyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, imidazopyrimidinyl, imidazolonopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, furylopyrimidinyl, thienopyrimidinyl, phthalimidyl, phthalimidinyl,

pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl, phthalazinyl, benzodioxyl, indolinyl, benzisothiazoline-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzoxapinyl, benzoxazepinyl;

wherein E2B is taken from the group consisting of phenyl, pyridyl, and pyrimidyl;

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, (CH₂)_p, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

each R₂ is selected from the group consisting of alkyl, branched alkyl, fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, and R₁₉ substituted C3-C8carbocyclyl wherein R₁₉ is H, and C1-C6alkyl;

X3 is selected from the group consisting of NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_q-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the either the E1B ring or E2B ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_q-, C2-C5alkenyl, and C2-C5alkynyl moieties of X3 may be further substituted by one or more C1-C6alkyl;

X4 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl;

each R2' is selected from the group consisting of halogen and R2;

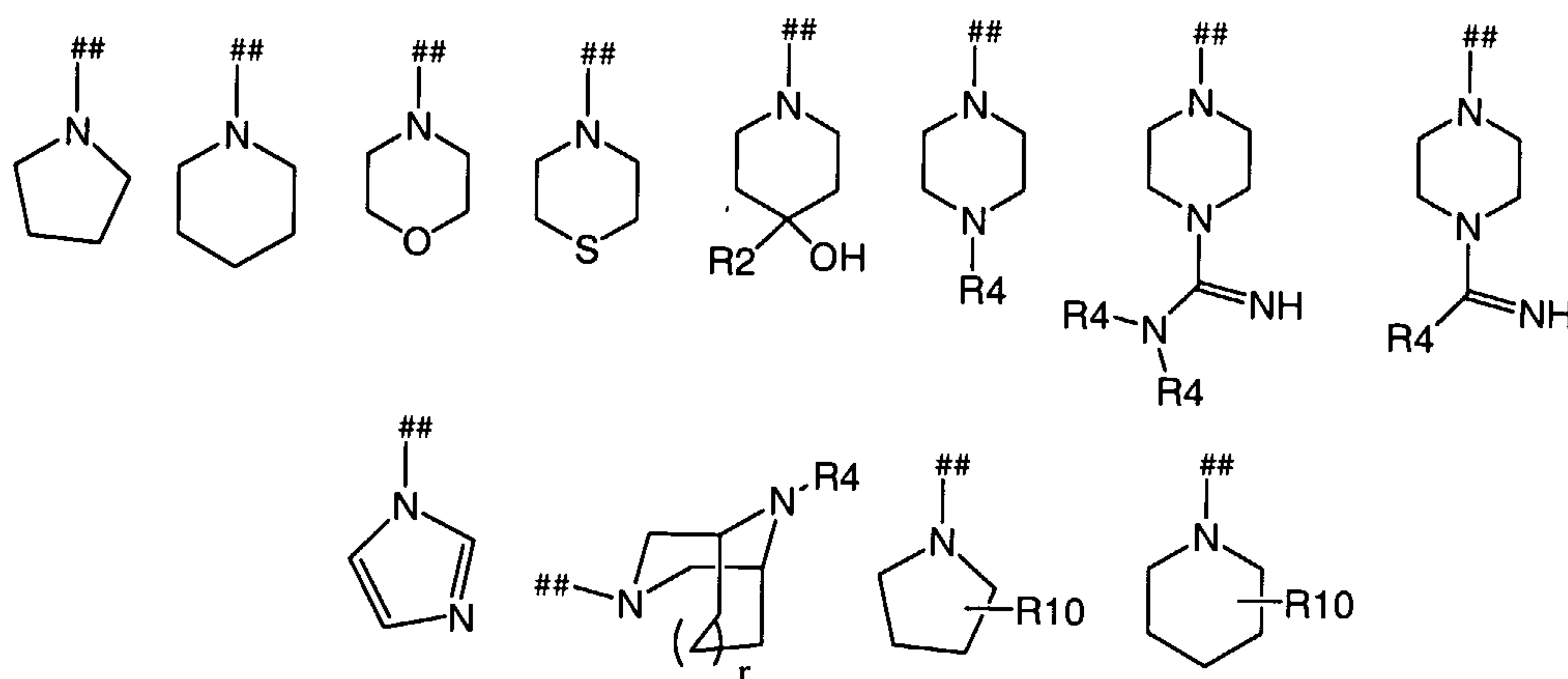
each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocyclyl ring;

each R5 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R8, R10, Z4, Z5, Z6 or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

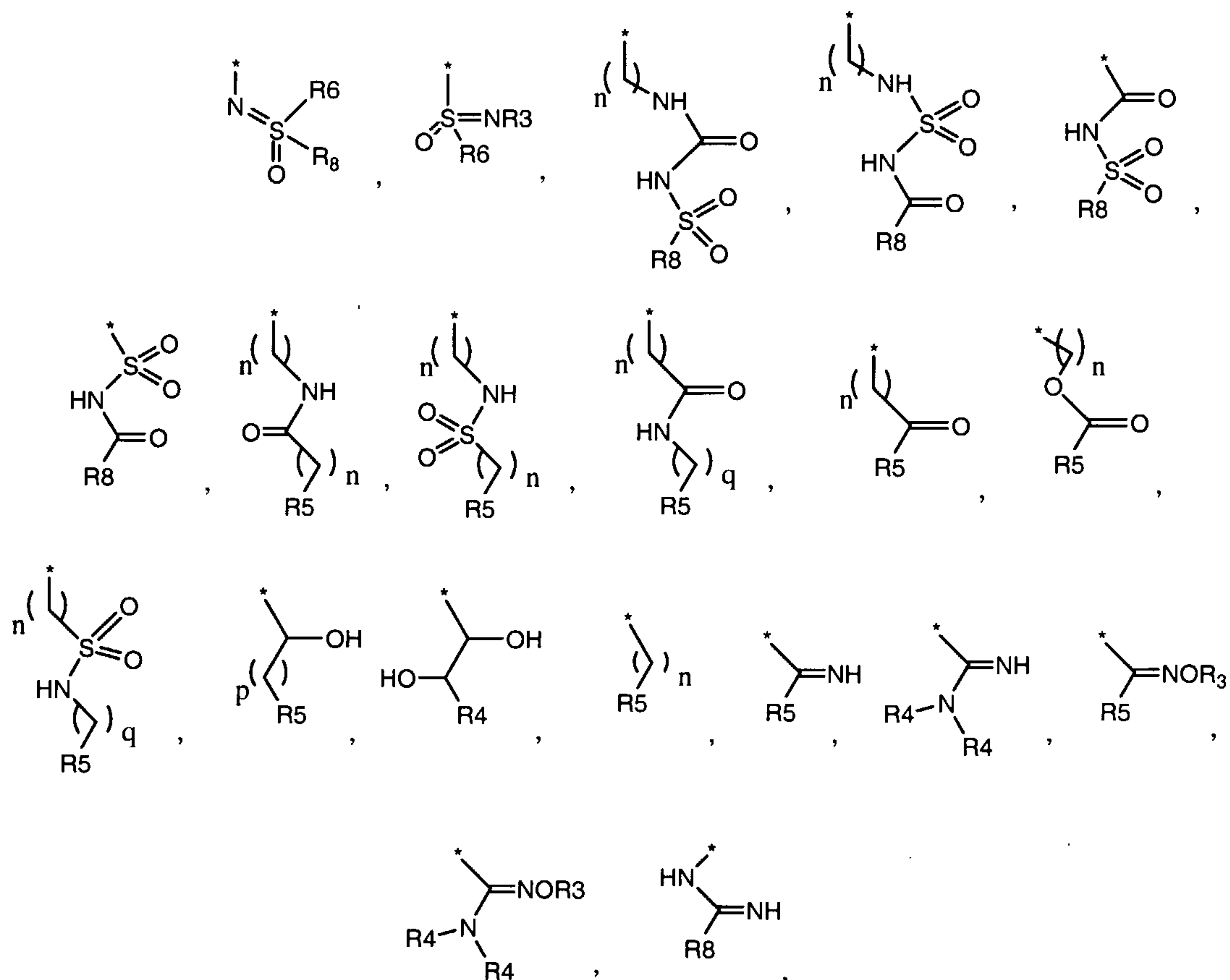
wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

each Z1 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC1-C6alkyl, C2-C6alkoxy, C1-C6alkoxyC1-

C6alkyl, (R₄)₂NC1-C6alkyl, (R₄)₂NC2-C6alkylN(R₄)-(CH₂)_n, (R₄)₂NC2-C6alkylO-(CH₂)_n, (R₃)₂N-C(=O)-, (R₄)₂N-C(=O)-, (R₄)₂N-CO-C1-C6alkyl, C1-C6alkoxycarbonyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, (R₃)₂NSO₂, SO₂R₃, (R₄)₂NSO₂, -SO₂R₃', -SO₂R₄, -C(=O)R₆, -C(=NOH)R₆, -C(=NOR₃)R₆, -(CH₂)_nN(R₄)C(O)R₈, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocycliloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocycliloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



In the foregoing definition of Z1, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

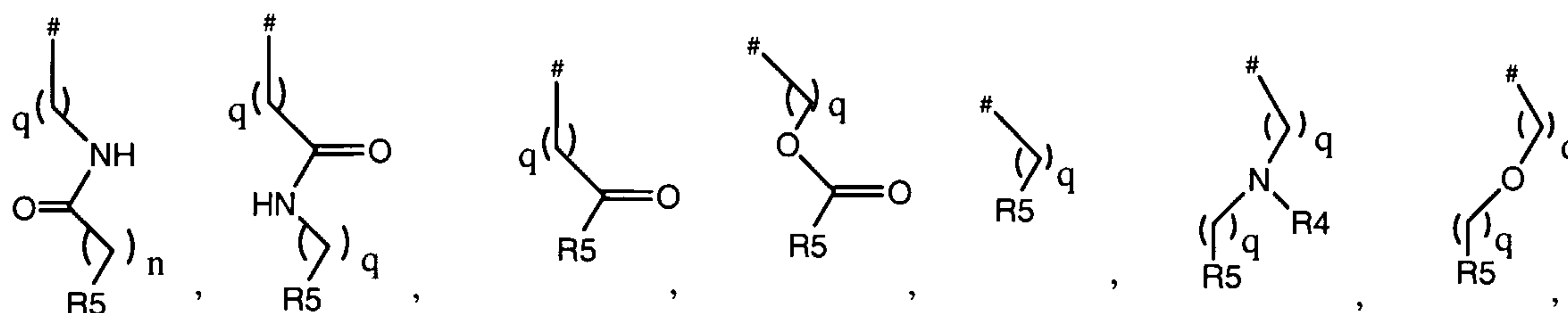
Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

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wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

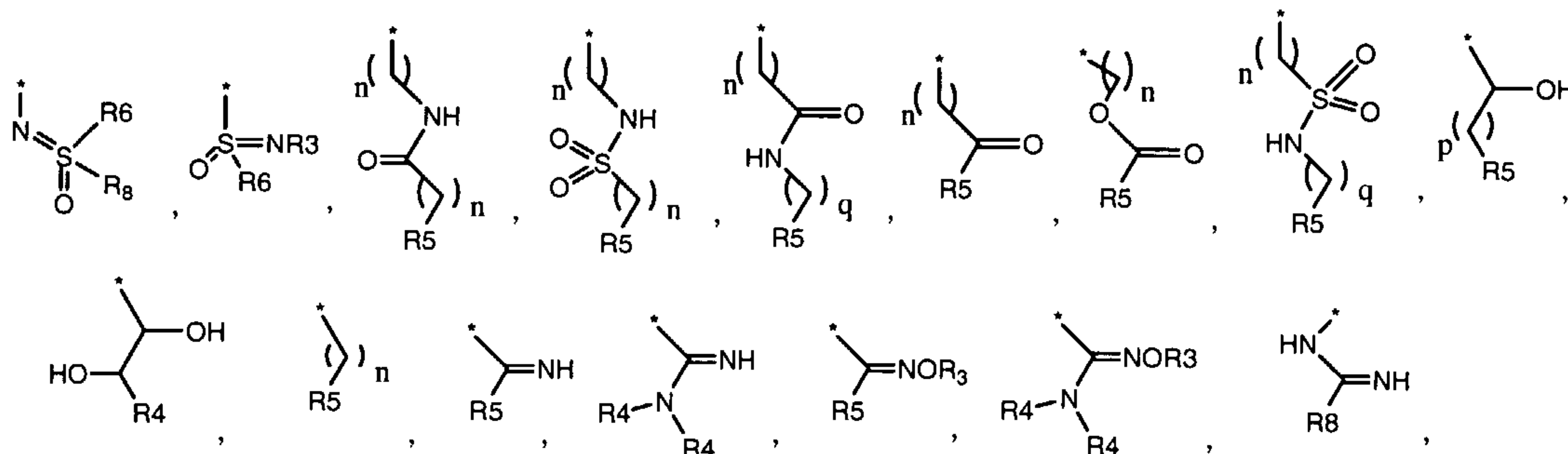
Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocycliloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

each Z7 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC1-C6alkyl,

(R₆)₂NC1-C6alkyl, (R₄)₂NC2-C6alkylN(R₄)-(CH₂)_n, (R₄)₂NC2-C6alkylO-(CH₂)_n, (R₃)₂N-CO, (R₄)₂N-CO, -SO₂R₃', SOR₃, -SOR₄, -C(=O)R₆, -C(=NOH)R₆, -C(=NOR₃)R₆, (CH₂)_nN(R₄)C(O)N(R₄)₂, (CH₂)_nN(R₄)C(O)R₅, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocycliloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocycliloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

In the foregoing definition of Z7, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z7 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R₃ moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z7 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R₄ moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z7 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

1.3.6b

The following specific compounds are most preferred: 1-(3-t-butyl-1-(3-(pyridin-3-yl)phenyl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(3-(1H-pyrazol-4-yl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(1-oxoisindolin-4-yl)phenyl)urea

1.3.7 Methods

1.3.7a Methods of Protein Modulation

The invention includes methods of modulating kinase activity of a variety of kinases, e.g. C-Abl kinase, BCR-Abl kinase. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 1.3 and 1.3.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

The methods of the invention may also involve the step of inducing, synergizing, or promoting the binding of a second modulator compound of said kinase, especially C-Abl kinase or BCR-Abl kinase, to form a ternary adduct, such co-incident binding resulting in enhanced biological modulation of the kinase when compared to the biological modulation of the protein affected by either of said compounds alone. The second compound may interact at a substrate, co-factor or regulatory site on the kinase, with the second site being distinct from the site of interaction of the first compound. For example, the second site may be an ATP co-factor site. The second compounds may be taken from the group consisting of N-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide(Gleevec®), N-(2-chloro-6-methylphenyl)-2-(6-(4-(2-

hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825); 6-(2,6-dichlorophenyl)-2-(3-(hydroxymethyl)phenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 166326); 6-(2,6-dichlorophenyl)-8-methyl-2-(3-(methylthio)phenylamino)pyrido[2,3-d]pyrimidin-7(8H)-one (PD 173955); 6-(2,6-dichlorophenyl)-2-(4-fluoro-3-methylphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD180970); 6-(2,6-dichlorophenyl)-2-(4-ethoxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 173958); 6-(2,6-dichlorophenyl)-2-(4-fluorophenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 173956); 6-(2,6-dichlorophenyl)-2-(4-(2-(diethylamino)ethoxy)phenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (PD 166285); 2-(4-(2-aminoethoxy)phenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one; N-(3-(6-(2,6-dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)phenyl)acetamide (SKI DV-MO16); 2-(4-aminophenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 1-10); 6-(2,6-dichlorophenyl)-2-(3-hydroxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV2-89); 2-(3-aminophenylamino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 2-43); N-(4-(6-(2,6-dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)phenyl)acetamide (SKI DV-M017); 6-(2,6-dichlorophenyl)-2-(4-hydroxyphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV-M017); 6-(2,6-dichlorophenyl)-2-(3-ethylphenylamino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (SKI DV 2 87).

1.3.7b Treatment Methods

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer and hyperproliferative diseases. These methods comprise administering to such individuals compounds of the invention, and especially those of section 1.3 and 1.3.6a. Exemplary conditions include chronic myelogenous leukemia, acute lymphocytic leukemia, gastrointestinal stromal tumors, and hypereosinophilic syndrome. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

1.3.8 Pharmaceutical Preparations

The compounds of the invention, especially those of 1.3 and 1.3.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a

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pharamaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stablilizers.

1.3.9 Kinase/Compound Adducts

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections *1.3* and *1.3.6a*.

2. *Second aspect of the invention – VEGFR and PDGFR Kinase Modulator Compounds, Methods, Preparations and Adducts*

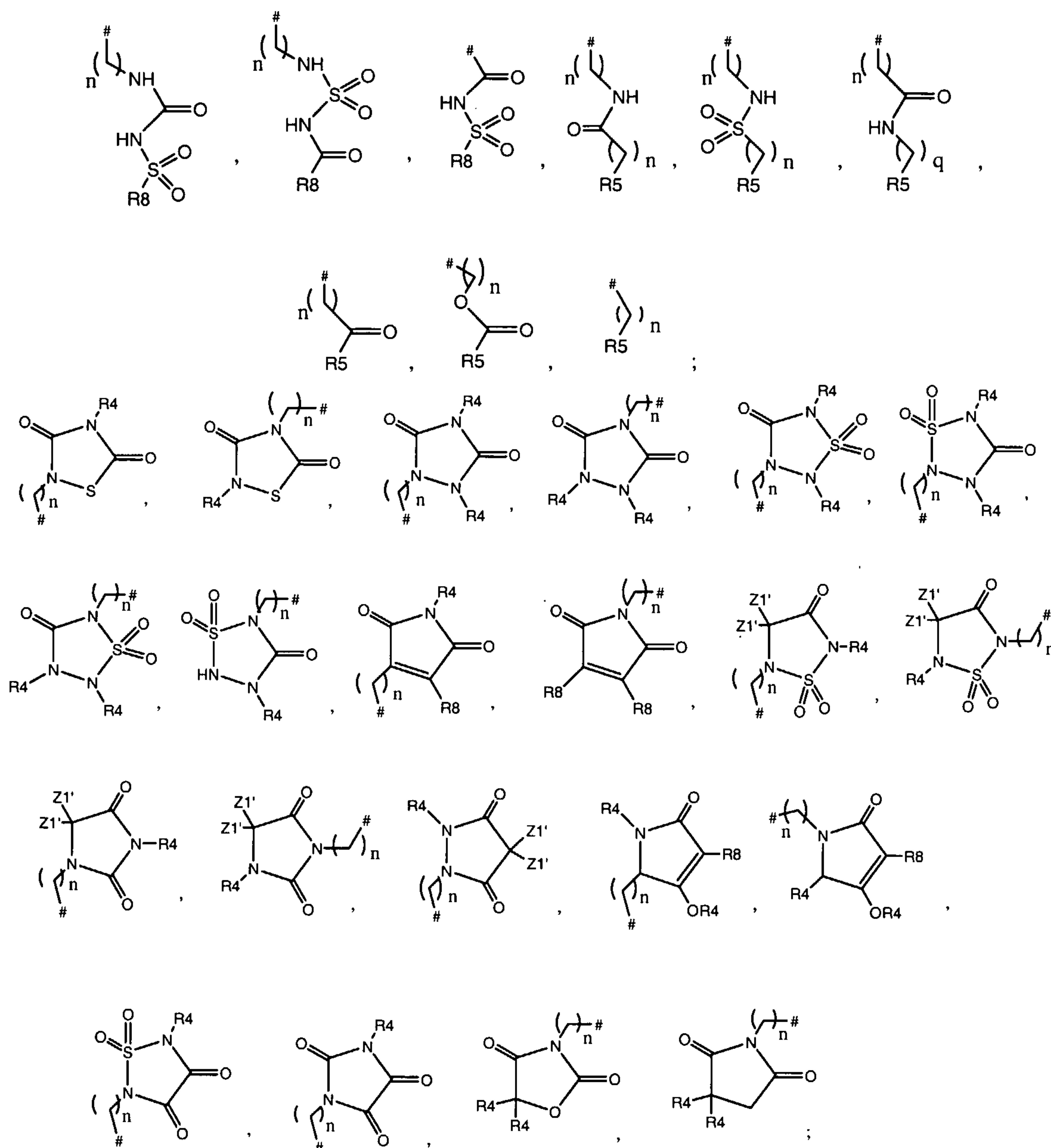
2.1 *Generally – A2 Bicyclic Compounds*

The invention includes compounds of formula I as defined in section 1.1, wherein each R₂ is selected from the group consisting of monocyclic heteroaryl, C₁-C₆alkyl, branched C₃-C₇alkyl, and R₁₉ substituted C₃-C₈carbocyclyl wherein R₁₉ is H, or C₁-C₆alkyl, C₁-C₆fluoroalkyl wherein the alkyl group is partially or fully fluorinated, phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents,

wherein Z₁' is independently and individually selected from the group consisting of H, C₁-C₆alkyl, C₃-C₇cycloalkyl, hydroxyC₁-C₆alkyl, C₁-C₆alkoxyC₁-C₆alkyl, (R₄)₂N-C₁-C₆alkyl, (R₄)₂N-C₂-C₆alkylN(R₄)-(CH₂)_p, (R₄)₂N-C₂-C₆alkylO-(CH₂)_p, (R₄)₂N-CO-C₁-C₆alkyl, carboxyC₁-C₆alkyl, C₁-C₆alkoxycarbonylC₁-C₆alkyl, -(CH₂)_pN(R₄)C(O)R₈, aryl, arylC₁-C₆alkyl, heteroaryl, heteroarylC₁-C₆alkyl, heterocyclyl, heterocyclylC₁-C₆alkyl, aryloxyC₁-C₆alkyl, , heteroaryloxyC₁-C₆alkyl, heterocycliloxyC₁-C₆alkyl, arylaminoC₁-C₆alkyl, heteroarylaminoC₁-C₆alkyl, or heterocyclylaminoC₁-C₆alkyl;

wherein two R₄ moieties independently and individually taken from the group consisting of C₁-C₆alkyl, branched C₃-C₆alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z₁' may cyclize to form a C₃-C₇ heterocyclyl ring;

each Z₂ is independently and individually selected from the group consisting of hydroxyl, hydroxyC₁-C₆alkyl, cyano, (R₃)₂N-, (R₄)₂N-, (R₄)₂NC₁-C₆alkyl, (R₄)₂NC₂-C₆alkylN(R₄)-(CH₂)_n, (R₄)₂NC₂-C₆alkylO-(CH₂)_n, (R₃)₂N-C(=O)-, (R₄)₂N-C(=O)-, (R₄)₂N-CO-C₁-C₆alkyl, carboxyl, carboxyC₁-C₆alkyl, C₁-C₆alkoxycarbonyl, C₁-C₆alkoxycarbonylC₁-C₆alkyl, (R₃)₂NSO₂, (R₄)₂NSO₂, -SO₂R₅-, -(CH₂)_nN(R₄)C(O)R₈, =O, =NOH, =N(OR₆), heteroarylC₁-C₆alkyl, heterocyclylC₁-C₆alkyl, heteroaryloxyC₁-C₆alkyl, heterocycliloxyC₁-C₆alkyl, arylaminoC₁-C₆alkyl, heteroarylaminoC₁-C₆alkyl, heterocyclylaminoC₁-C₆alkyl, or moieties of the formulae

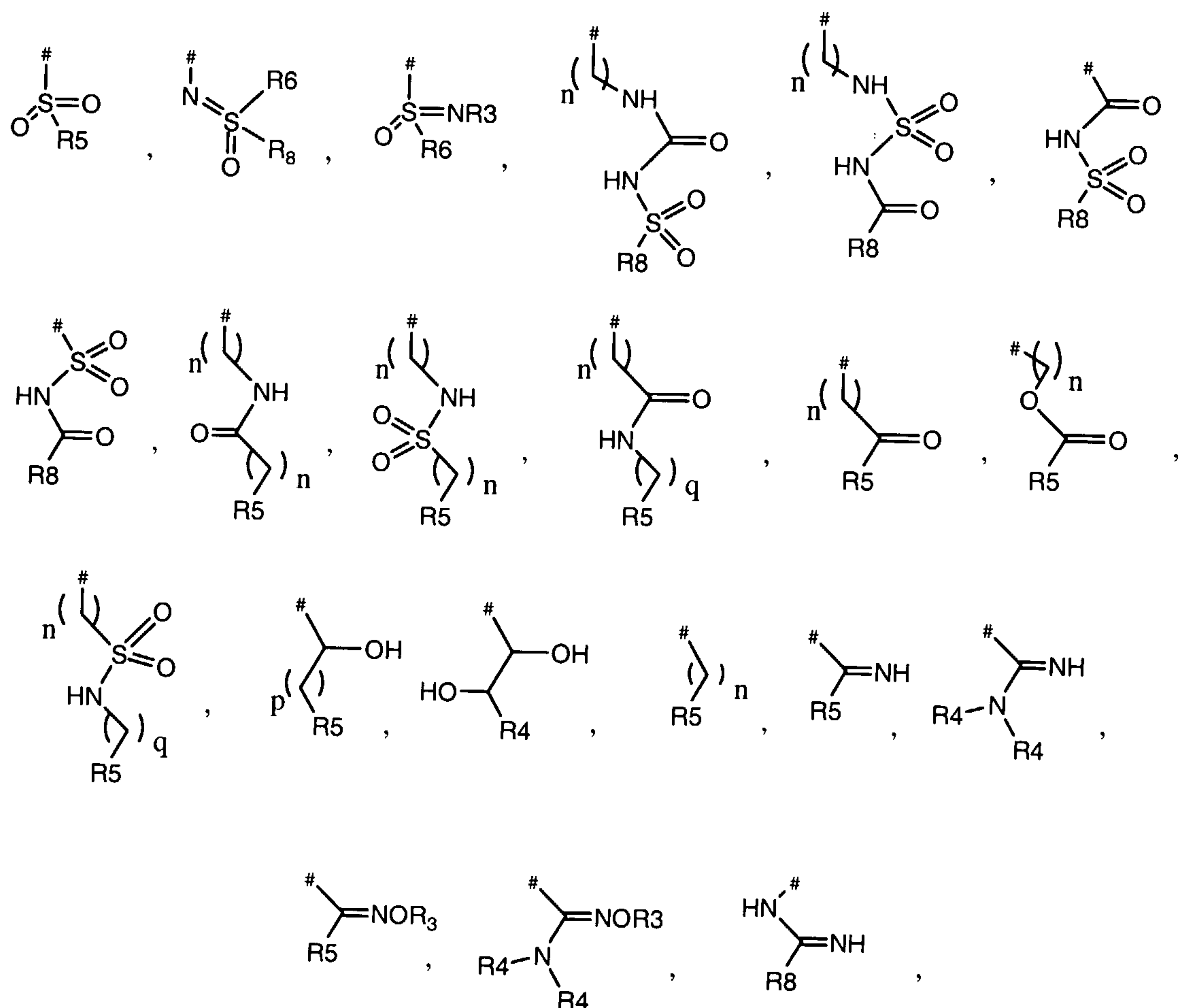


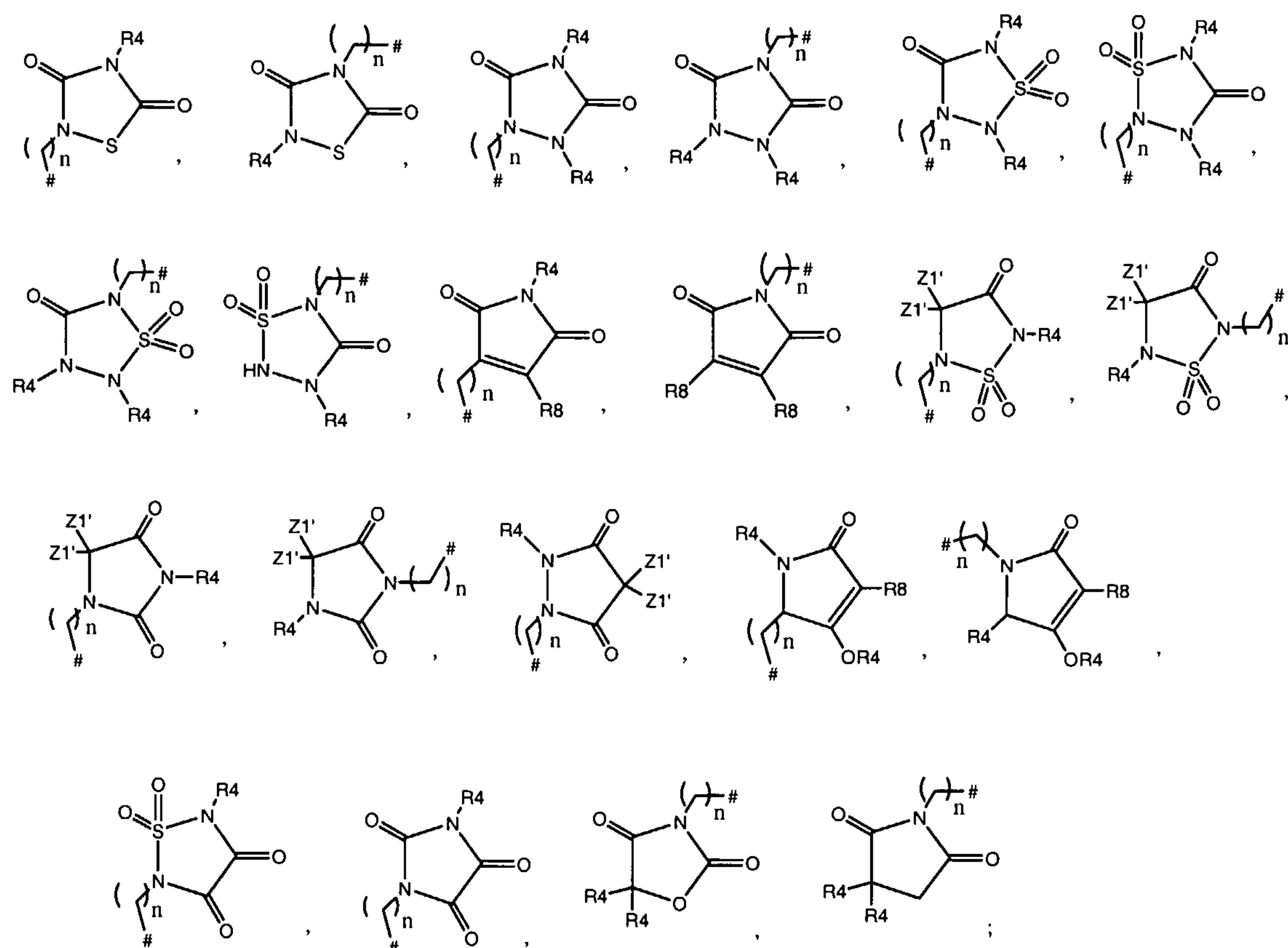
wherein the symbol (#) indicates the point of attachment of the Z2 moiety to the A2 ring of formula I;

in the event that Z2 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z2 may cyclize to form a C3-C7 heterocyclyl ring;

each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyl, hydroxyC1-C6alkyl, cyano, C1-C6alkoxy, C1-C6alkoxyC1-C6alkyl, halogen, CF₃, (R₃)₂N-, (R₄)₂N-, (R₄)₂NC1-C6alkyl, (R₄)₂NC2-C6alkylN(R₄)-(CH₂)_n, (R₄)₂NC2-C6alkylO-(CH₂)_n, R₈CO-, (R₄)₂N-CO-C1-C6alkyl, carboxyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R₃)₂NSO₂, -SO₂R₃, SOR₃, (R₄)₂NSO₂, -SO₂R₄, -SOR₄, -(CH₂)_nN(R₄)C(O)R₈, -C=(NOH)R₆, -C=(NOR₃)R₆, heteroaryl, heterocyclyl, heteroarylC1-C6alkyl, heterocyclylC1-C6alkyl, heteroaryloxy, heterocyclyoxy, heteroaryloxyC1-C6alkyl, heterocyclyoxyC1-C6alkyl, arylamino, heteroarylamino, heterocyclylamino, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocyclylaminoC1-C6alkyl, or moieties of the formulae





wherein the symbol (#) indicates the point of attachment of the Z3 moiety to the A2 ring of formula I;

in the event that Z3 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

2.1.1 Preferred D Moieties

2.1.1a

Preferred compounds of Formula I as defined above in section 2.1 contain D moieties as defined in section 1.1.1a.

2.1.1b

Additionally preferred compounds of Formula I as defined above in section 2.1 contain D moieties as defined in section 1.1.1b.

2.1.1c

More preferred compounds of Formula I as defined above in section 2.1.1b contain D moieties as defined in section 1.1.1c.

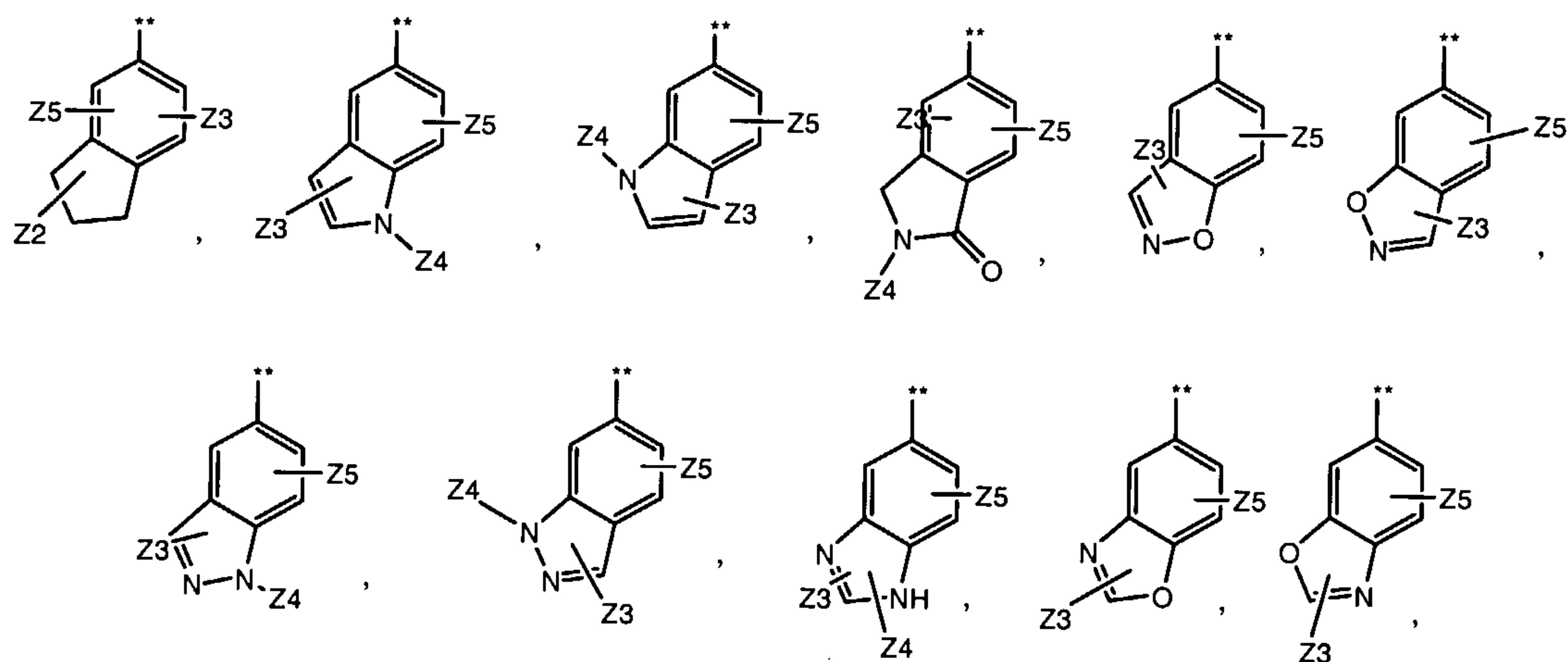
2.1.2 Preferred A2 moieties

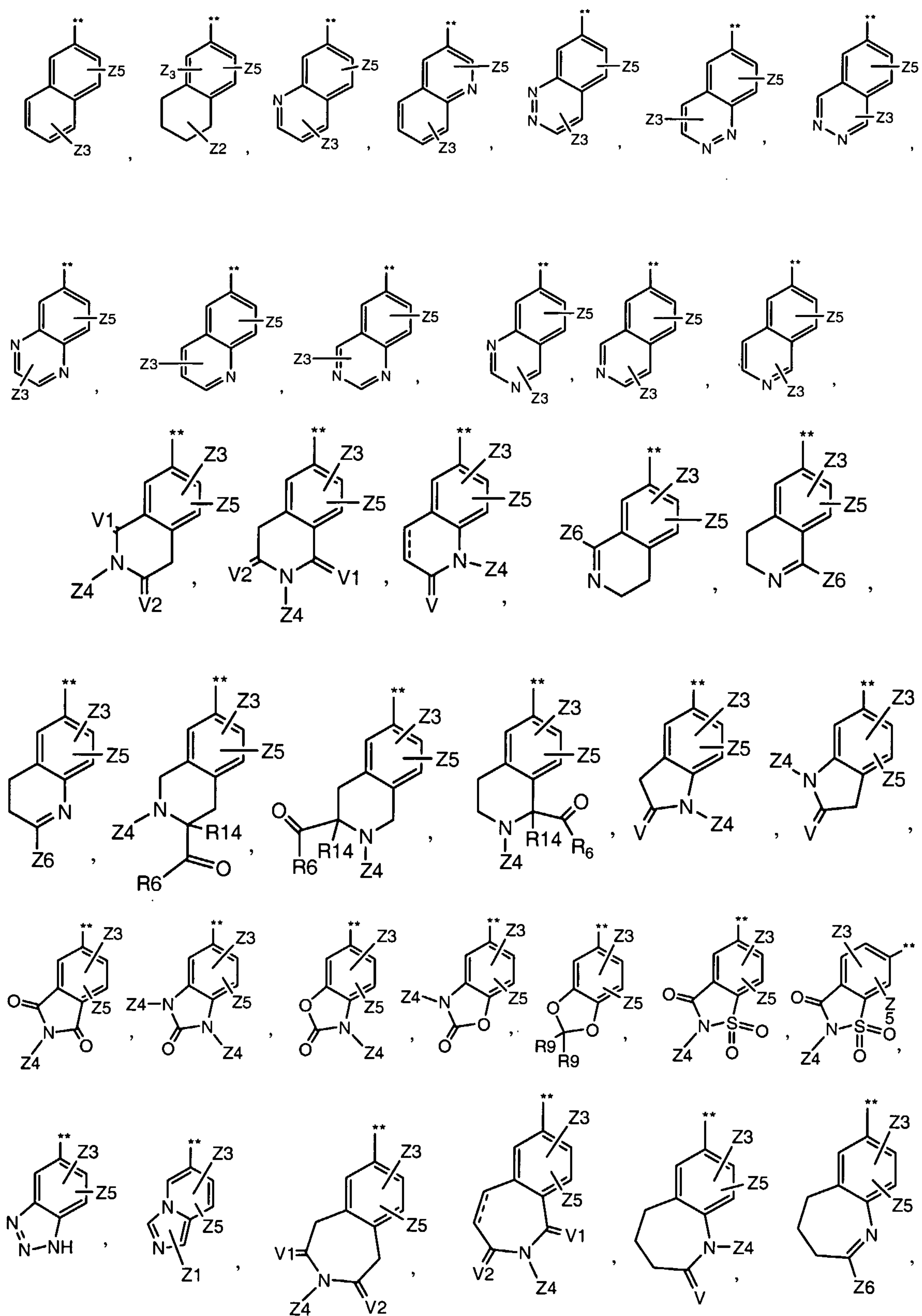
2.1.2a

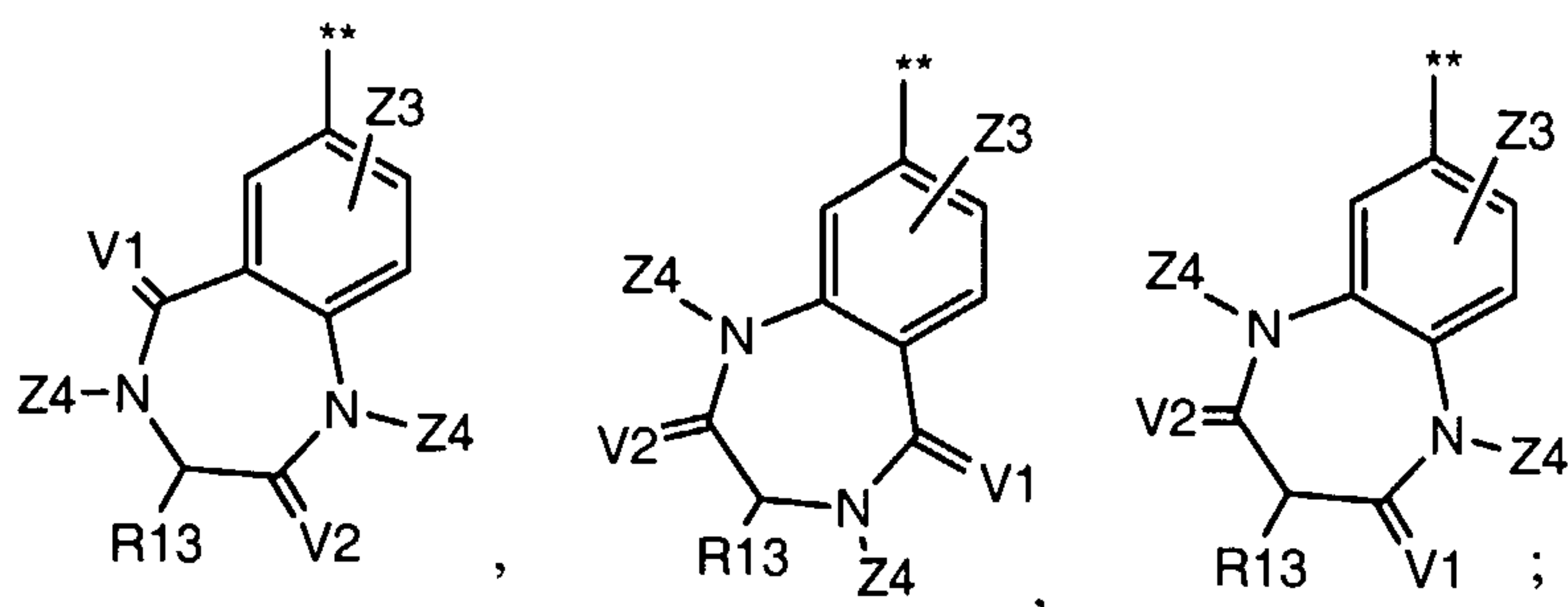
Compounds of Formula I as defined above in section 2.1 have preferred A2 moieties as defined in section 1.1.2a;

2.1.2b More preferred A2 moieties

Compounds of Formula I as defined above in section 2.1 have more preferred A2 moieties selected from group consisting of





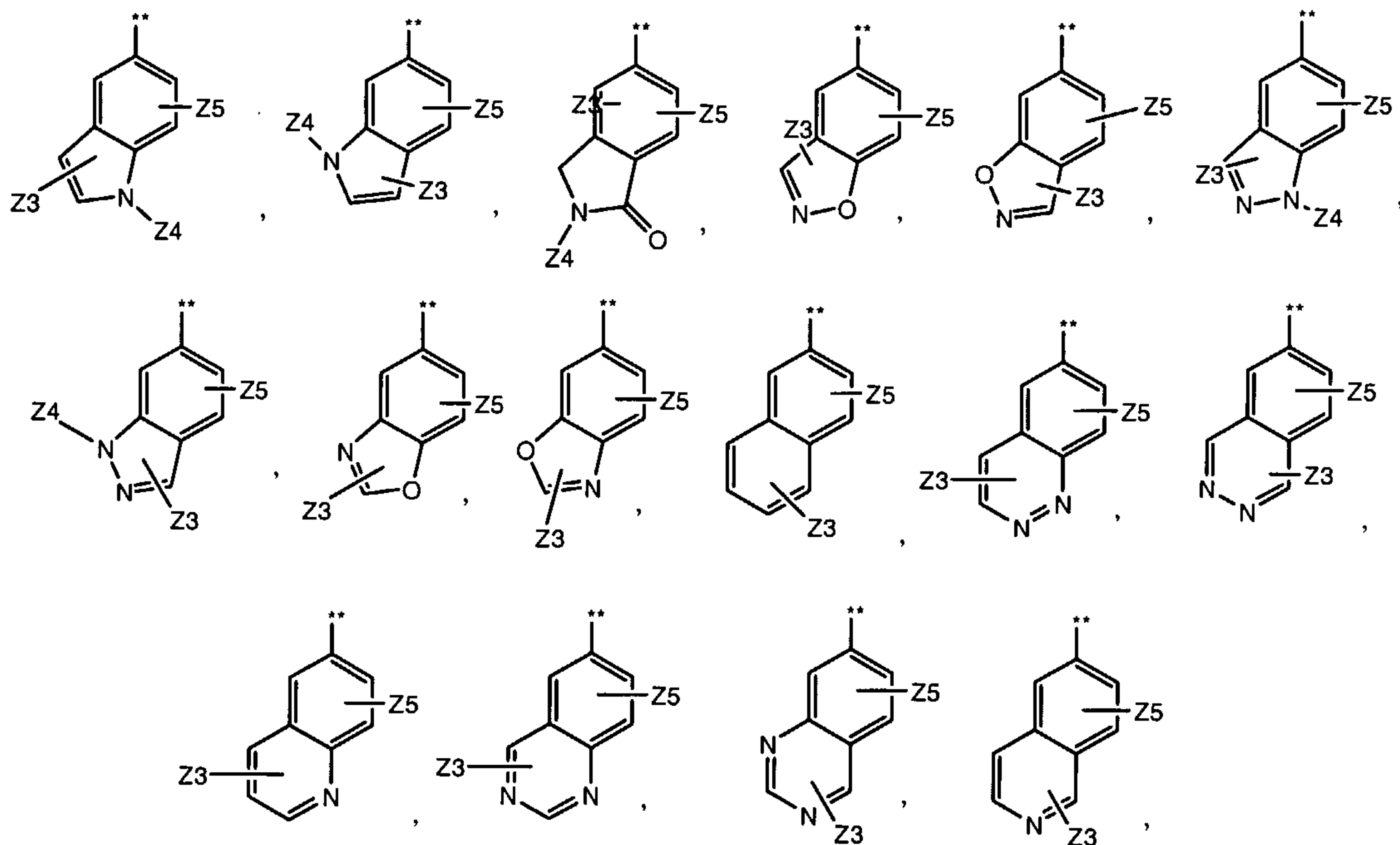


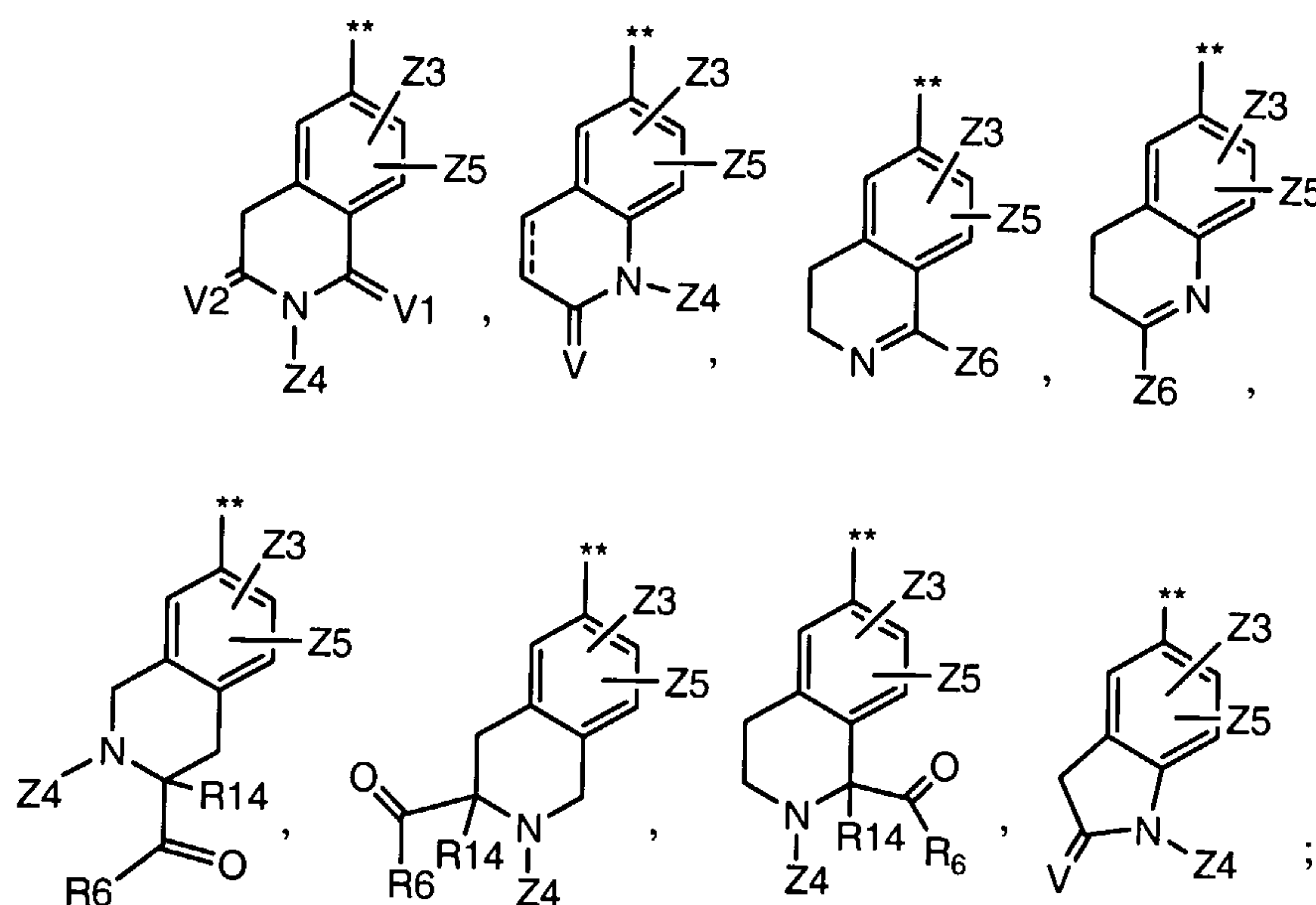
and wherein the symbol (**) is the point of attachment to the A1 ring for formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring.

2.1.2c

Still more preferred compounds of Formula I as defined above in section 2.1 have A2 moieties selected from group consisting of





and wherein the symbol (**) is the point of attachment to the A1 ring of formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring.

2.1.3 Preferred Classes of Compounds

2.1.3a

Compounds as defined in 2.1.1a wherein the A2 group is defined in 2.1.2a.

2.1.3b

Compounds as defined in 2.1.3a wherein the A2 group is defined in 2.1.2b.

2.1.3c

Compounds as defined in 2.1.3a wherein the A2 group is defined in 2.1.2c.

2.1.3d

Compounds as defined in 2.1.1b wherein the A2 group is defined in 2.1.2a.

2.1.3e

Compounds as defined in 2.1.3c wherein the A2 group is defined in 2.1.2b.

2.1.3f

Compounds as defined in 2.1.3c wherein the A2 group is defined in 2.1.2c.

2.1.4 Preferred A1 Moieties

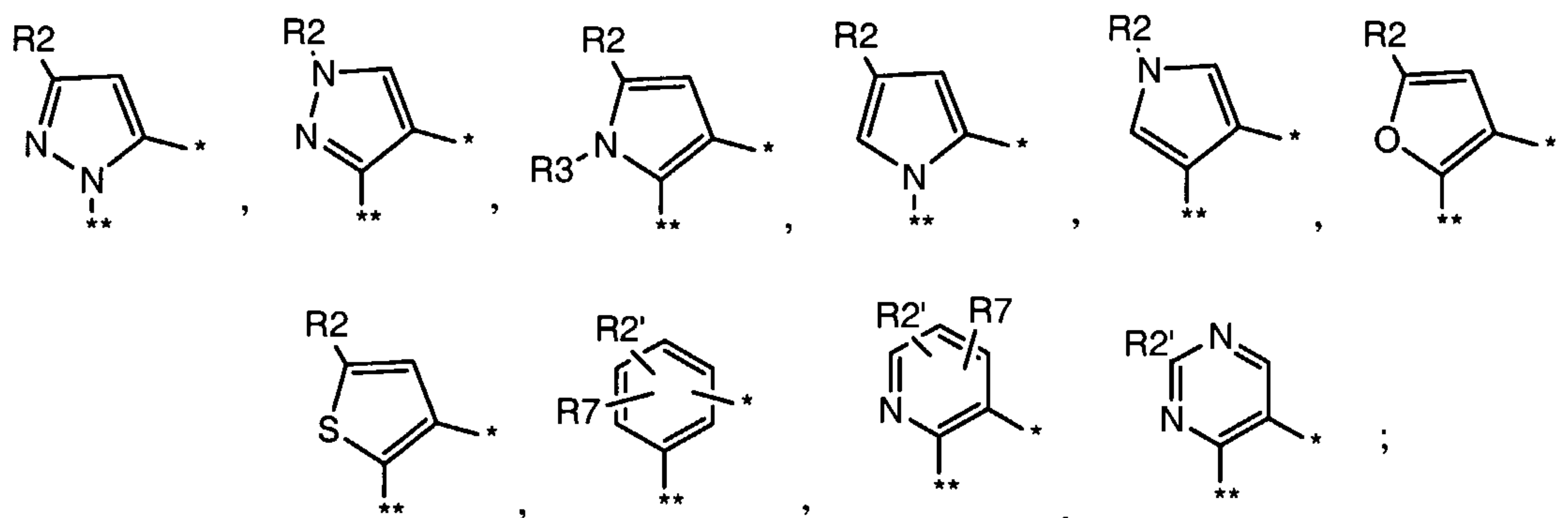
2.1.4a

Compounds of Formula I as defined above in section 2.1 have preferred A1 moieties selected from group defined in section 1.1.4a;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

2.1.4b

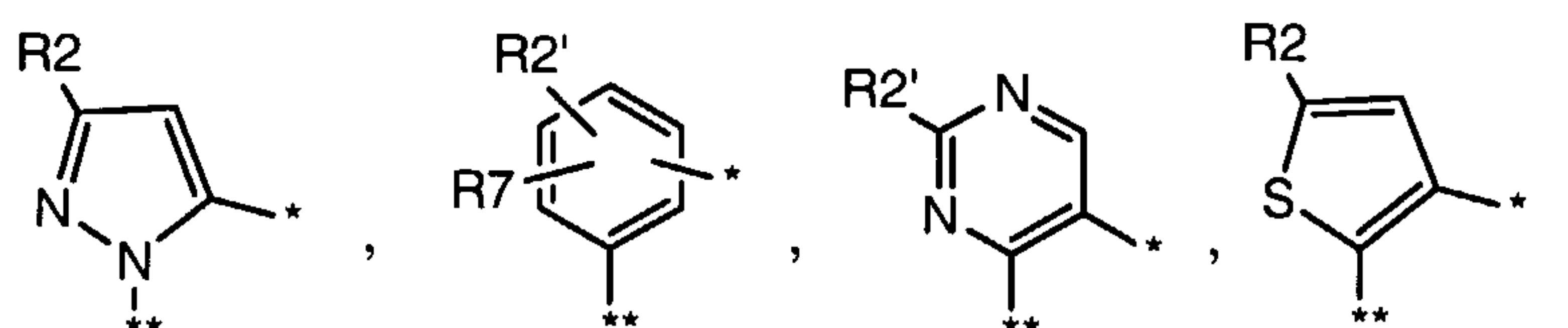
Compounds of Formula I as defined above in section 2.1 have more preferred A1 moieties selected from group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I.

2.1.4c

Compounds of Formula I as defined above in section 2.1 have even more preferred A1 moieties selected from group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I.

2.1.5 Preferred W and Y Moieties

2.1.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR⁴ and X=O; or (3) W=CHR⁴, Y=NH, and X=O.

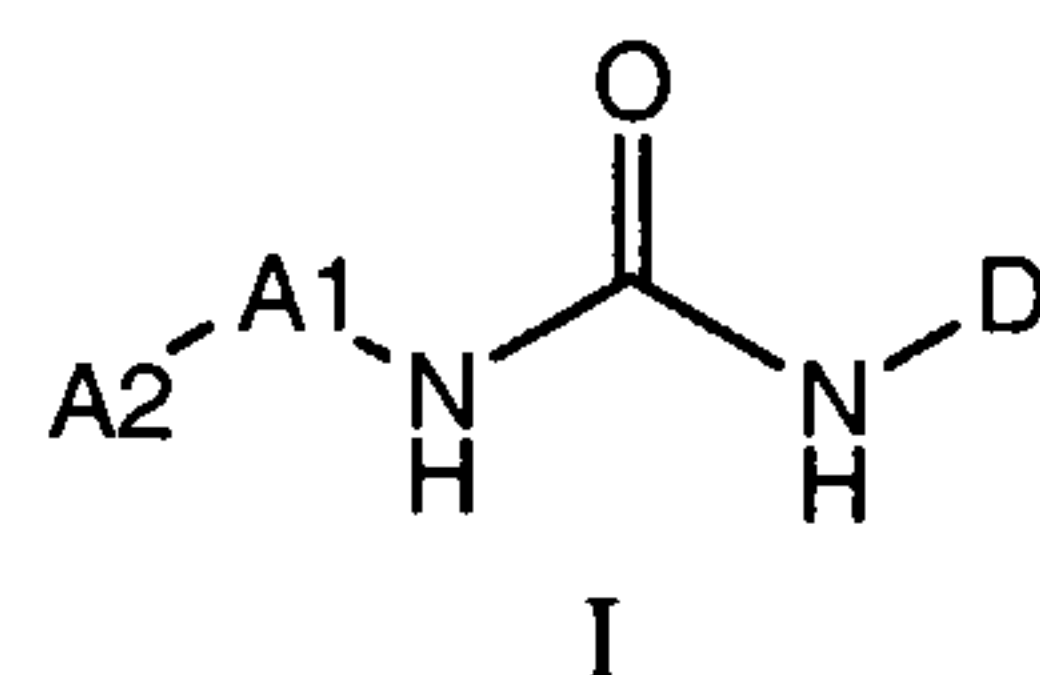
2.1.5b

W and Y are each NH and X=O.

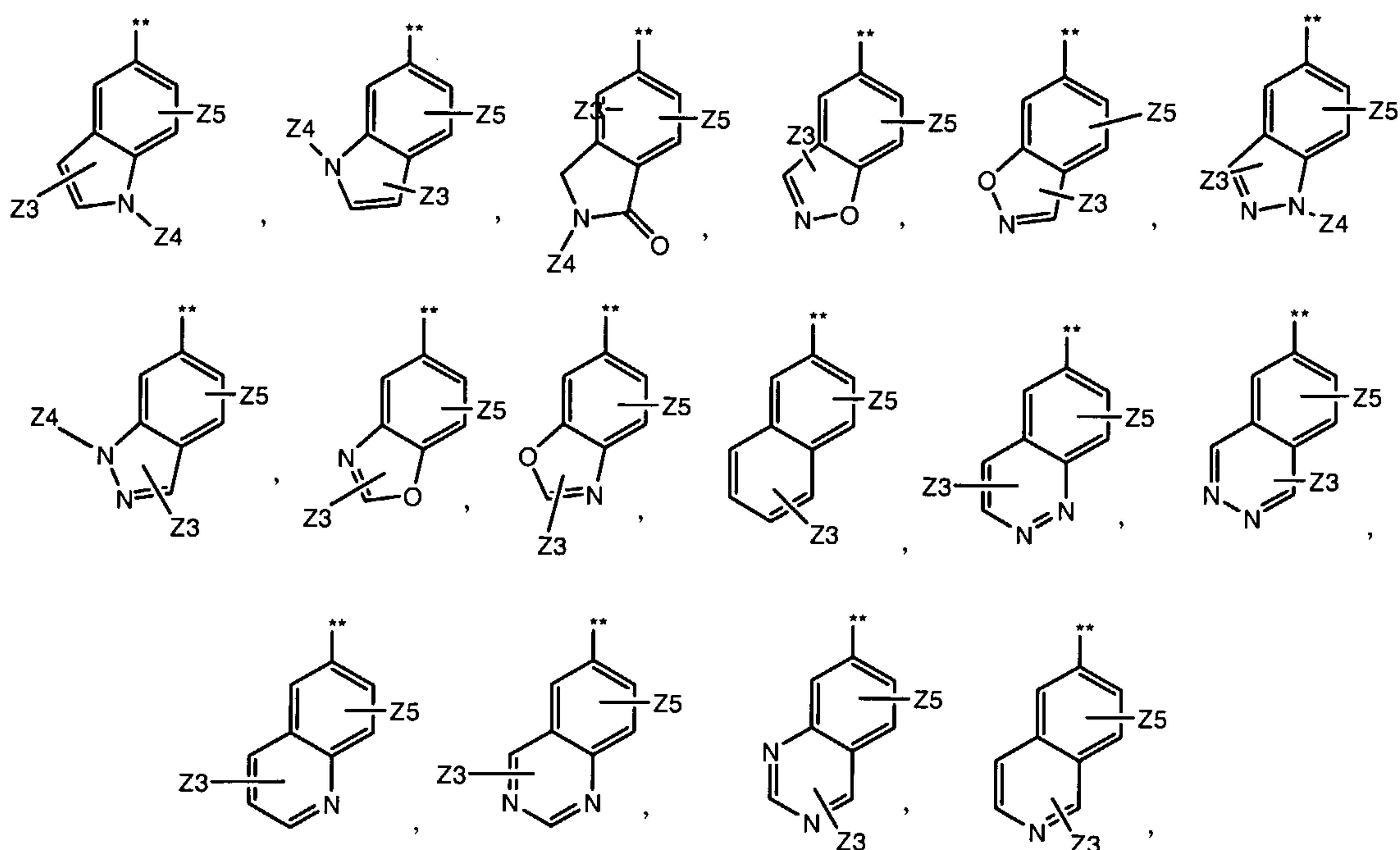
2.1.6 Further Preferred Compounds

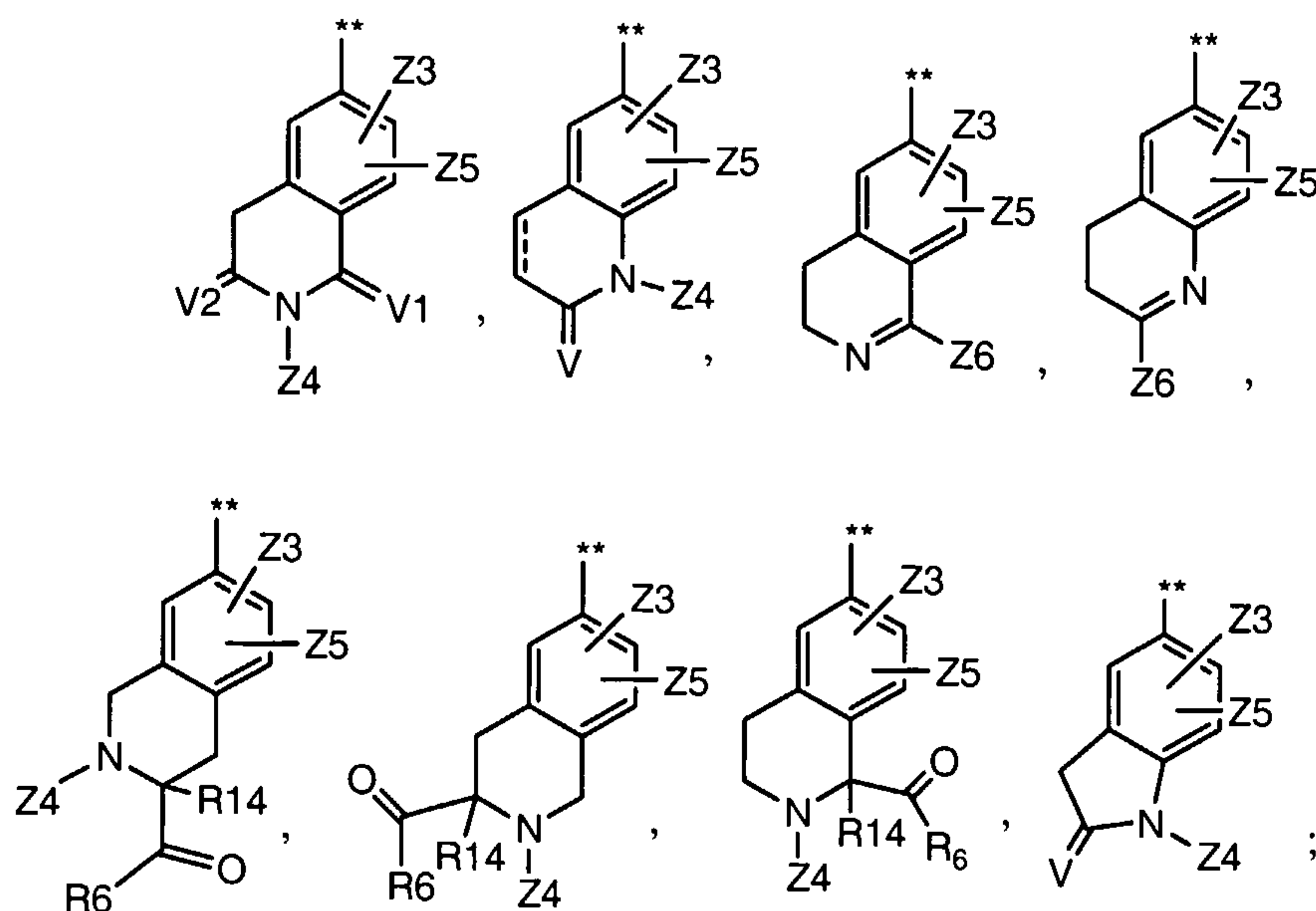
2.1.6a

Further preferred compounds are of the formula



wherein A2 is selected from the group consisting of

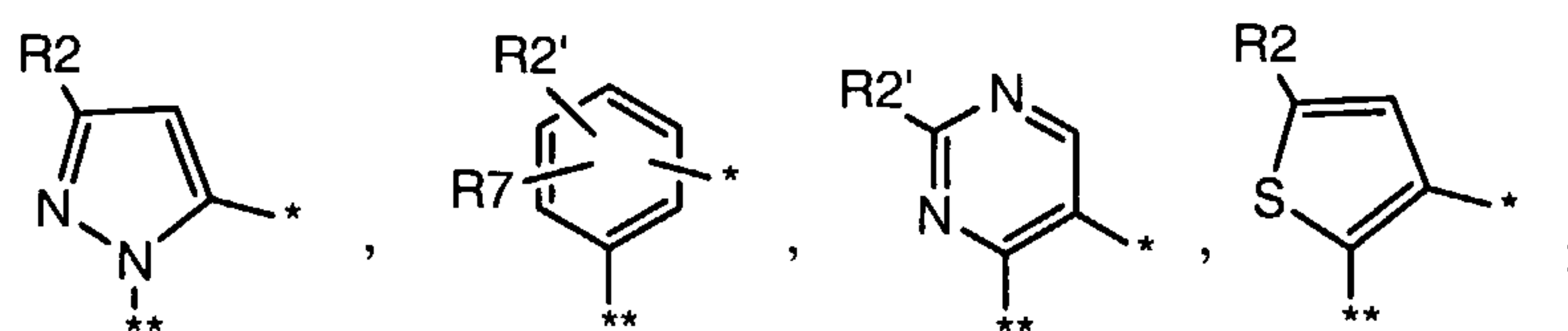




wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring;

wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

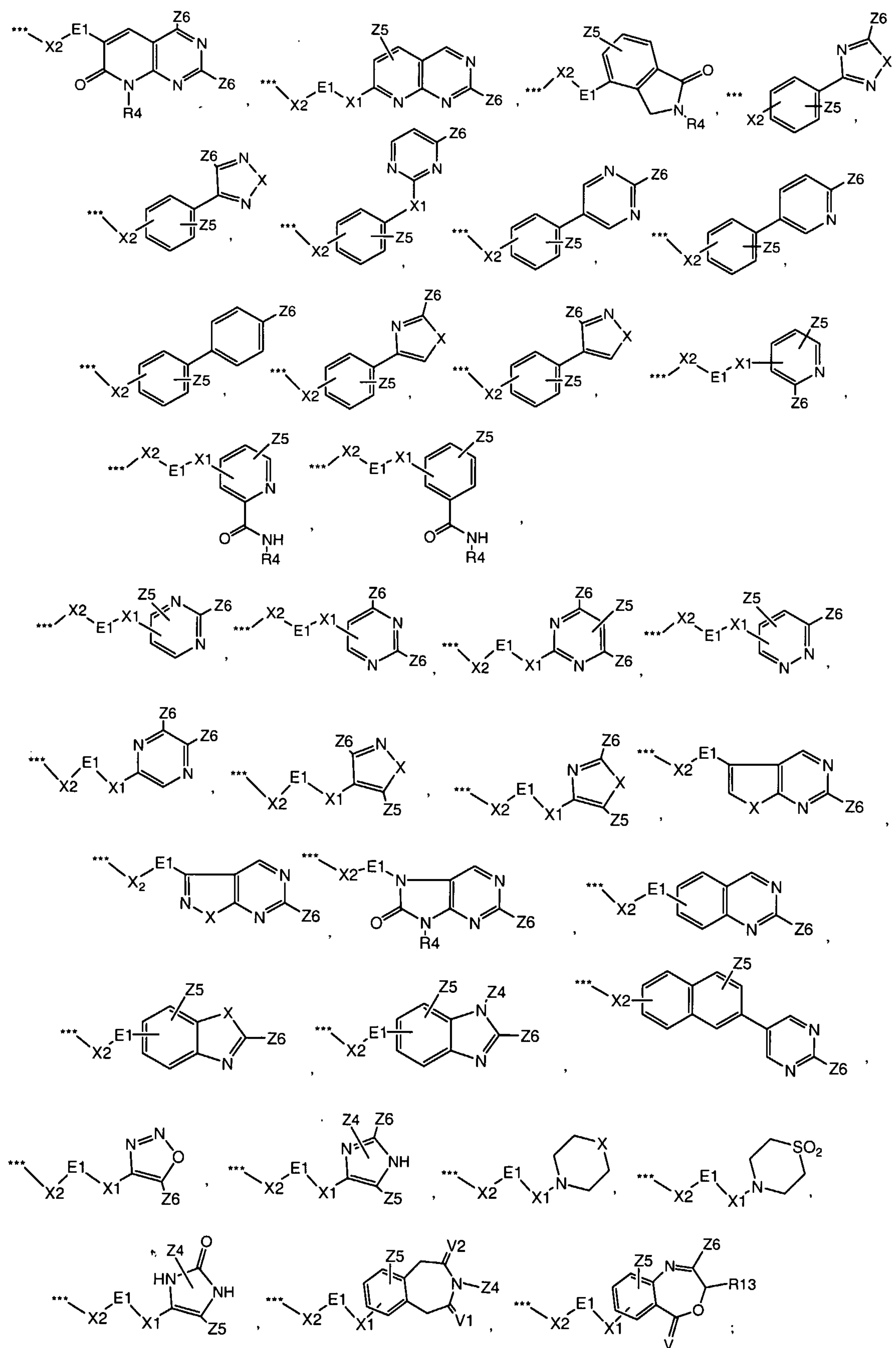
A1 is selected from the group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR₃;

D comprises a member of 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 4-chlorophenyl, 3-chlorophenyl, 3-bromophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 3,4,5-trifluorophenyl, 4-cyanophenyl, 3-(R₈SO₂)-phenyl, 3-phenoxyphenyl, 4 phenoxyphenyl,



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wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, (CH₂)_p, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

each R₂ is selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, and R₁₉ substituted C3-C8carbocyclyl wherein R₁₉ is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents, or monocyclic heteroaryl;

each R₂' is selected from the group consisting of halogen and R₂;

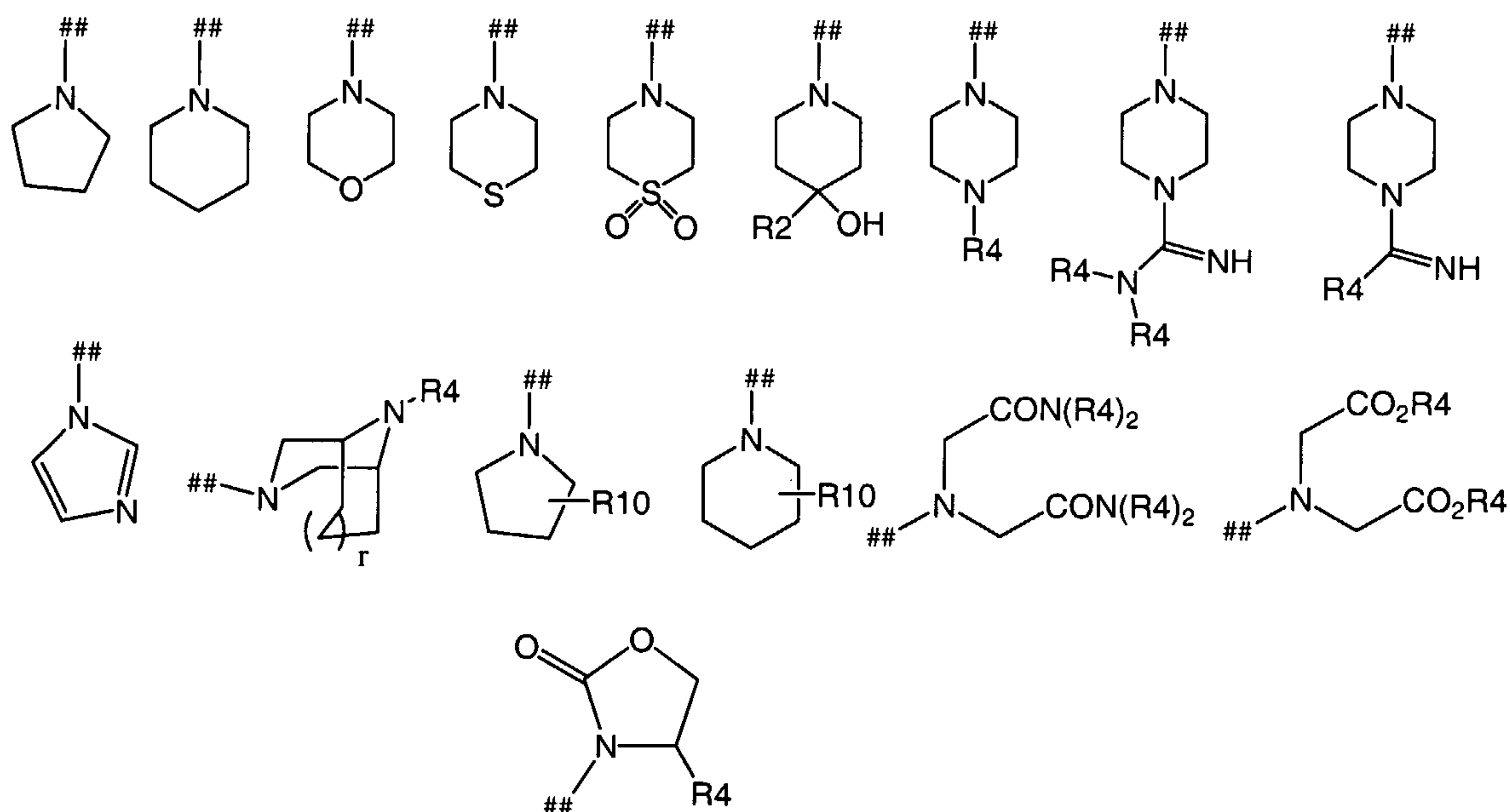
each R₃ is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R₃ moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R₃ moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocyclyl ring;

each R5 is independently and individually selected from the group consisting of



;

and wherein the symbol (##) is the point of attachment to respective R8, R10, R13, Z2, Z3, Z4, Z5, or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branchedC4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

each R13 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, hydroxyC2-C7alkyl, C1-C6alkoxyC2-C7alkyl, (R4)₂N-CO, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_q, R5-C2-C6alkylN(R4)-(CH₂)_q, (R4)₂N-C2-C6alkylO-(CH₂)_q, R5-C2-C6alkyl-O-(CH₂)_q, -(CH₂)_qN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC2-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, and heterocyclylaminoC2-C6alkyl;

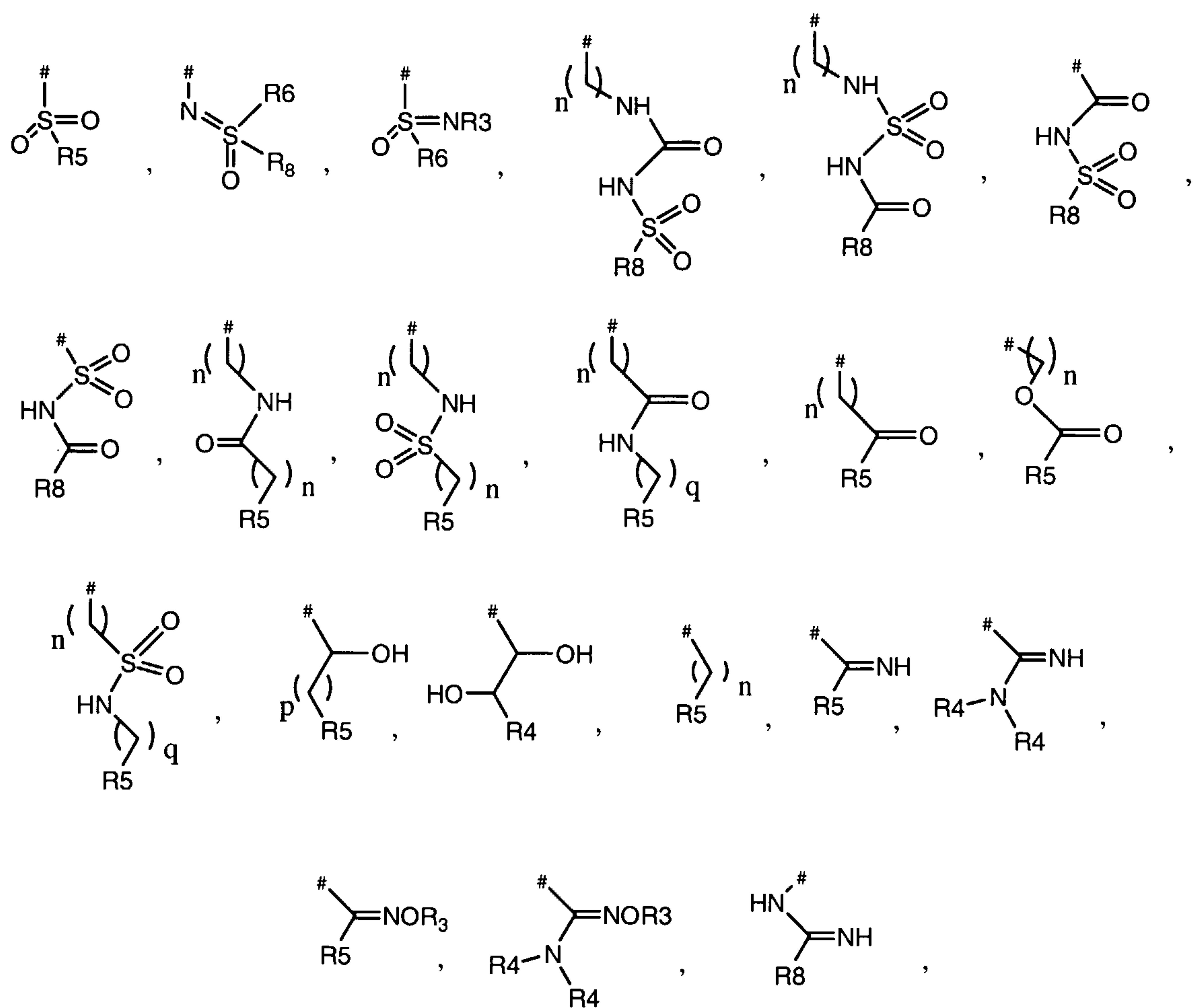
wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R13 may cyclize to form a C3-C7 heterocyclyl ring;

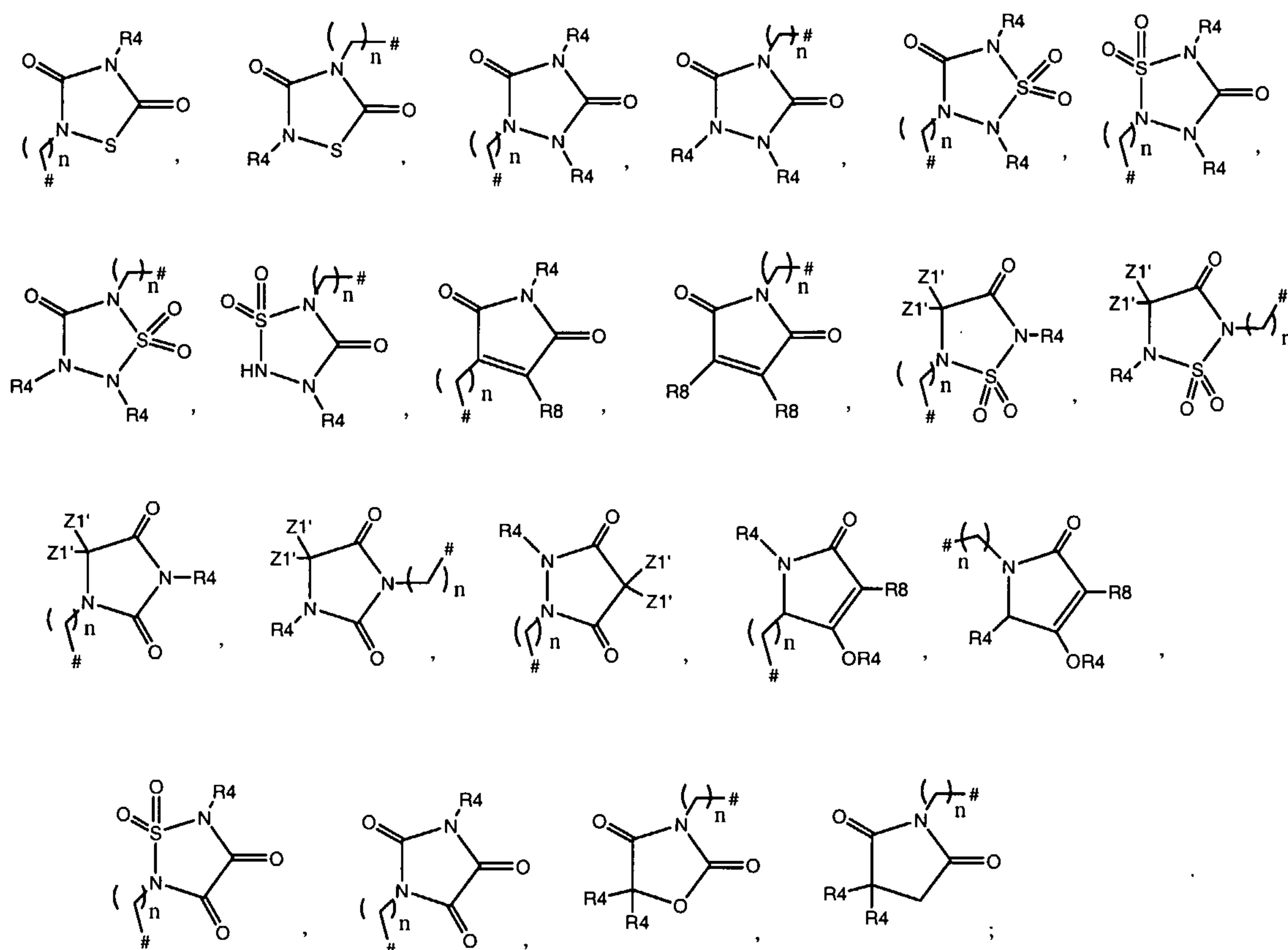
each R14 is independently and respectively selected from the group consisting of H and C1-C6alkyl;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_p, (R4)₂N-C2-C6alkylO-(CH₂)_p, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, , heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyl, hydroxyC1-C6alkyl, cyano, C1-C6alkoxy, C1-C6alkoxyC1-C6alkyl, halogen, CF₃, (R3)₂N-, (R4)₂N-, (R4)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, R8CO-, (R4)₂N-CO-C1-C6alkyl, carboxyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)₂NSO₂, -SO₂R3, SOR3, (R4)₂NSO₂, -SO₂R4, -SOR4, -(CH₂)_nN(R4)C(O)R8, -C=(NOH)R6, -C=(NOR3)R6, heteroaryl, heterocyclyl, heteroarylC1-C6alkyl, heterocyclylC1-C6alkyl, heteroaryloxy, heterocycliloxy, heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylamino, heteroarylamino, heterocyclylamino, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocyclylaminoC1-C6alkyl, or moieties of the formulae





wherein the symbol (#) indicates the point of attachment of the Z3 moiety to the A2 ring of formula I;

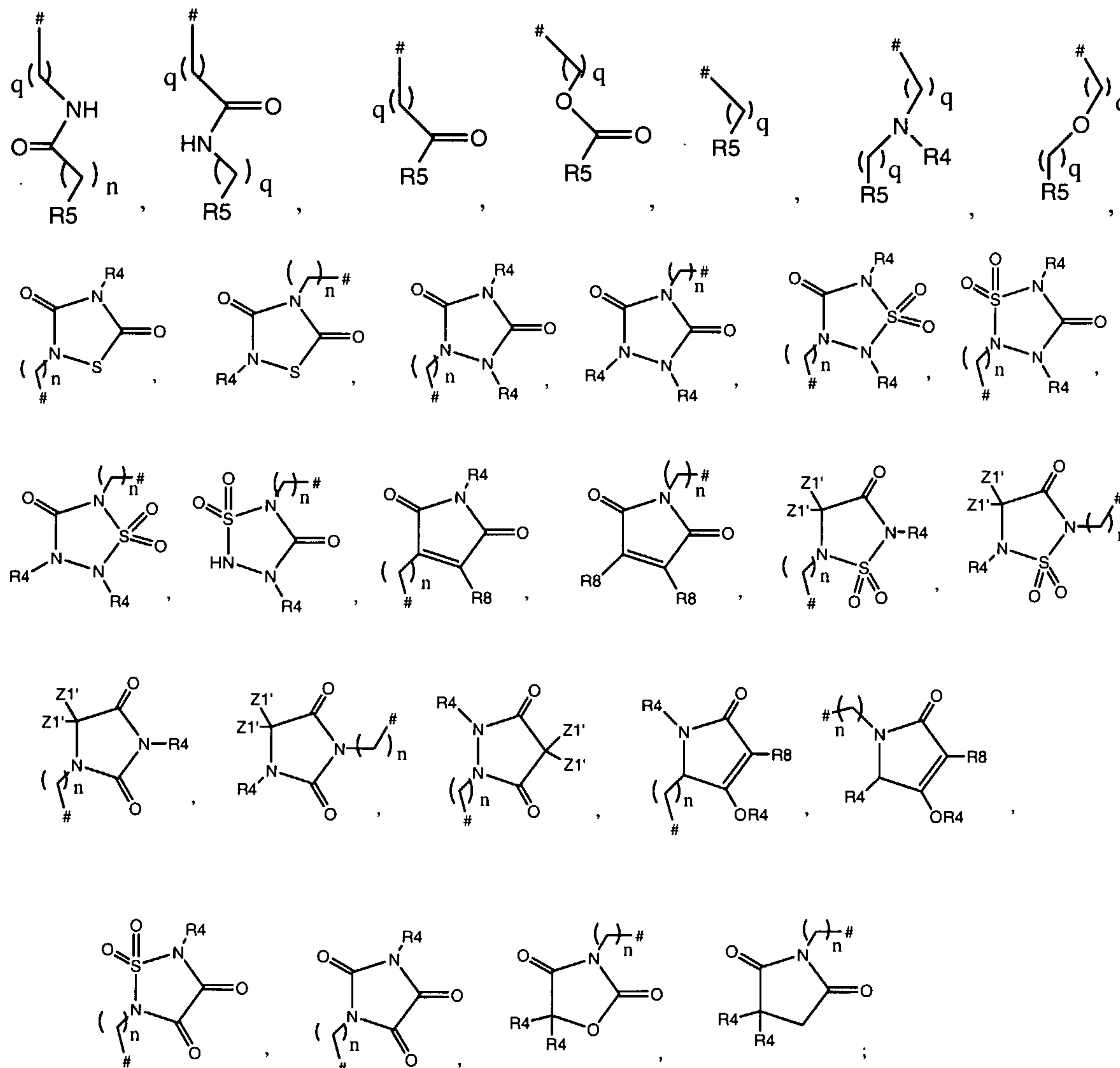
in the event that Z3 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

each Z4 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-

C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocycliloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R⁴ moieties independently and individually taken from the group consisting of C₁-C₆alkyl, branched C₃-C₆alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z₆ may cyclize to form a C₃-C₇ heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

V, V₁, and V₂ are each independently and respectively selected from the group consisting of O and H₂;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs, and salts of any of the foregoing.

2.1.6b

The following specific compounds of Formula I are more preferred:

1-(3-t-butyl-1-(1-methyl-1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1H-indazol-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 2-(3-(3-t-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)naphthalen-1-yl)acetic acid, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-carbamimidoyl-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,3-difluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,5-difluorophenyl)urea, 1-(3-t-butyl-1-(1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-

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(pyridin-3-yloxy)phenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(5-chloropyridin-3-yloxy)phenyl)urea, 6-(3-t-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1-(3-t-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(3-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(1-((2,3-dihydroxypropyl)carbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(2-(2-aminoethylamino)quinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-(dimethylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-((R)-3-(dimethylamino)pyrrolidin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(2-aminoquinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-(methylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-

tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(1-oxoisoindolin-4-yl)phenyl)urea, 1-(3-t-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(4-(1-oxoisoindolin-4-yl)phenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(4-(1-oxoisoindolin-4-yl)phenyl)urea, 6-(3-t-butyl-5-(3-(4-(1-oxoisoindolin-4-yl)phenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 6-(3-t-butyl-5-(3-(4-(1-oxoisoindolin-4-yl)phenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,

2.1.7 *Methods*

2.1.7a *Methods of Protein Modulation*

The invention includes methods of modulating kinase activity of a variety of kinases, e.g. receptor tyrosine kinases including VEGFR1, VEGFR2, FLT-1, FLT-3, PDGFRa, PDGFRb, FGFR1, FGFR2, FGFR3, FGFR4, TrkA, TrkB, EGFR, EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHA9, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4, EPHB5, EPHB6, EPHB7, EPHB8. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 2.1 and 2.1.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

2.1.7b *Treatment Methods*

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer, secondary cancer growth arising from metastasis, hyperproliferative diseases, and diseases characterized by hyper-vascularization. These methods comprise administering to such individuals compounds of the invention, and especially those of section 2.1 and 2.1.6a. Exemplary conditions include glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary solid tumor secondary sites, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies including diabetic retinopathy and age-related macular degeneration, or

rheumatoid arthritis characterized by the in-growth of a vascularized pannus. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

2.1.8 *Pharmaceutical Preparations*

The compounds of the invention, especially those of 2.1 and 2.1.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

2.1.9 *Kinase/Compound Adducts*

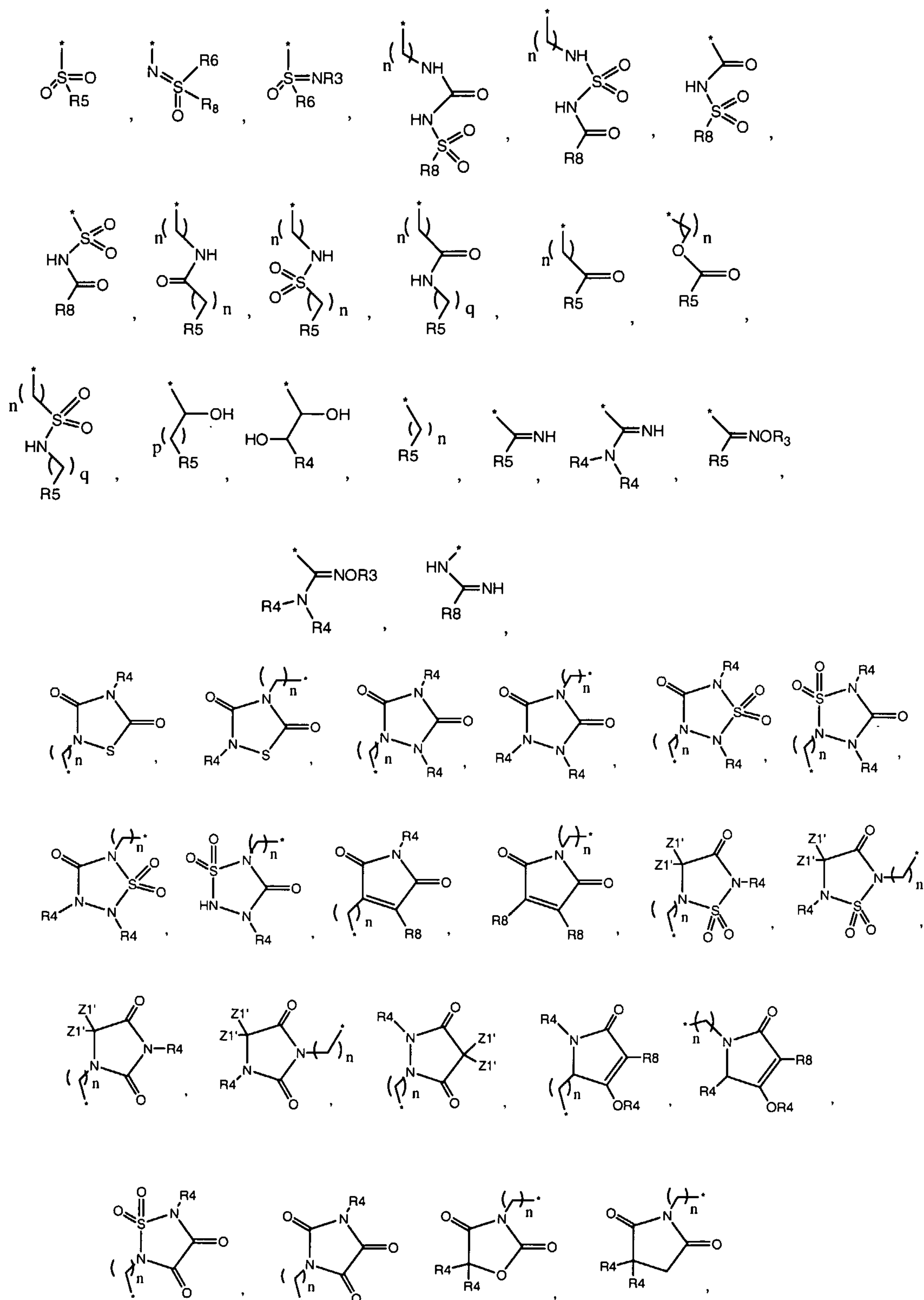
The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 2.1 and 2.1.6a.

2.2 *Generally – Monocyclic A2 Compounds with Polycyclic E2 Rings*

The invention includes compounds of the formula I as defined in section 1.2 wherein each R2 is selected from the group consisting of monocyclic heteroaryl, C1-C6alkyl, branched C3-C7alkyl, and R19 substituted C3-C8carbocyclyl wherein R19 is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents;

each Z1 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC1-C6alkyl, C2-C6alkoxy, C1-C6alkoxyC1-C6alkyl, (R4)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, (R3)₂N-C(=O)-, (R4)₂N-C(=O)-, (R4)₂N-CO-C1-C6alkyl, C1-C6alkoxycarbonyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)₂NSO₂, SOR3, (R4)₂NSO₂, -SO₂R3', -SOR4, -C(=O)R6, -C(=NOH)R6, -C(=NOR3)R6, -(CH₂)_nN(R4)C(O)R8, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocycliloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocycliloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic

heteroarylaminoC1-C6alkyl, monocyclic heterocyclaminoC1-C6alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

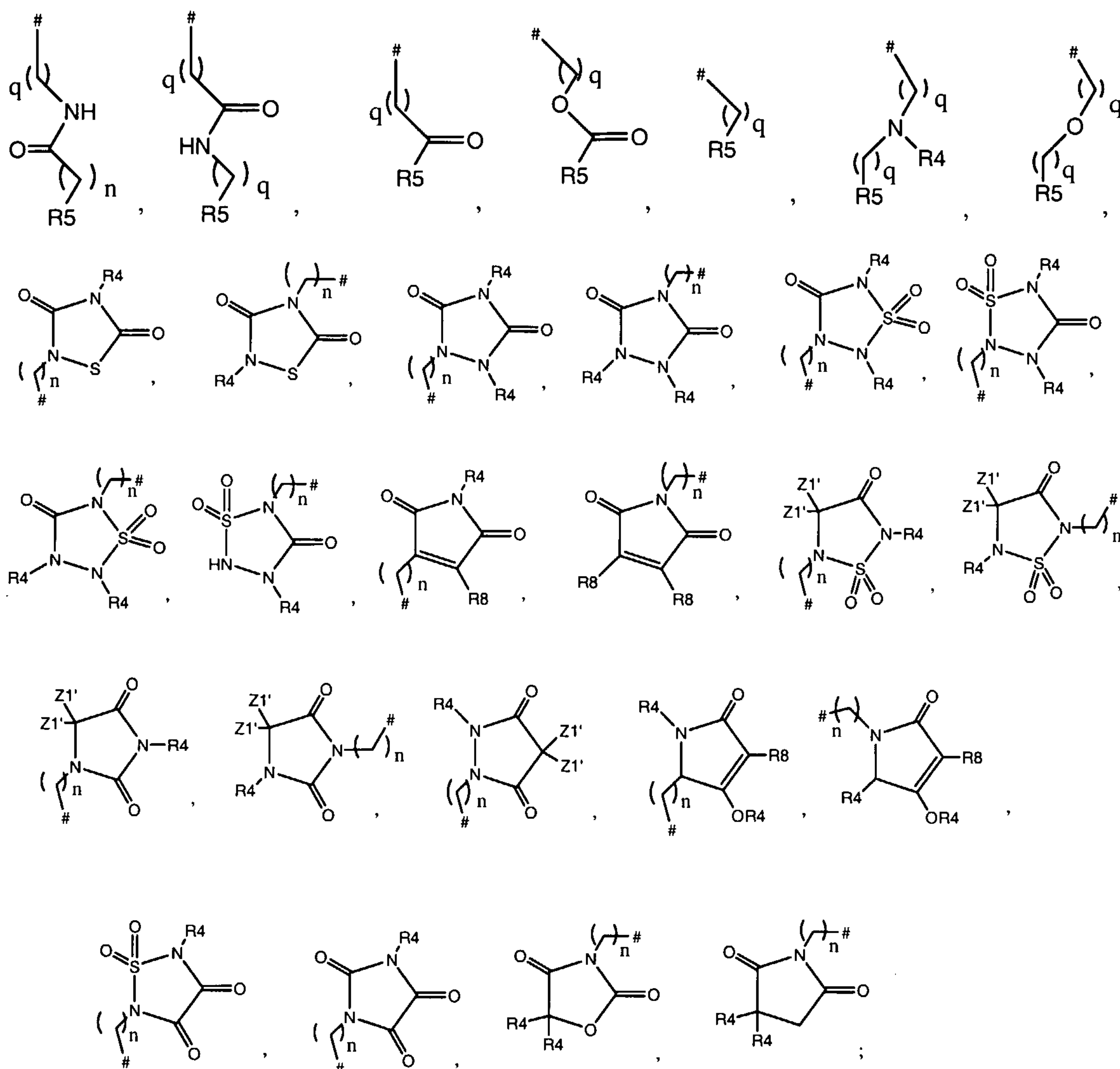
wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_p, (R4)₂N-C2-C6alkylO-(CH₂)_p, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, , heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z4' is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl,

heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoc2-C6alkyl, heterocyclylaminoc2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4' moiety to the A1 ring of formula I;

in the event that Z4' contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4' may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R₄ moieties independently and individually taken from the group consisting of C₁-C₆alkyl, branched C₃-C₆alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z₄' may cyclize to form a C₃-C₇ heterocyclyl ring;

2.2.1 Preferred D Moieties

2.2.1a

Preferably, the compounds of formula I in 2.2 contain D moieties wherein E₁ and E₂ are as defined in section 1.2.1

2.2.1b

Additionally preferred D moieties of formula I in 2.2 are as defined in section 1.2.1b

2.2.1c

More preferred D moieties of 2.2.1b are wherein E₂ is defined as in section 1.2.1c

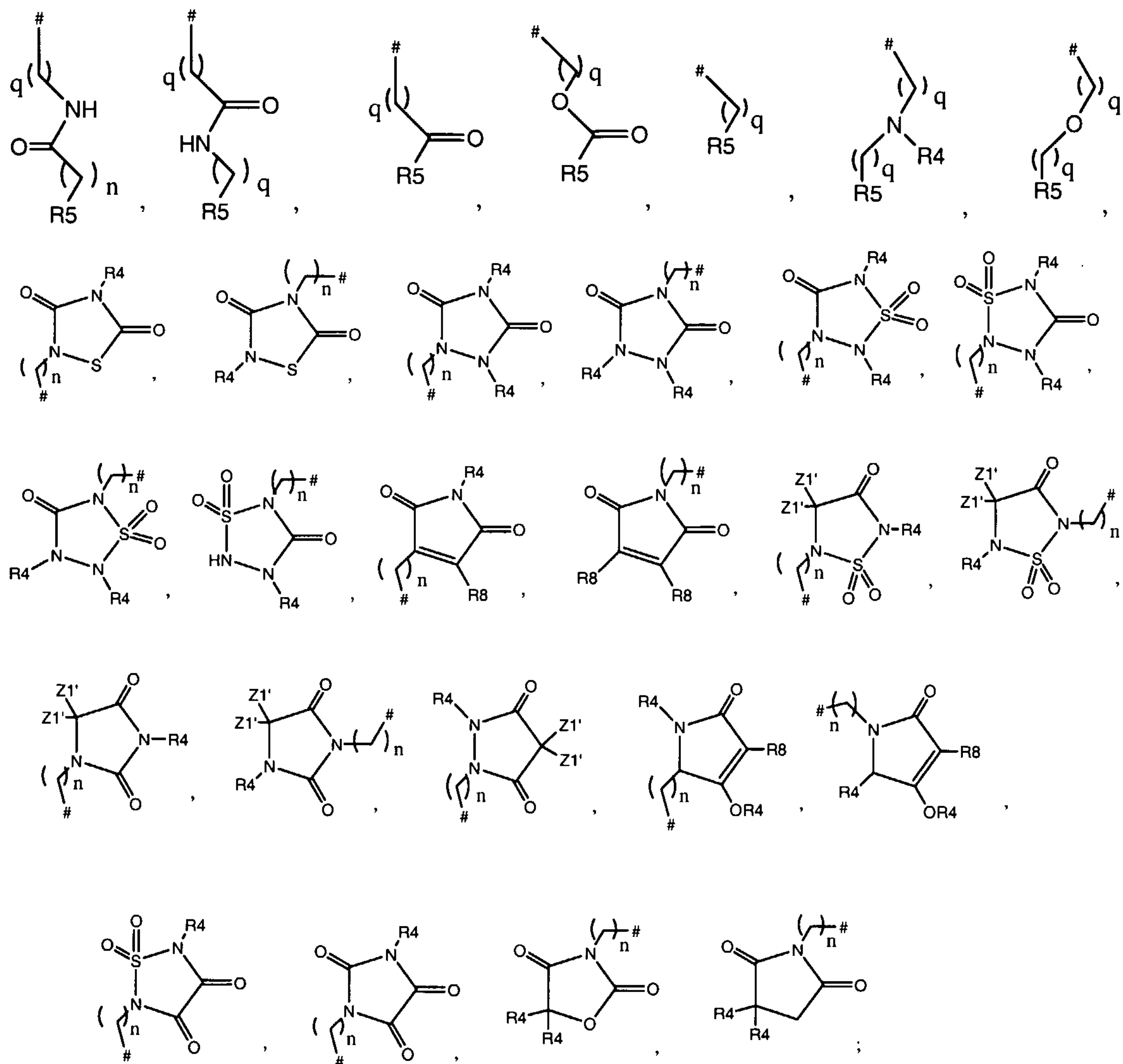
2.2.2 Preferred A₂ moieties

2.2.2a

Compounds of Formula I as defined above in section 2.2 have preferred A₂ moieties as defined in section 1.2.2a;

wherein two R₄ moieties independently and individually taken from the group consisting of C₁-C₆alkyl, branched C₃-C₆alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z₁' may cyclize to form a C₃-C₇ heterocyclyl ring;

each Z₄ is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C₁-C₆alkyl, hydroxyC₂-C₆alkyl, C₁-C₆alkoxyC₂-C₆alkyl, (R₄)₂N-C₂-C₆alkyl, (R₄)₂N-C₂-C₆alkylN(R₄)-C₂-C₆alkyl, (R₄)₂N-C₂-C₆alkyl-O-C₂-C₆alkyl, (R₄)₂N-CO-C₂-C₆alkyl, carboxyC₂-C₆alkyl, C₁-C₆alkoxycarbonylC₂-C₆alkyl, -C₂-C₆alkylN(R₄)C(O)R₈, R₈-C(=NR₃)-, -SO₂R₈, -COR₈, heteroaryl, heteroarylC₁-C₆alkyl, heterocyclyl, heterocyclylC₁-C₆alkyl, heteroaryloxyC₂-C₆alkyl, heterocyclyloxyC₂-C₆alkyl, arylaminoC₂-C₆alkyl, heteroarylaminoC₂-C₆alkyl, heterocyclylaminoC₂-C₆alkyl, and moieties of the formulae



wherein the symbol ($\#$) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

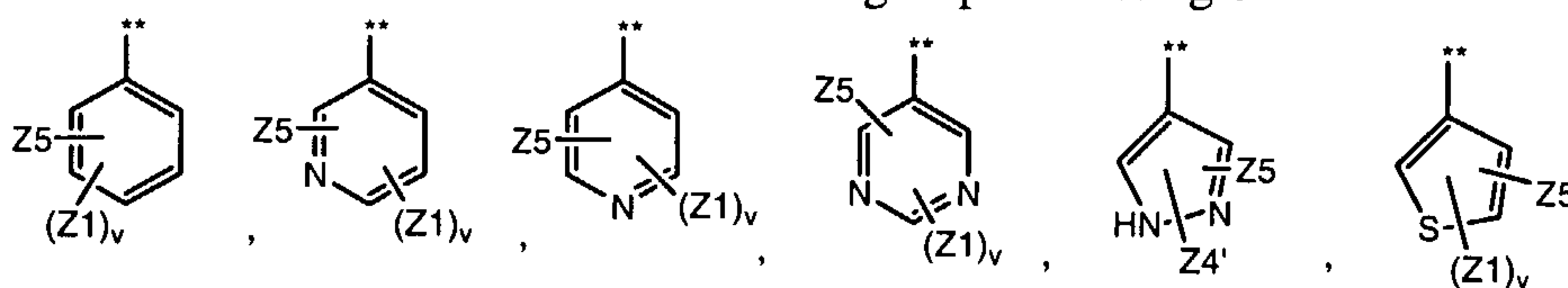
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2.

2.2.2b

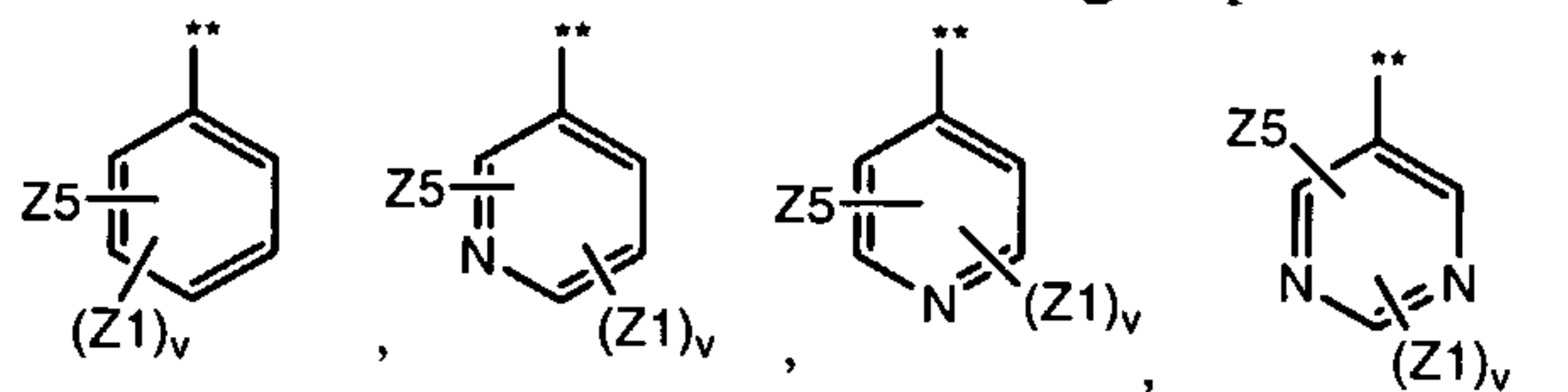
More preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring for formula I.

2.2.2c

Even more preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I.

2.2.3 Preferred Classes of Compounds

2.2.3a

Compounds as defined in 2.2.1a wherein the A2 group is defined in 2.2.2a.

2.2.3b

Compounds as defined in 2.2.3a wherein the A2 group is defined in 2.2.2b.

2.2.3c

Compounds as defined in 2.2.3a wherein the A2 group is defined in 2.2.2c.

2.2.3d

Compounds as defined in 2.2.1b wherein the A2 group is defined in 2.2.2a.

2.2.3e

Compounds as defined in 2.2.3c wherein the A2 group is defined in 2.2.2b.

2.2.3f

Compounds as defined in 2.2.3c wherein the A2 group is defined in 2.2.2c.

2.2.4 Preferred A1 Moieties

2.2.4a

These preferred A1 moieties are defined in 2.1.4a.

2.2.4b

These more preferred A1 moieties are defined in 2.1.4b.

2.2.4c

These even more preferred A1 moieties are defined in 2.1.4c.

2.2.5 Preferred W and Y Moieties

2.2.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR₄ and X=O; or (3) W=CHR₄, Y=NH, and X=O.

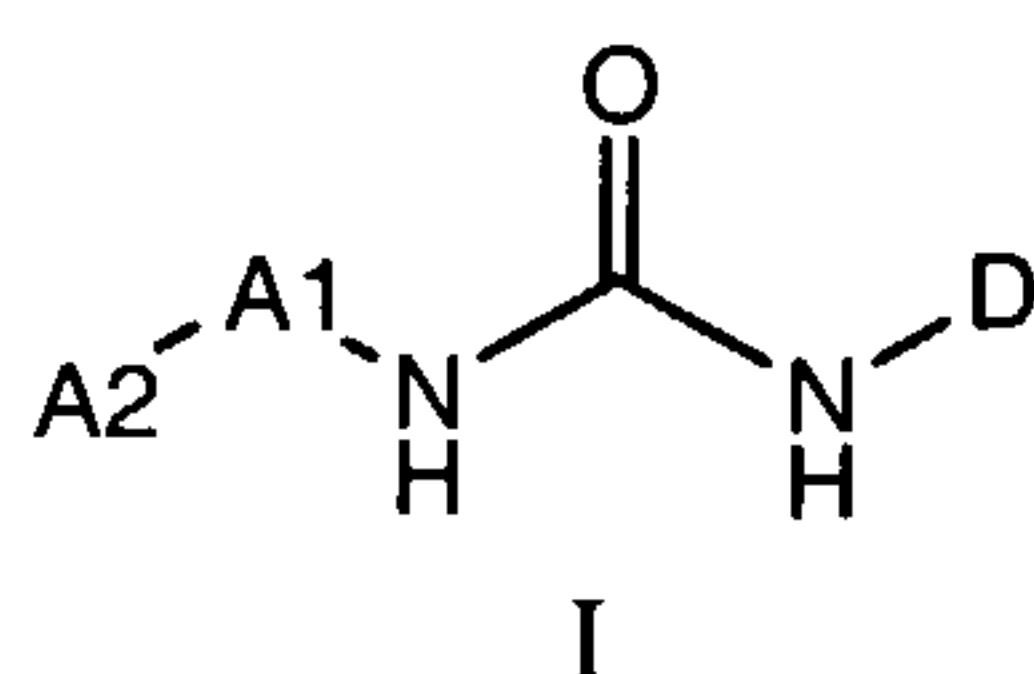
2.2.5b

W and Y are each NH and X=O.

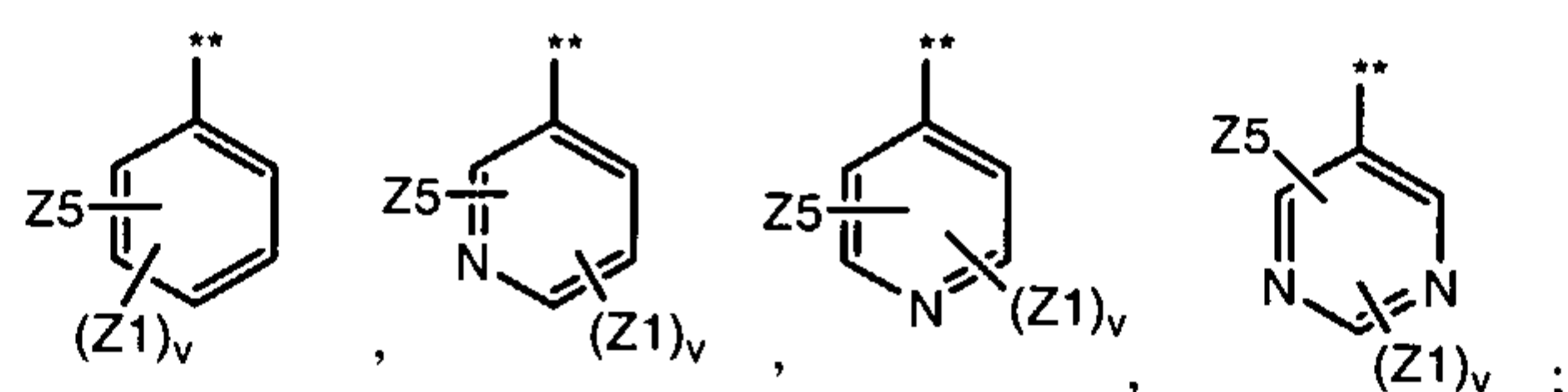
2.2.6 Further Preferred Compounds

2.2.6a

Further preferred compounds are of the formula

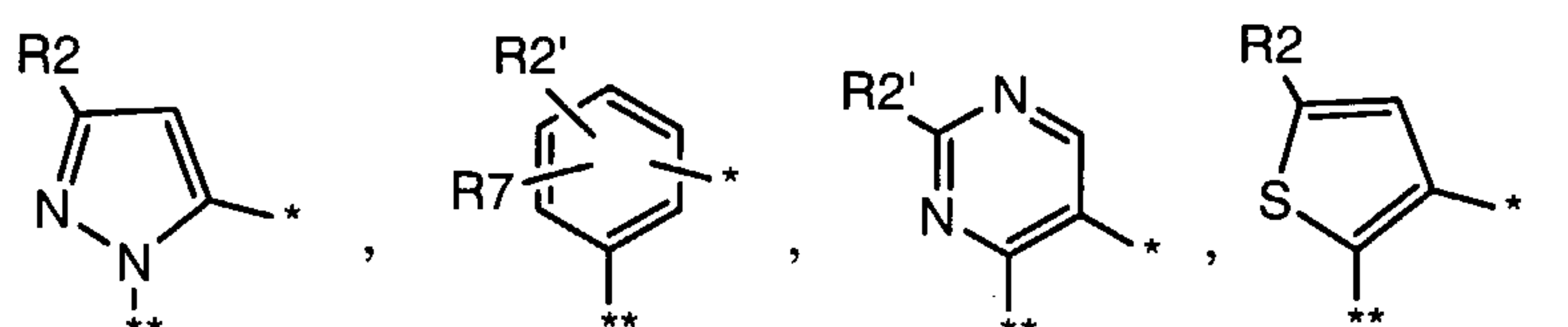


wherein A2 is selected from the group consisting of



wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

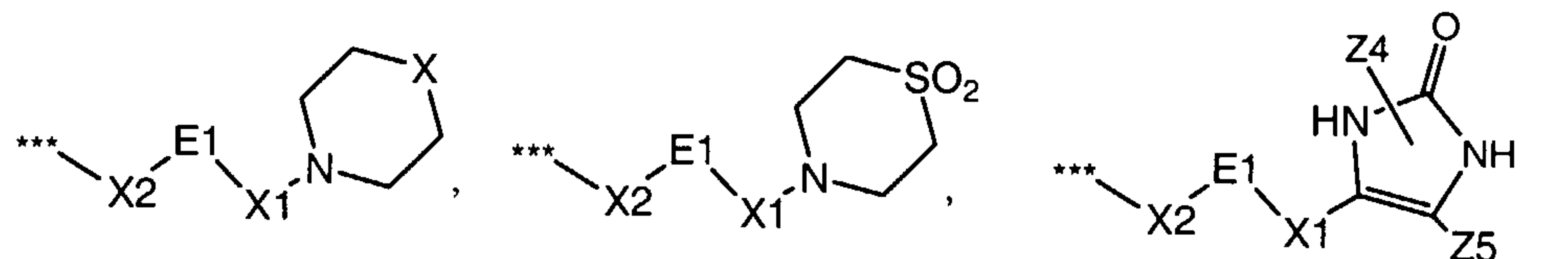
A1 is selected from the group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR₃;

D comprises a member of



wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-

C(=O)-, $-(\text{CH}_2)_n\text{-N(R}_4\text{)-C(=O)(CH}_2)_n\text{-}$, $-(\text{CH}_2)_n\text{-CO-N(R}_4\text{)-}$, $-(\text{CH}_2)_p\text{-}$, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of $-(\text{CH}_2)_n\text{-}$, $-(\text{CH}_2)_q\text{-}$, $(\text{CH}_2)_p\text{-}$, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

each R2 is selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, and R19 substituted C3-C8carbocyclyl wherein R19 is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents, or monocyclic heteroaryl;

each R2' is selected from the group consisting of halogen and R2;

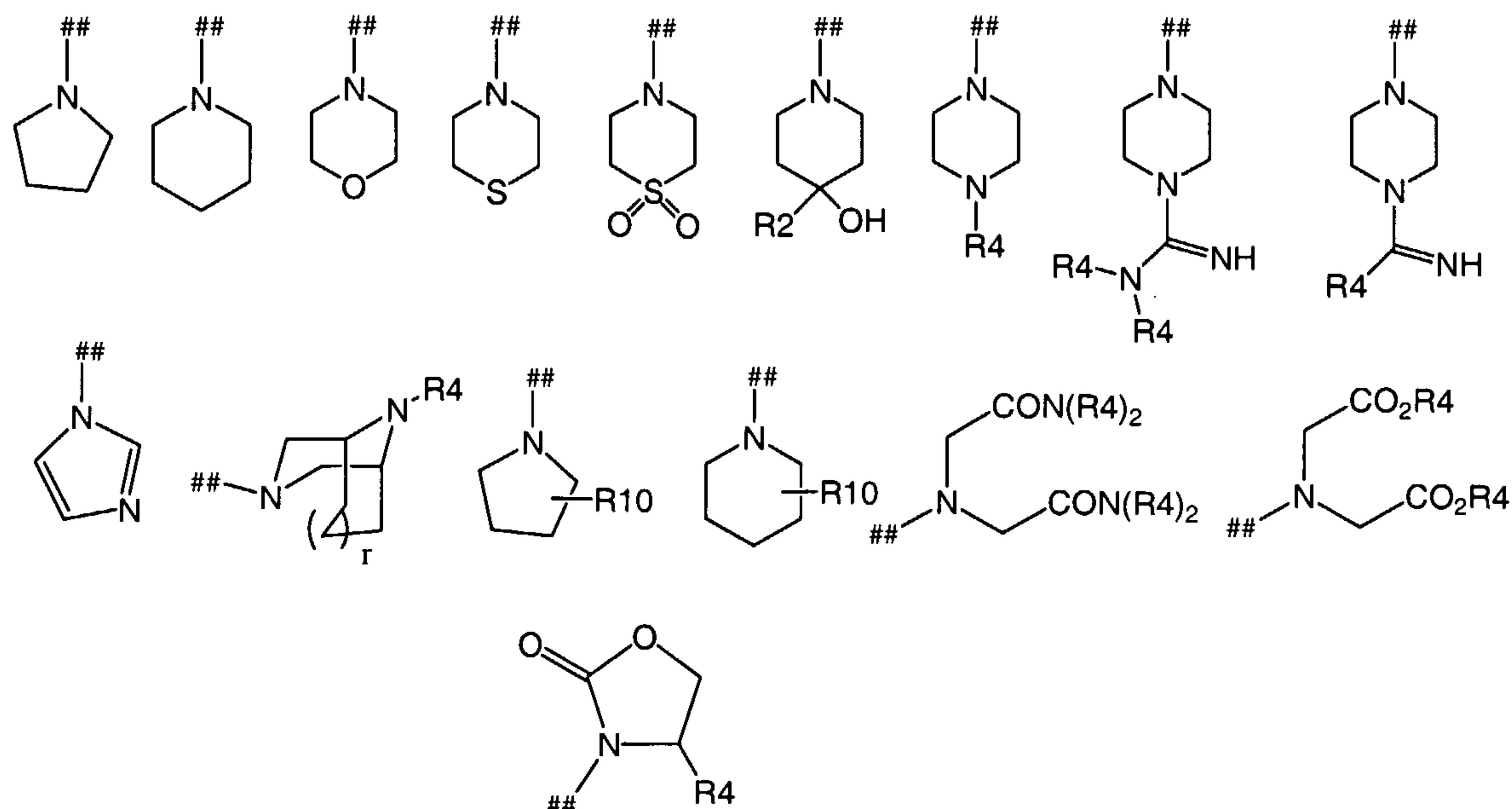
each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyc1-C6 alkyl, dihydroxyc1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyc1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyc1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocyclyl ring;

each R5 is independently and individually selected from the group consisting of



;

and wherein the symbol (##) is the point of attachment to respective R8, R10, Z1, Z4, Z5, Z6 or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

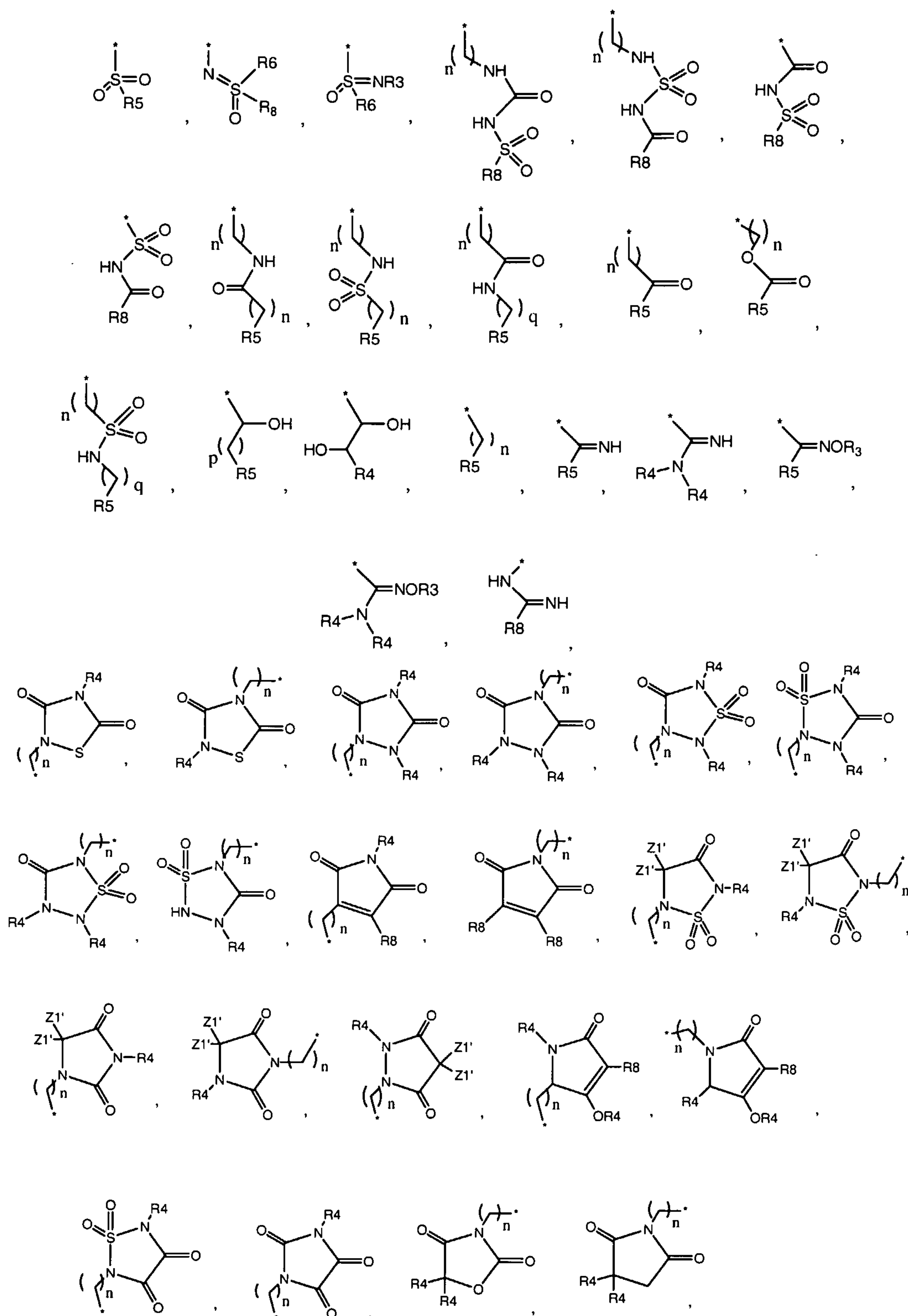
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

each Z1 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC1-C6alkyl, C2-C6alkoxy, C1-C6alkoxyC1-C6alkyl, (R4)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, (R3)₂N-C(=O)-, (R4)₂N-C(=O)-, (R4)₂N-CO-C1-C6alkyl, C1-C6alkoxycarbonyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)₂NSO₂, SOR3, (R4)₂NSO₂, -SO₂R3', -SOR4, -C(=O)R6, -C(=NOH)R6, -C(=NOR3)R6, -(CH₂)_nN(R4)C(O)R8, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocycliloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocycliloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

In the foregoing definition of Z1, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

In the foregoing definition of Z1, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

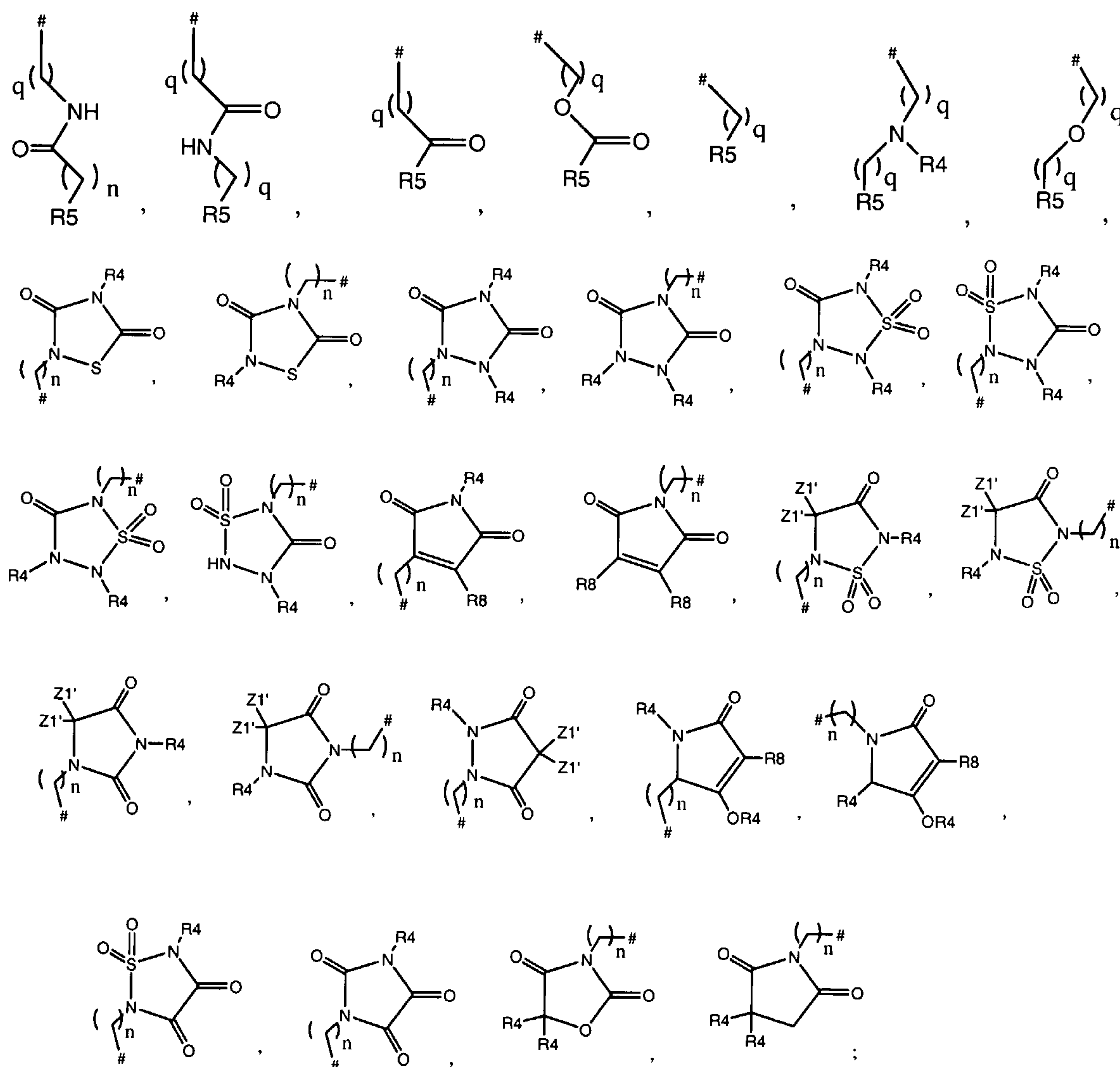
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_p, (R4)₂N-C2-C6alkylO-(CH₂)_p, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, , heteroaryloxyC1-C6alkyl, heterocyclyloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R⁴ moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z₄ is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R⁴)₂N-C2-C6alkyl, (R⁴)₂N-C2-C6alkylN(R⁴)-C2-C6alkyl, (R⁴)₂N-C2-C6alkyl-O-C2-C6alkyl, (R⁴)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R⁴)C(O)R₈, R₈-C(=NR₃)-, -SO₂R₈, -COR₈, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclioxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

2.2.6b

The following specific compounds of Formula I are more preferred: 1-(1-(3-(1H-pyrazol-4-yl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(6-(thiazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(2-(3-(2-amino-2-oxoethyl)phenyl)-5-t-butylthiophen-3-yl)-3-(4-(4-(pyridin-3-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(4-(isoxazol-4-yl)pyrimidin-2-yl)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(4-(pyridin-3-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-(3-(1H-pyrazol-4-yl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(4-(pyridin-3-yl)pyrimidin-2-yloxy)phenyl)urea

2.2.7 Methods

2.2.7a Methods of Protein Modulation

The invention includes methods of modulating kinase activity of a variety of kinases, e.g. receptor tyrosine kinases including VEGFR1, VEGFR2, FLT-1, FLT-3, PDGFRa, PDGFRb, FGFR1, FGFR2, FGFR3, FGFR4, TrkA, TrkB, EGFR, EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHA9, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4, EPHB5, EPHB6, EPHB7, EPHB8. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 2.2 and 2.2.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid

acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

2.2.7b Treatment Methods

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer, secondary cancer growth arising from metastasis, hyperproliferative diseases, and diseases characterized by hyper-vascularization. These methods comprise administering to such individuals compounds of the invention, and especially those of section 2.2 and 2.2.6a. Exemplary conditions include glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary solid tumor secondary sites, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies including diabetic retinopathy and age-related macular degeneration, or rheumatoid arthritis characterized by the in-growth of a vascularized pannus. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

2.2.8 Pharmaceutical Preparations

The compounds of the invention, especially those of 2.2 and 2.2.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

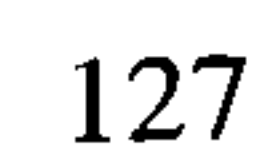
2.2.9 Kinase/Compound Adducts

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 2.2 and 2.2.6a.

2.3 Generally – Monocyclic A2 Compounds with Monocyclic E2 Rings

The invention includes compounds of the formula I as defined in section 1.3 wherein each R2 is selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, and R19 substituted C3-C8carbocyclyl wherein R19 is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents, or monocyclic heteroaryl;

wherein each Z1 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC1-C6alkyl, C2-C6alkoxy, C1-C6alkoxyC1-C6alkyl, (R4)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, (R3)₂N-C(=O)-, (R4)₂N-C(=O)-, (R4)₂N-CO-C1-C6alkyl, C1-C6alkoxycarbonyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)₂NSO₂, SOR3, (R4)₂NSO₂, -SO₂R3', -SOR4, -C(=O)R6, -C(=NOH)R6, -C(=NOR3)R6, -(CH₂)_nN(R4)C(O)R8, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocycliloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocycliloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

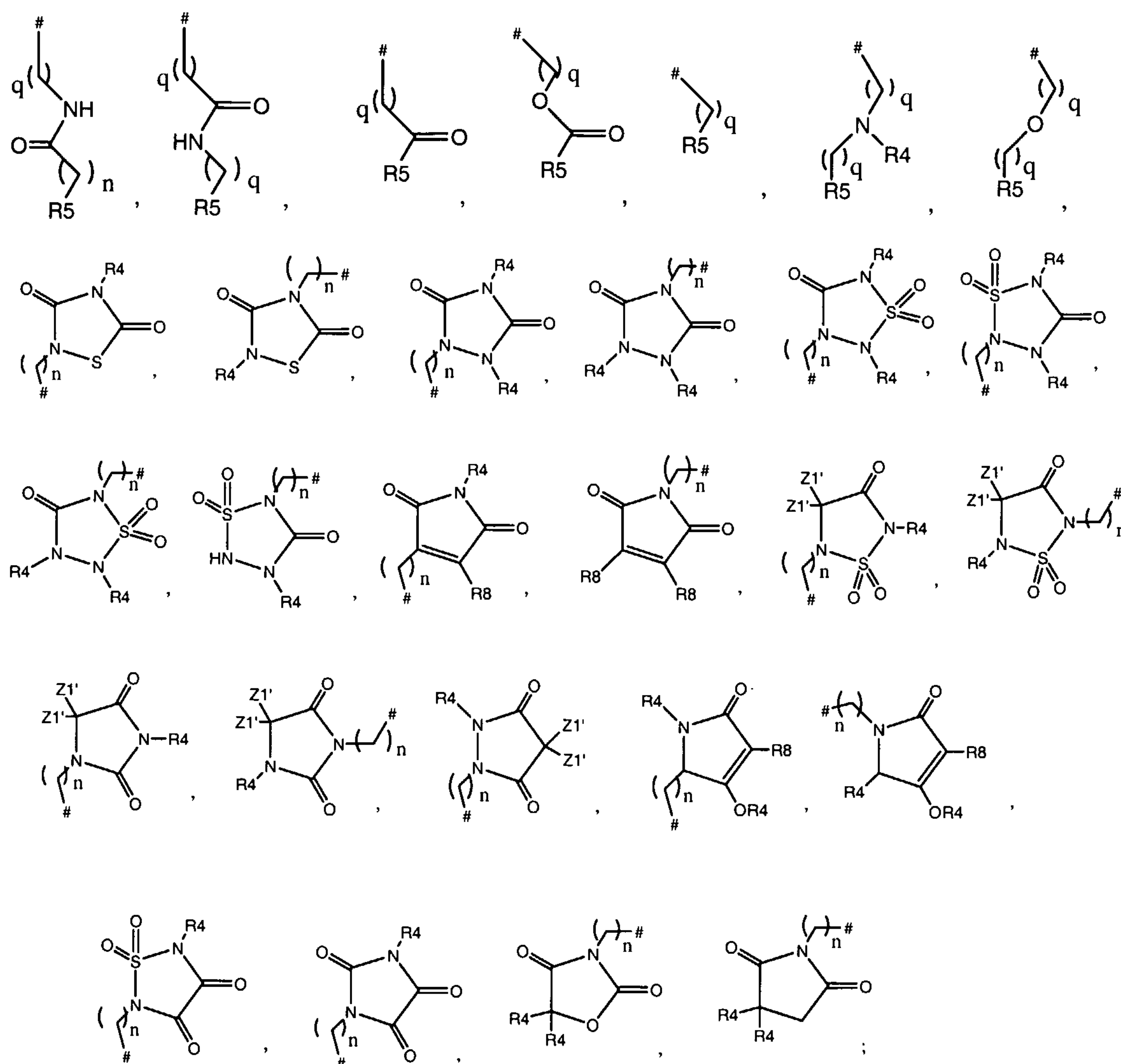
wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_p, (R4)₂N-C2-C6alkylO-(CH₂)_p, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, , heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z4' is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl,

heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoc2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



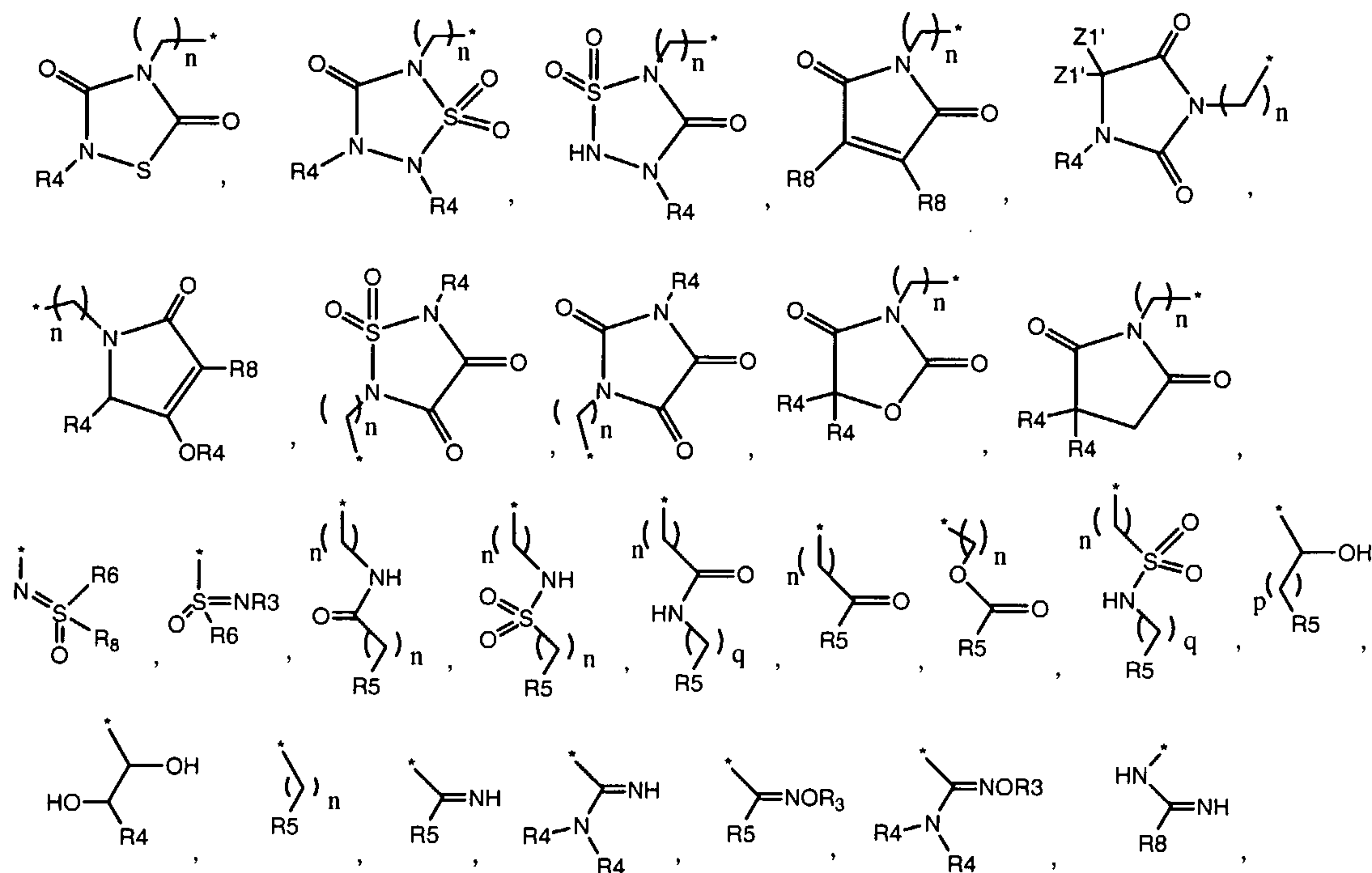
wherein the symbol (#) indicates the point of attachment of the Z4' moiety to the A1 ring of formula I;

in the event that Z4' contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

each Z7 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC1-C6alkyl, $(\text{R}_6)_2\text{NC1-C6alkyl}$, $(\text{R}_4)_2\text{NC2-C6alkylN}(\text{R}_4)\text{-(CH}_2)_n$, $(\text{R}_4)_2\text{NC2-C6alkylO}(\text{CH}_2)_n$, $(\text{R}_3)_2\text{N-}$

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CO, (R₄)₂N-CO, -SO₂R₃', SOR₃, -SOR₄, -C(=O)R₆, -C(=NOH)R₆, -C(=NOR₃)R₆, (CH₂)_nN(R₄)C(O)N(R₄)₂, (CH₂)_nN(R₄)C(O)R₅, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocyclyloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocyclyloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

In the foregoing definition of Z7, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z7 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z7 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z7 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6, r is 0 or 1;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs, and salts of any of the foregoing.

2.3.1 Preferred D Moieties

2.3.1a

Preferably, the compounds of formula I in 2.3 contain D moieties wherein E1 and E2 are as defined in section 1.3.1a.

2.3.1b

Additionally preferred D moieties of formula I in 2.3 are as defined in section 1.3.1b.

2.3.1c

More preferred D moieties of 2.2.1b are wherein E2 is defined as in section 1.3.1c.

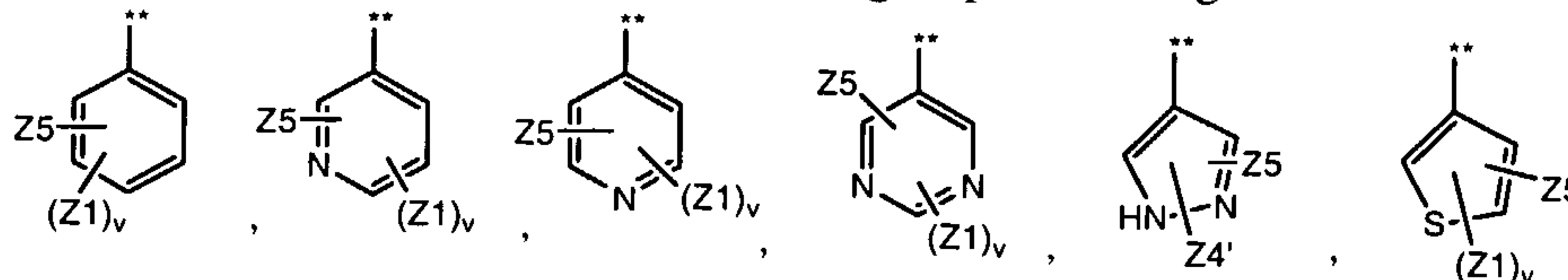
2.3.2 Preferred A2 moieties

2.3.2a

Compounds of Formula I as defined above in section 2.3 have preferred A2 moieties as defined in section 2.2.2a.

2.3.2b

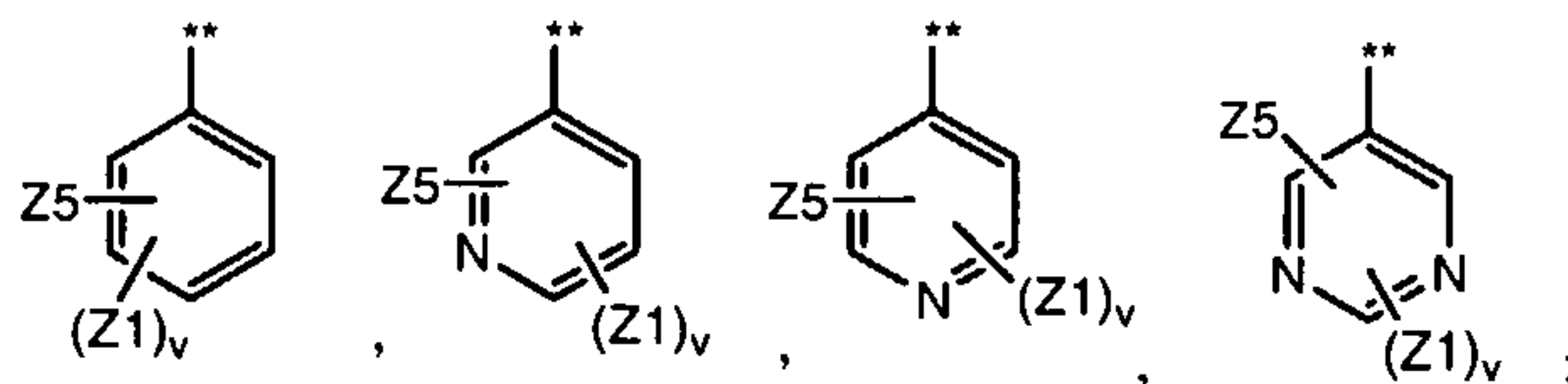
More preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring for formula I.

2.3.2c

Even more preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I.

2.3.3 Preferred Classes of Compounds

2.3.3a

Compounds as defined in 2.3.1a wherein the A2 group is defined in 2.3.2a.

2.3.3b

Compounds as defined in 2.3.3a wherein the A2 group is defined in 2.3.2b.

2.3.3c

Compounds as defined in 2.3.3a wherein the A2 group is defined in 2.3.2c.

2.3.3d

Compounds as defined in 2.3.1b wherein the A2 group is defined in 2.3.2a.

2.3.3e

Compounds as defined in 2.3.3c wherein the A2 group is defined in 2.3.2b.

2.3.3f

Compounds as defined in 2.3.3c wherein the A2 group is defined in 2.3.2c.

2.3.4 Preferred A1 Moieties

2.3.4a

These preferred A1 moieties are defined in 2.1.4a.

2.3.4b

These more preferred A1 moieties are defined in 2.1.4b.

2.3.4c

These even more preferred A1 moieties are defined in 2.1.4c.

2.3.5 Preferred W and Y Moieties

2.3.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR₄ and X=O; or (3) W=CHR₄, Y=NH, and X=O.

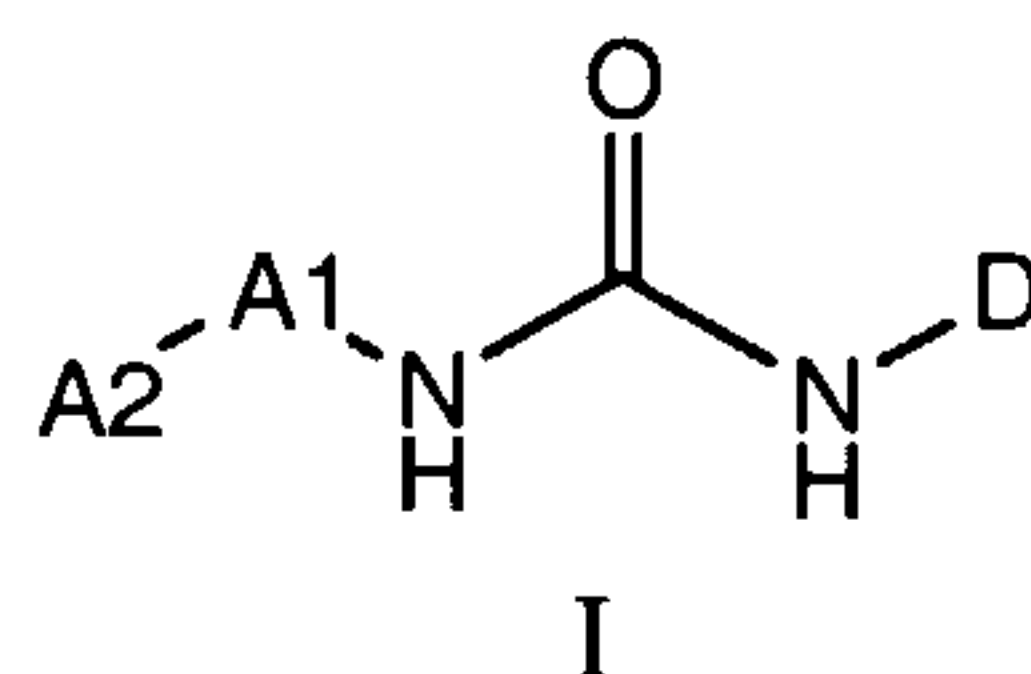
2.3.5b

W and Y are each NH and X=O.

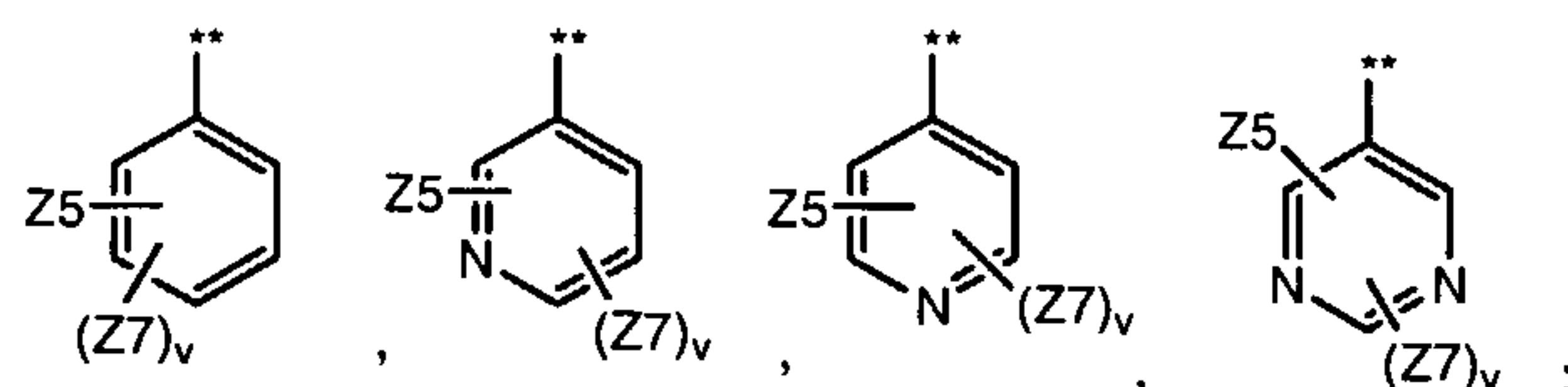
2.3.6 Further Preferred Compounds

2.3.6a

Further preferred compounds are of the formula

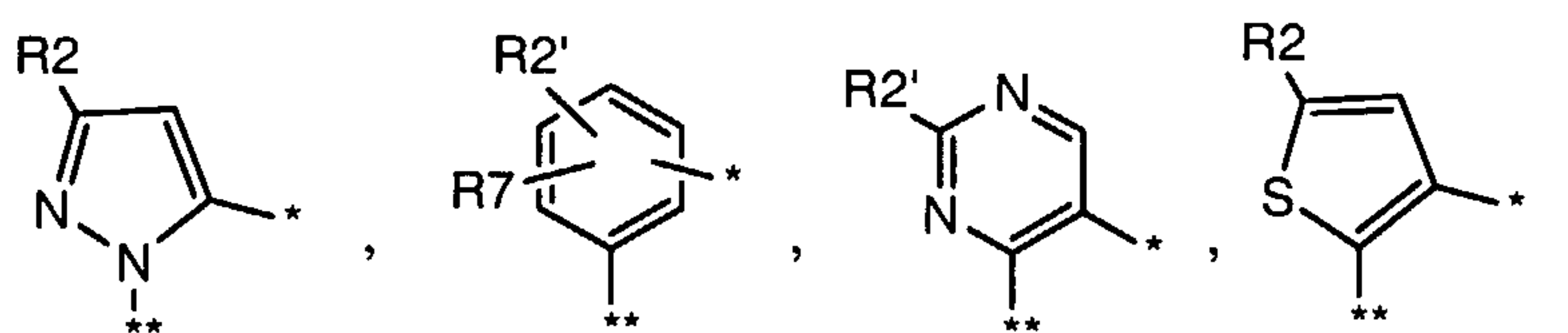


wherein A2 is selected from the group consisting of



wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

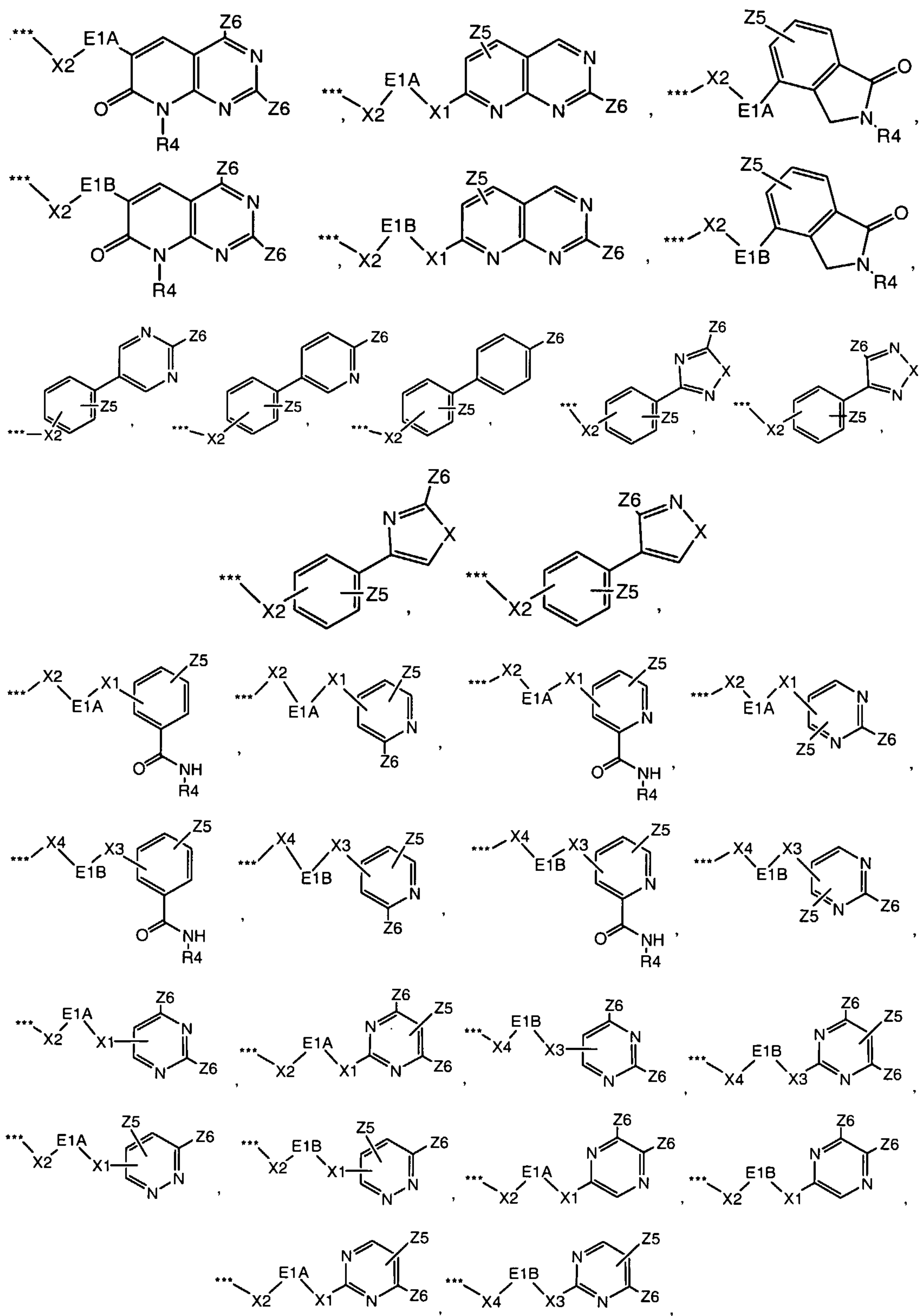
A1 is selected from the group consisting of

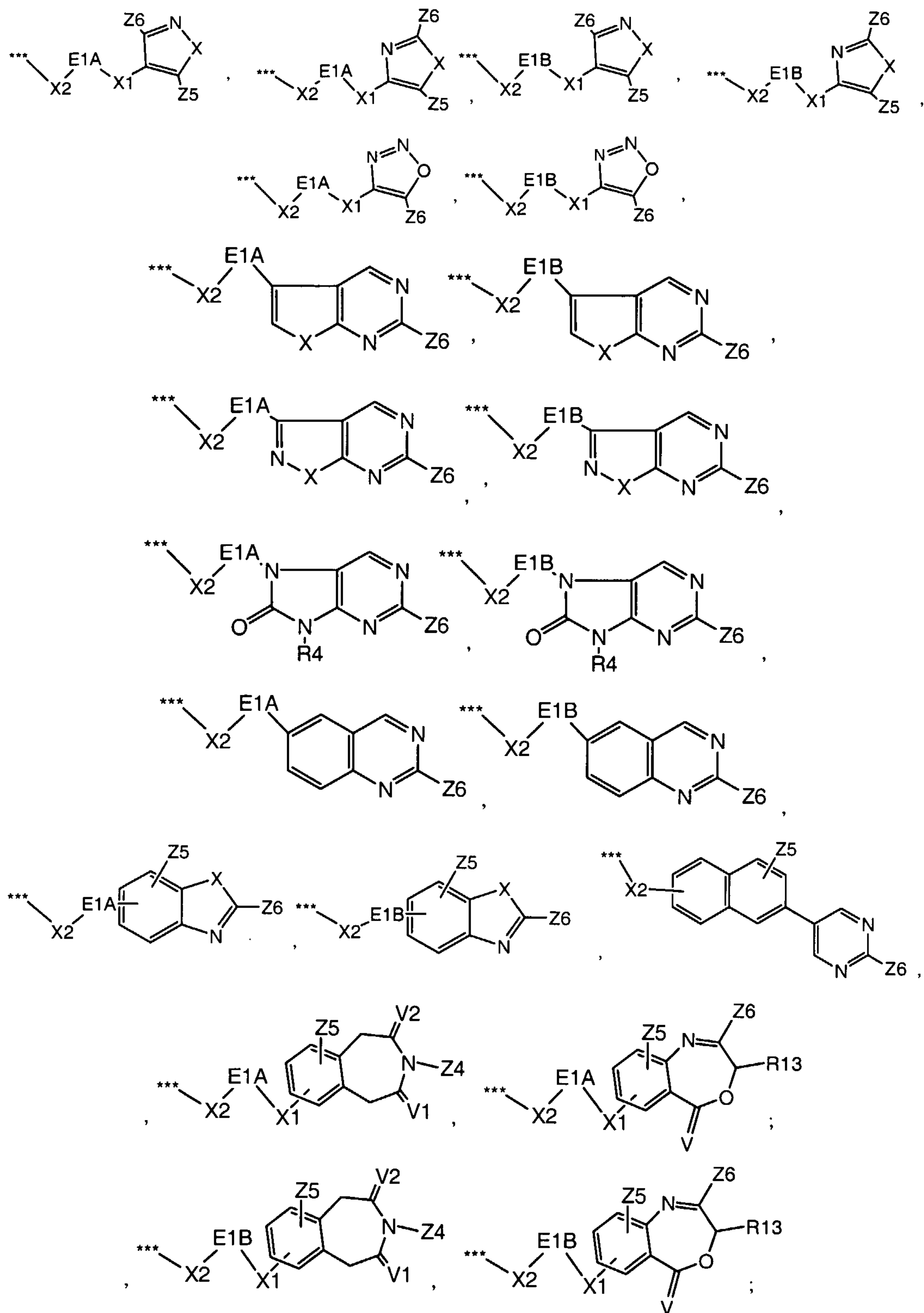


wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR₃;

D comprises a member of 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 4-chlorophenyl, 3-chlorophenyl, 3-bromophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 3,4,5-trifluorophenyl, 4-cyanophenyl, 3-(R₈SO₂)-phenyl, 3-phenoxyphenyl, 4 phenoxyphenyl,





wherein E1A is taken from the groups consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, and pyrimidinyl;

wherein E1B is taken from the groups consisting of phenyl and naphthyl;

wherein E2A is taken from the group comprising naphthyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, triazinyl and fused bicyclic rings selected from the group comprising indolyl, isoindolyl, isoindolinyl, isoindolonyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, imidazopyrimidinyl, imidazolonopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, furylopyrimidinyl, thienopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl, phthalazinyl, benzodioxyl, indolinyl, benzisothiazoline-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzoxapinyl, benzoxazepinyl;

wherein E2B is taken from the group consisting of phenyl, pyridyl, and pyrimidyl;

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, (CH₂)_p-, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

each R2 is selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, and R19 substituted C3-C8carbocyclyl wherein R19 is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents, or monocyclic heteroaryl;

X3 is selected from the group consisting of NR3, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR3-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR3-, -N(R3)-(CH₂)_q-N(R3)-, -(CH₂)_n-N(R4)-C(=O)-, -(CH₂)_n-N(R4)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R4)-, -(CH₂)_q-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the either the E1B ring or E2B ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_q-, C2-C5alkenyl, and C2-C5alkynyl moieties of X3 may be further substituted by one or more C1-C6alkyl;

X4 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl;

each R2' is selected from the group consisting of halogen and R2;

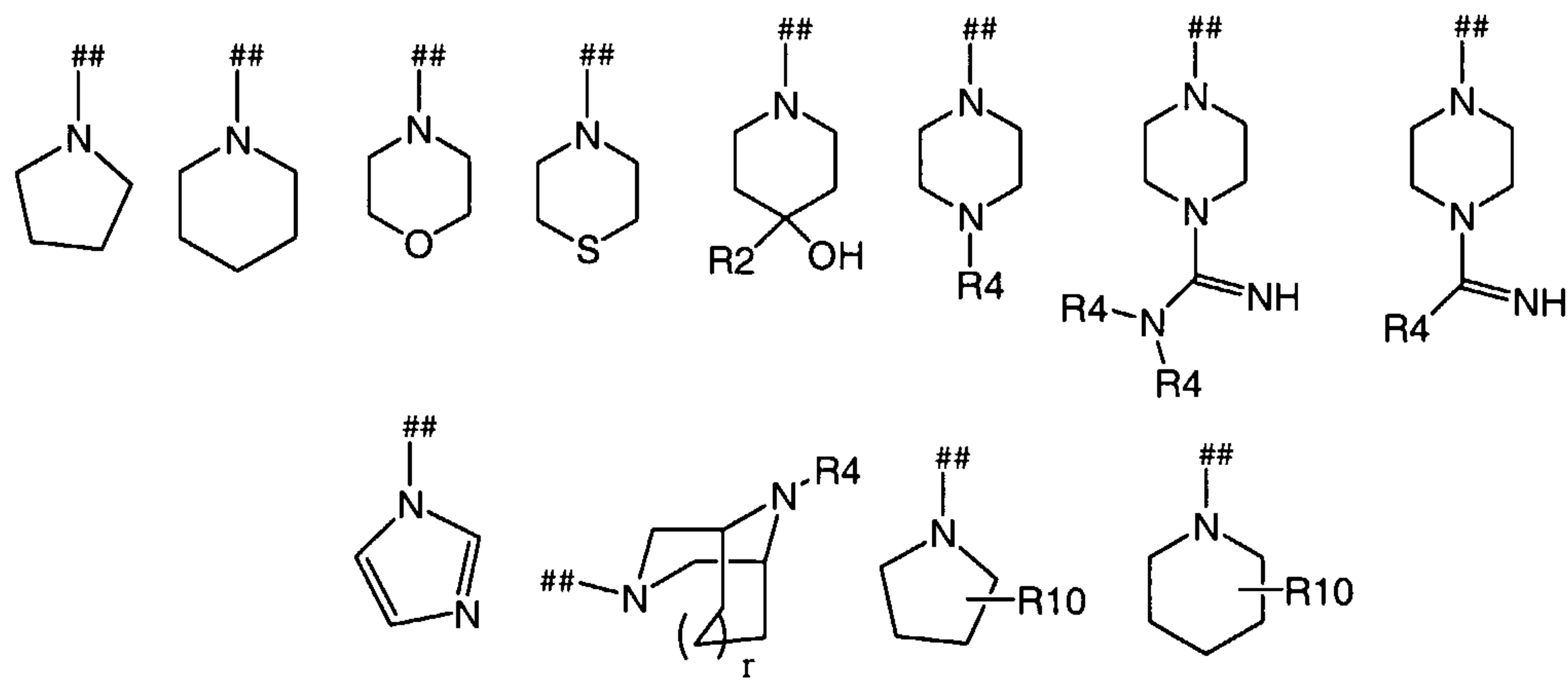
each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R₄ moieties independently and individually taken from the group consisting of C₁-C₆alkyl, branched C₃-C₆alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C₃-C₇ heterocyclyl ring;

each R₅ is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R₈, R₁₀, Z₄, Z₅, Z₆ or A₂ ring moieties containing a R₅ moiety;

wherein two R₄ moieties independently and individually taken from the group consisting of C₁-C₆alkyl, branched C₃-C₆alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R₅ may cyclize to form a C₃-C₇ heterocyclyl ring;

wherein each R₆ is independently and individually selected from the group consisting of C₁-C₆alkyl, branched C₃-C₇alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R₇ is selected from the group consisting of H, halogen, C₁-C₃fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C₁-C₃alkyl, cyclopropyl, cyano, or C₁-C₃alkoxy;

each R₈ is independently and individually selected from the group consisting of C₁-C₆alkyl, C₁-C₆ fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C₄-C₇alkyl, carbocyclyl, phenyl, C₁-C₆phenylalkyl, heteroaryl or heteroarylC₁-C₆alkyl, heterocyclyl, heterocyclylC₁-C₆alkyl, OH, C₁-C₆alkoxy, N(R₃)₂, N(R₄)₂, or R₅;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

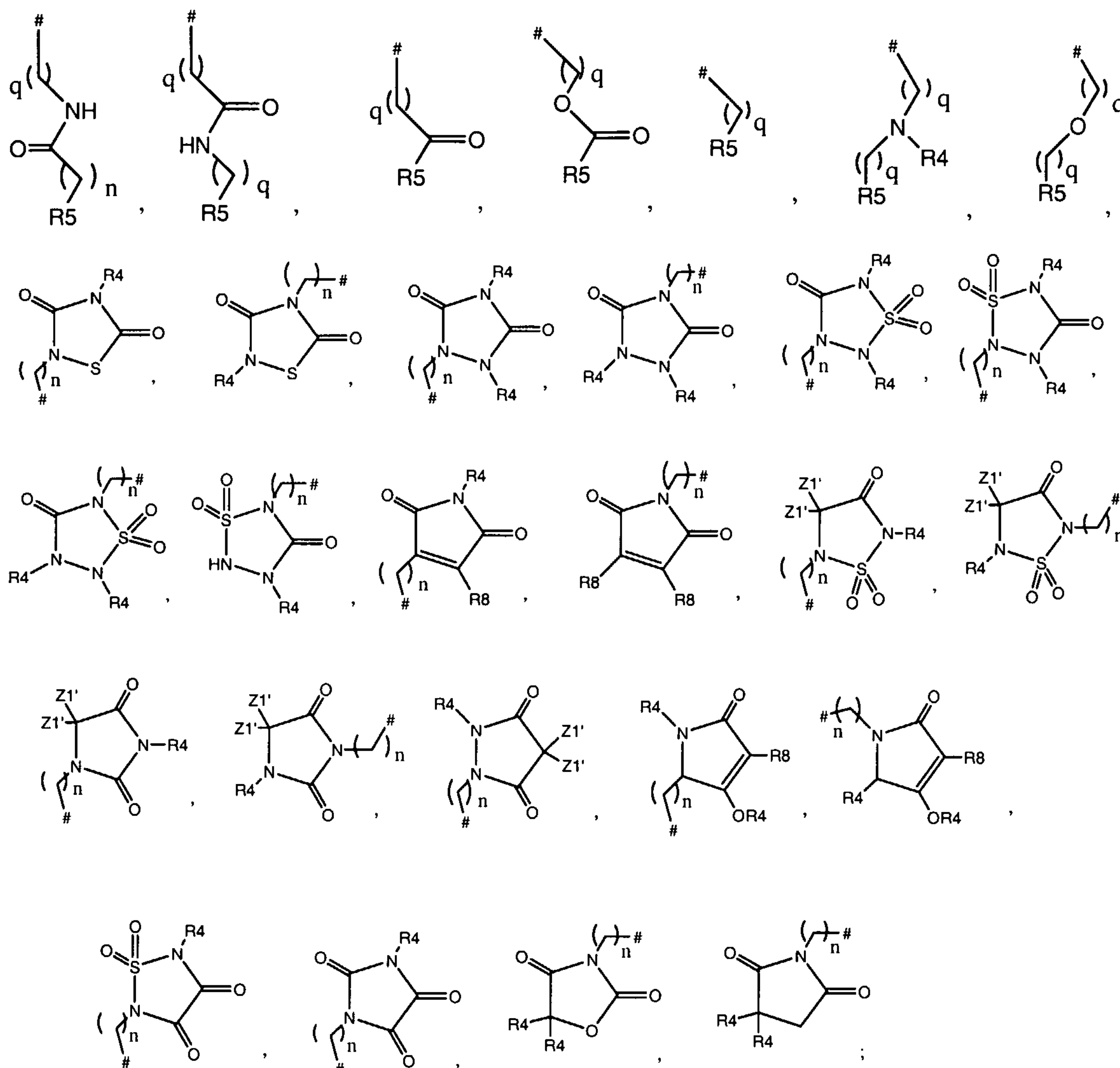
wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_p, (R4)₂N-C2-C6alkylO-(CH₂)_p, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, , heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl,

heterocycloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoc2-C6alkyl, heterocyclaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocycl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

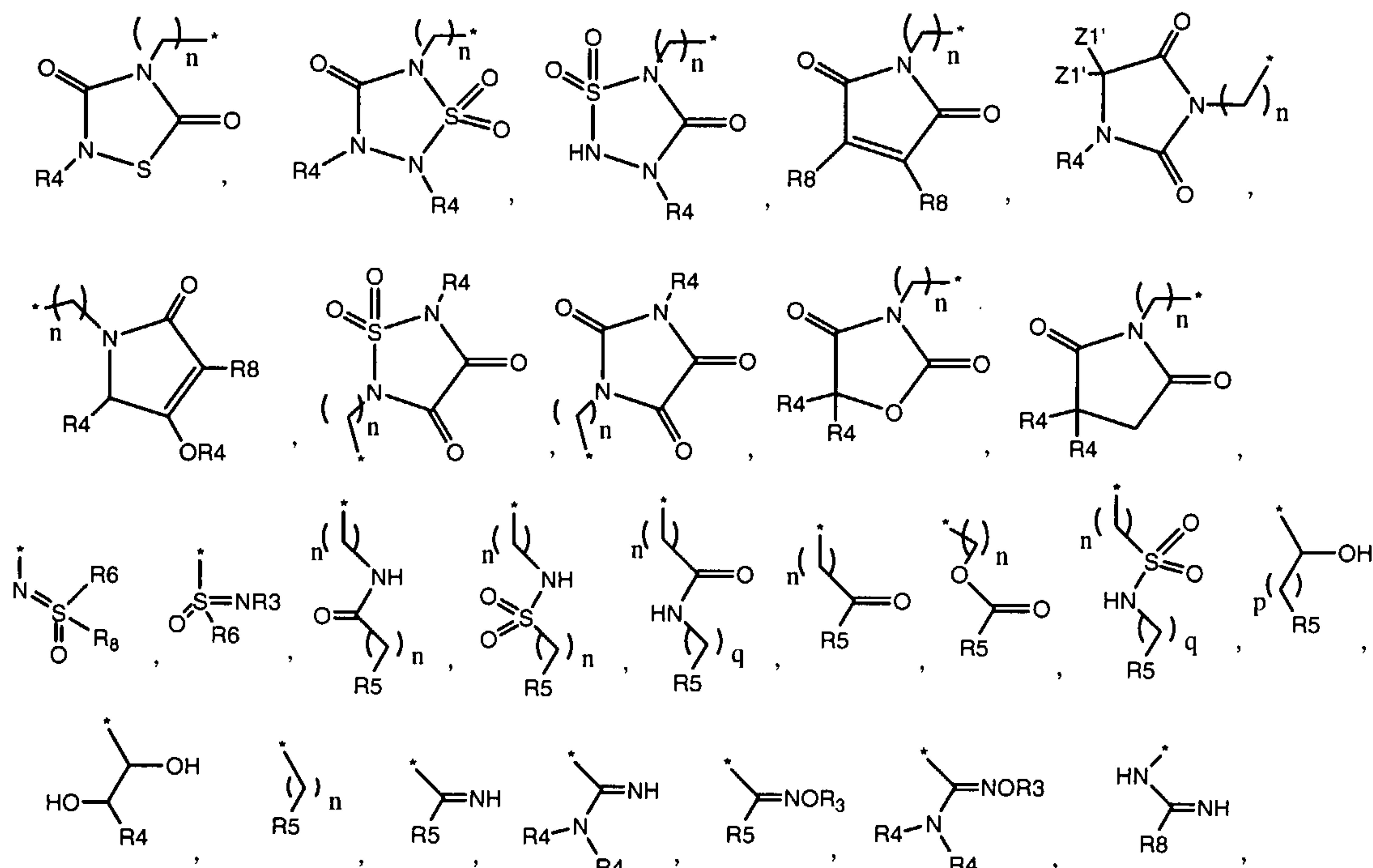
Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocycliloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

each Z7 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC1-C6alkyl,

(R₆)₂NC1-C6alkyl, (R₄)₂NC2-C6alkylN(R₄)-(CH₂)_n, (R₄)₂NC2-C6alkylO-(CH₂)_n, (R₃)₂N-CO, (R₄)₂N-CO, -SO₂R₃', SOR₃, -SOR₄, -C(=O)R₆, -C(=NOH)R₆, -C(=NOR₃)R₆, (CH₂)_nN(R₄)C(O)N(R₄)₂, (CH₂)_nN(R₄)C(O)R₅, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocycliloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocycliloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

In the foregoing definition of Z7, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z7 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R³ moieties are independently and individually taken from the group consisting of C₁-C₆alkyl and branched C₃-C₆alkyl and are attached to the same nitrogen heteroatom of Z⁷ may cyclize to form a C₃-C₇ heterocyclyl ring;

wherein two R⁴ moieties independently and individually taken from the group consisting of C₁-C₆alkyl, branched C₃-C₆alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z⁷ may cyclize to form a C₃-C₇ heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

2.3.6b

The following specific compounds of Formula I are more preferred: 1-(1-(3-(1H-pyrazol-4-yl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(3-(pyridin-3-yl)phenyl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyrazin-2-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(1-oxoisindolin-4-yl)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-cyclopentyl-1H-pyrazol-5-yl)-3-(4-(1-oxoisindolin-4-yl)phenyl)urea, 1-(1-(3-(1H-pyrazol-4-yl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(1-oxoisindolin-4-yl)phenyl)urea

2.3.7 Methods

2.3.7a Methods of Protein Modulation

The invention includes methods of modulating kinase activity of a variety of kinases, e.g. receptor tyrosine kinases including VEGFR1, VEGFR2, FLT-1, FLT-3, PDGFR_a, PDGFR_b, FGFR1, FGFR2, FGFR3, FGFR4, TrkA, TrkB, EGFR, EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHA9, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4, EPHB5, EPHB6, EPHB7, EPHB8. The kinases may be wildtype kinases, oncogenic forms

thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 2.3 and 2.3.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

2.3.7b Treatment Methods

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer, secondary cancer growth arising from metastasis, hyperproliferative diseases, and diseases characterized by hyper-vascularization. These methods comprise administering to such individuals compounds of the invention, and especially those of section 2.3 and 2.3.6a. Exemplary conditions include glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary solid tumor secondary sites, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies including diabetic retinopathy and age-related macular degeneration, or rheumatoid arthritis characterized by the in-growth of a vascularized pannus. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

2.3.8 Pharmaceutical Preparations

The compounds of the invention, especially those of 2.3 and 2.3.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

2.3.9 Kinase/Compound Adducts

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion

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proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 2.3 and 2.3.6a.

3. *First aspect of the invention –Raf Kinase Modulator Compounds, Methods, Preparations and Adducts*

3.1 *Generally – A2 Bicyclic Compounds*

The invention includes compounds of formula I as defined in section 2.1, wherein each R₂ is independently and individually selected from the group consisting of C₁-C₆alkyl, branched C₃-C₇alkyl, C₁-C₆fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, monocyclic heteroaryl, and R₁₉ substituted C₃-C₈carbocyclyl wherein R₁₉ is H, and C₁-C₆alkyl.

3.1.1 *Preferred D Moieties*

3.1.1a

Preferred compounds of Formula I as defined above in section 3.1 contain D moieties as defined in section 1.1.1a.

3.1.1b

Additionally preferred compounds of Formula I as defined above in section 3.1 contain D moieties as defined in section 1.1.1b.

3.1.1c

More preferred compounds of Formula I as defined above in section 3.1.1b contain D moieties as defined in section 1.1.1c.

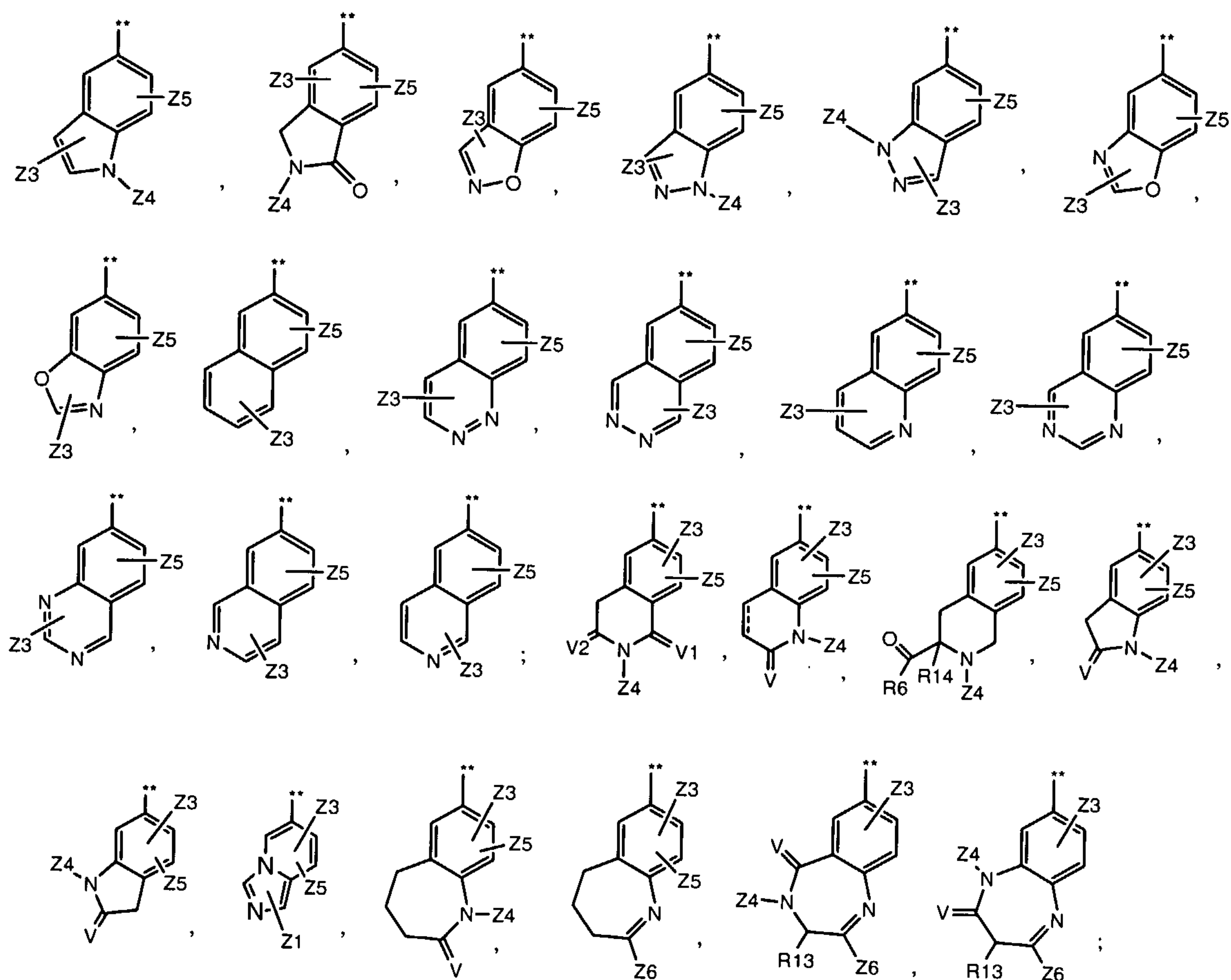
3.1.2 *Preferred A2 moieties*

3.1.2a

Compounds of Formula I as defined above in section 3.1 have preferred A₂ moieties as defined in section 1.1.2a.

3.1.2b *More preferred A2 moieties*

Compounds of Formula I as defined above in section 3.1 have more preferred A₂ moieties selected from group consisting of

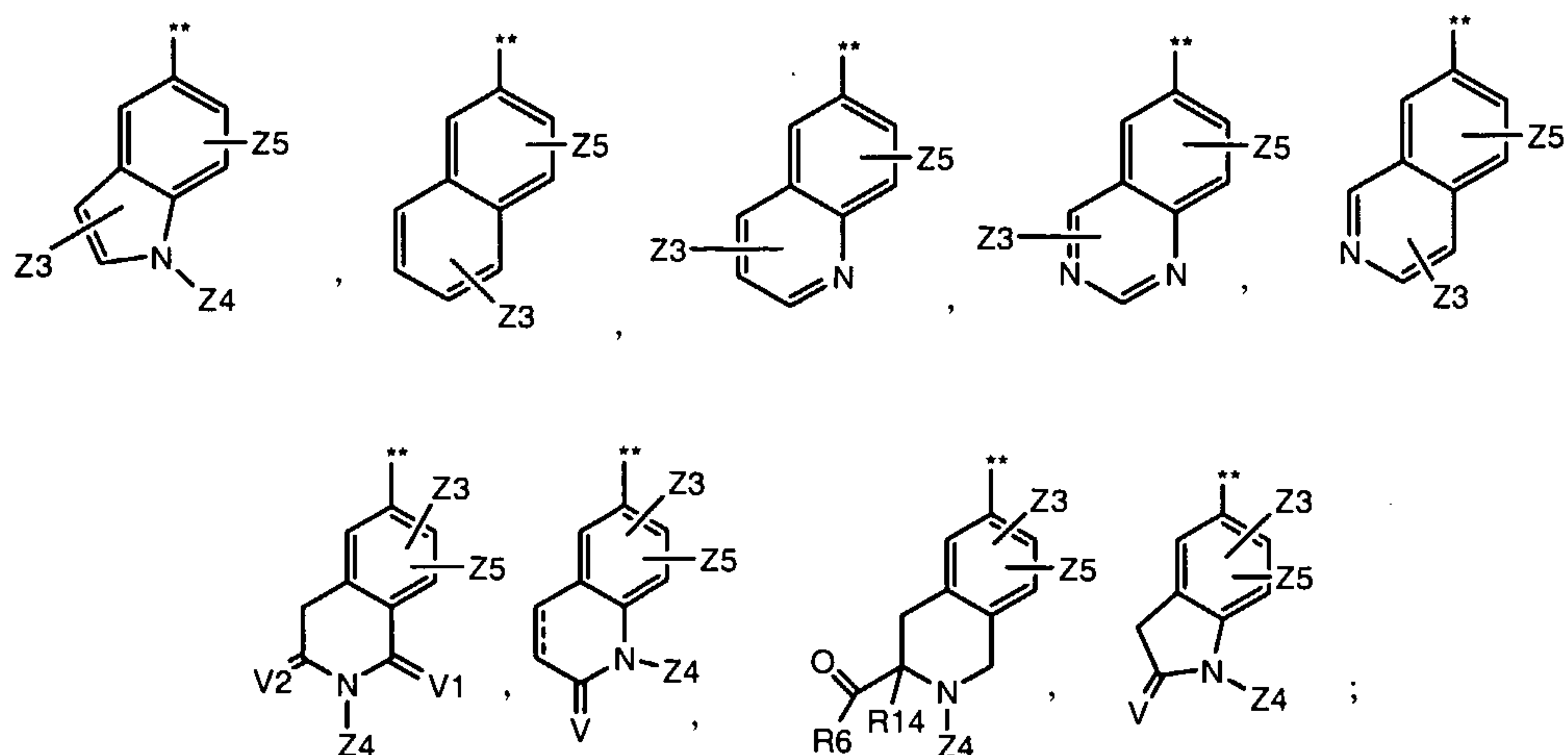


and wherein the symbol (**) is the point of attachment to the A1 ring for formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring.

3.1.2c

Still more preferred compounds of Formula I as defined above in section 3.1 have A2 moieties selected from group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring.

3.1.3 Preferred Classes of Compounds

3.1.3a

Compounds as defined in 3.1.1a wherein the A2 group is defined in 3.1.2a.

3.1.3b

Compounds as defined in 3.1.3a wherein the A2 group is defined in 3.1.2b.

3.1.3c

Compounds as defined in 3.1.3a wherein the A2 group is defined in 3.1.2c.

3.1.3d

Compounds as defined in 3.1.1b wherein the A2 group is defined in 3.1.2a.

3.1.3e

Compounds as defined in 3.1.3c wherein the A2 group is defined in 3.1.2b.

3.1.3f

Compounds as defined in 3.1.3c wherein the A2 group is defined in 3.1.2c.

3.1.4 Preferred A1 Moieties

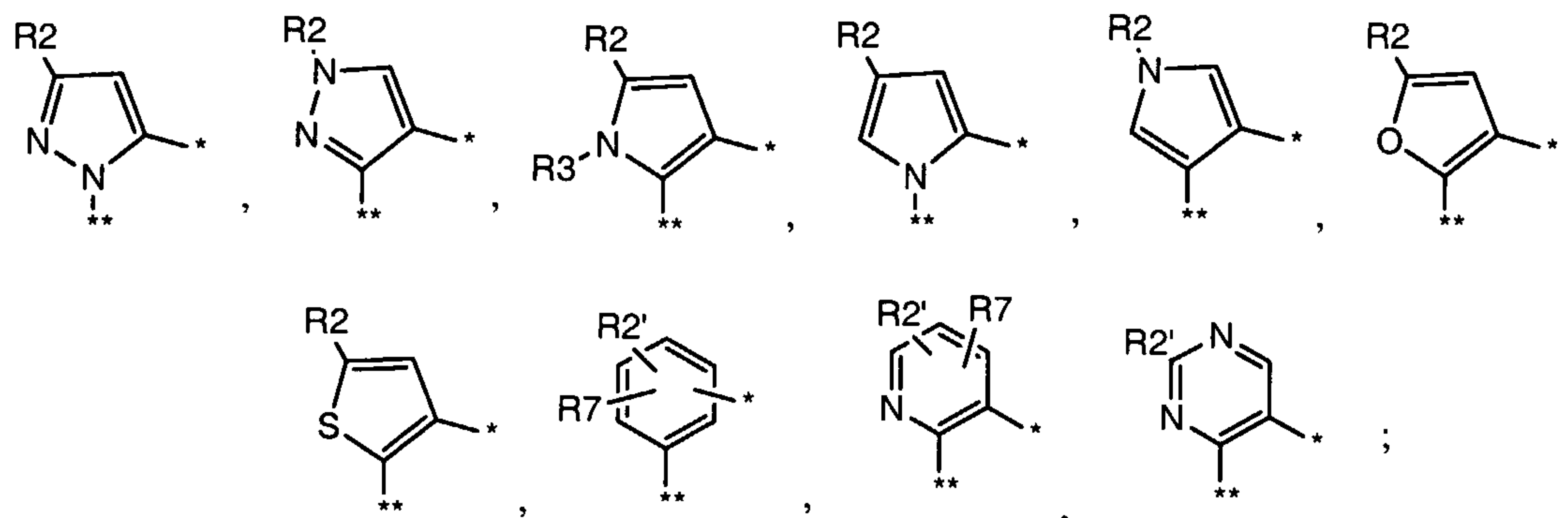
3.1.4a

Compounds of Formula I as defined above in section 3.1 have preferred A1 moieties selected from group defined in section 1.1.4a;

wherein each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

3.1.4b

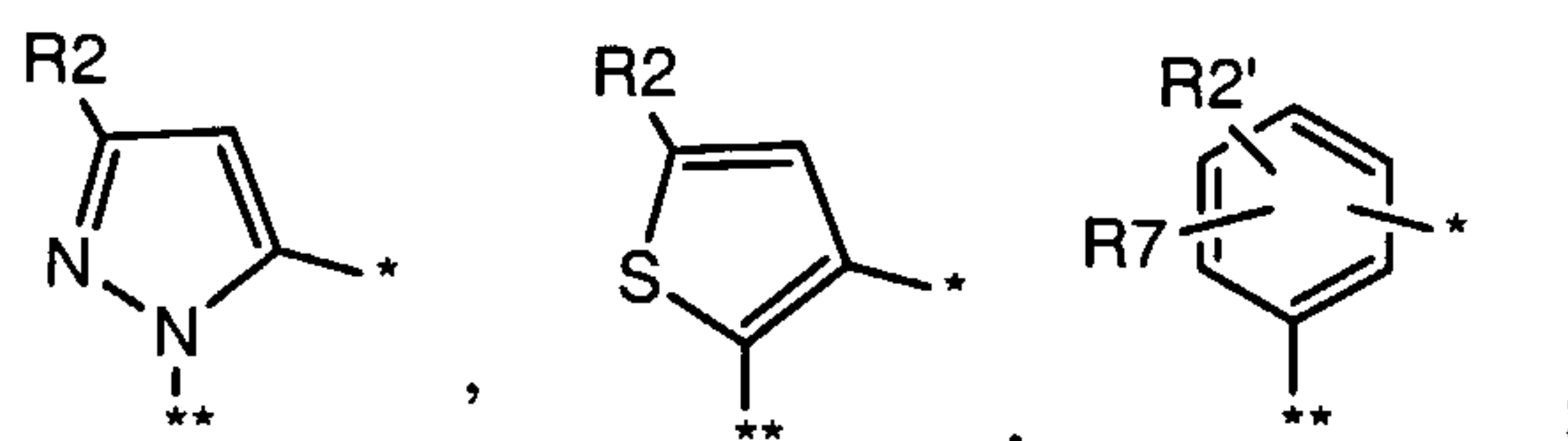
Compounds of Formula I as defined above in section 3.1 have more preferred A1 moieties selected from group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I.

3.1.4c

Compounds of Formula I as defined above in section 3.1 have even more preferred A1 moieties selected from group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I.

3.1.5 Preferred W and Y Moieties

3.1.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR4 and X=O; or (3) W=CHR4, Y=NH, and X=O.

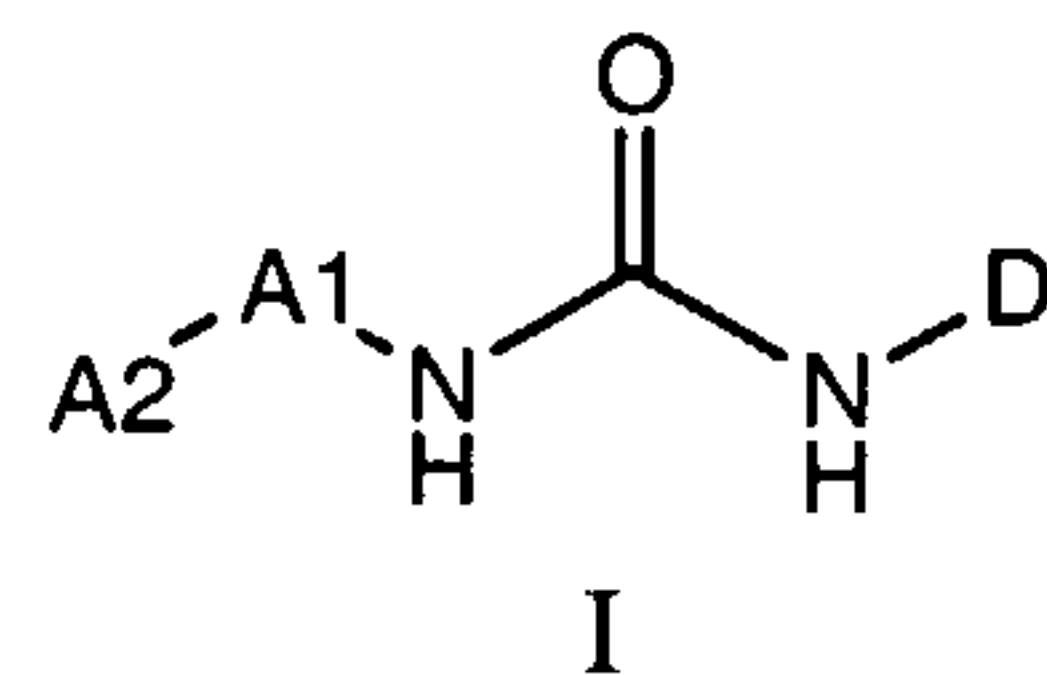
3.1.5b

W and Y are each NH and X=O.

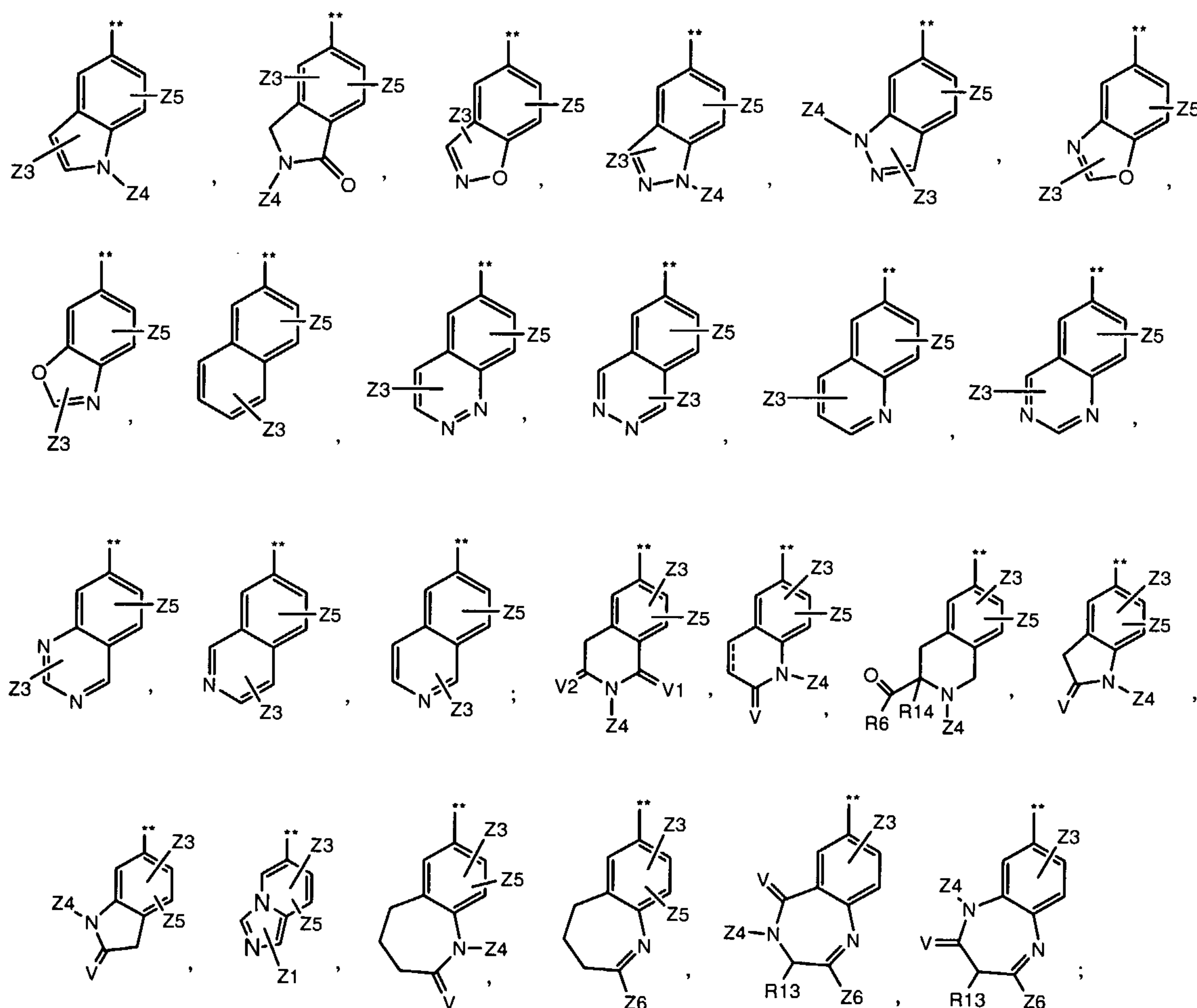
3.1.6 Further Preferred Compounds

3.1.6a

Further preferred compounds are of the formula



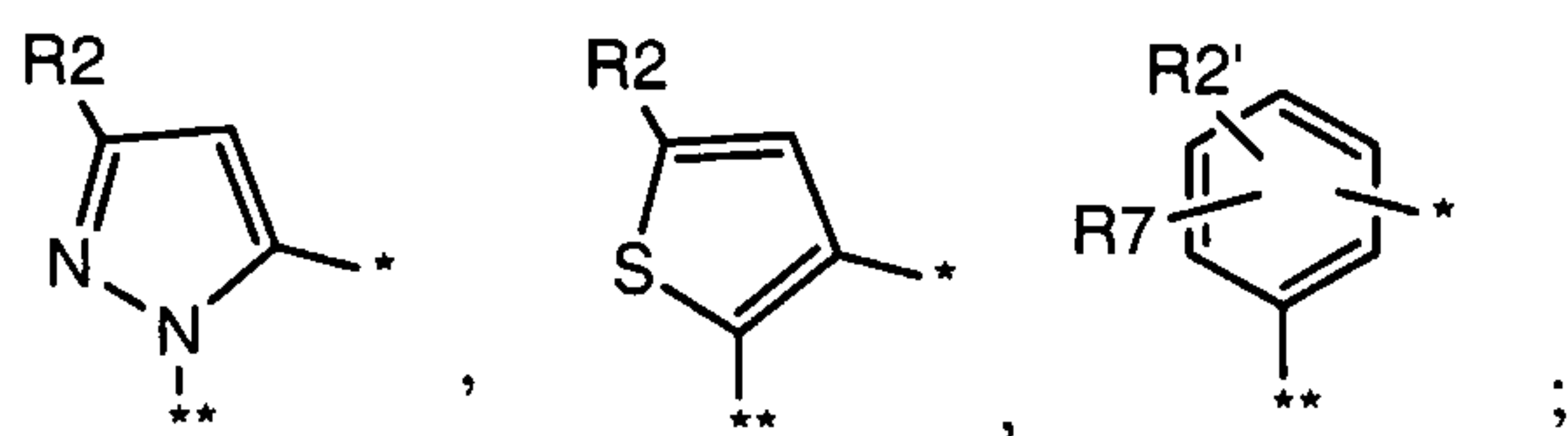
wherein A2 is selected from the group consisting of



wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring;

wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

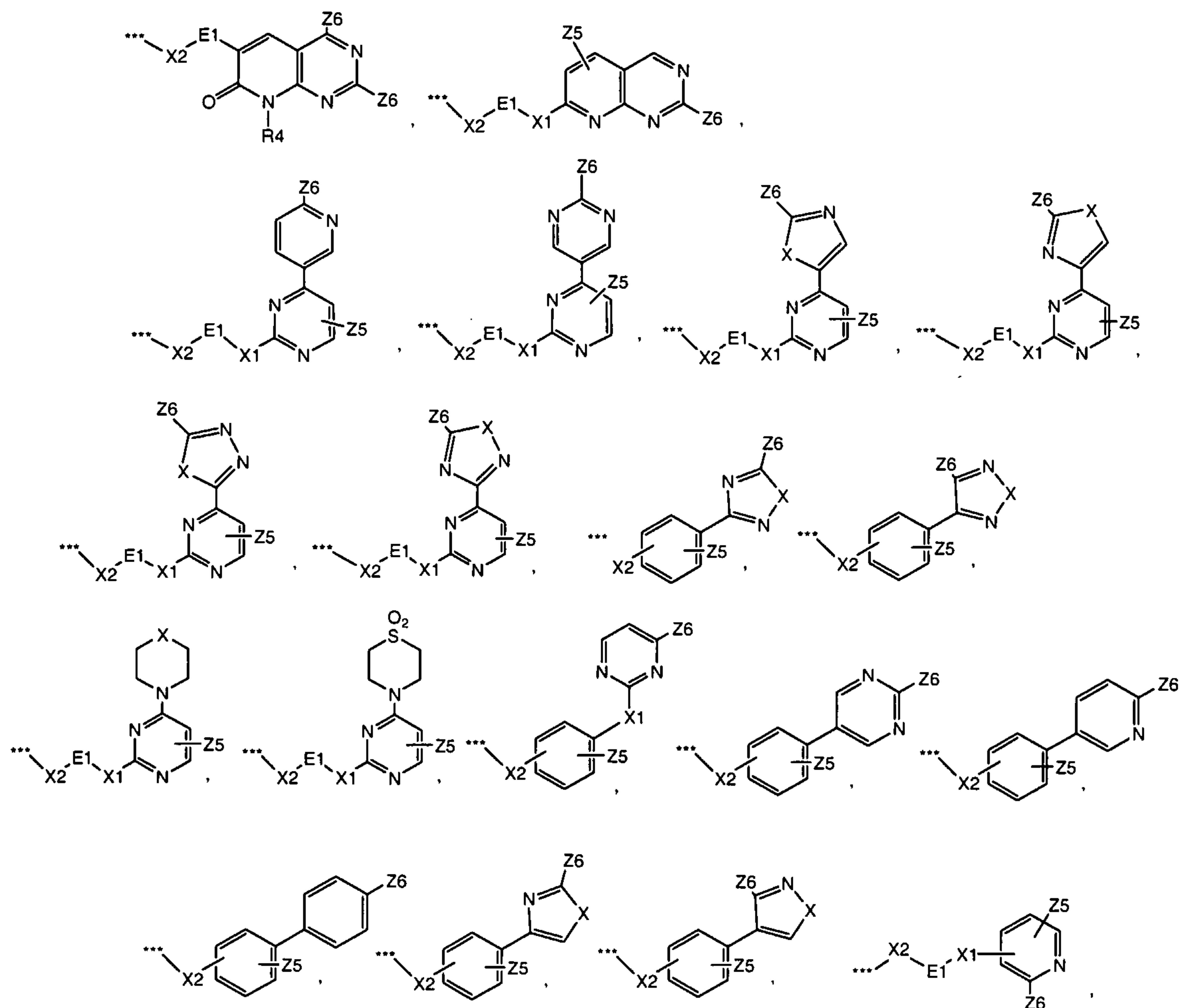
A1 is selected from the group consisting of

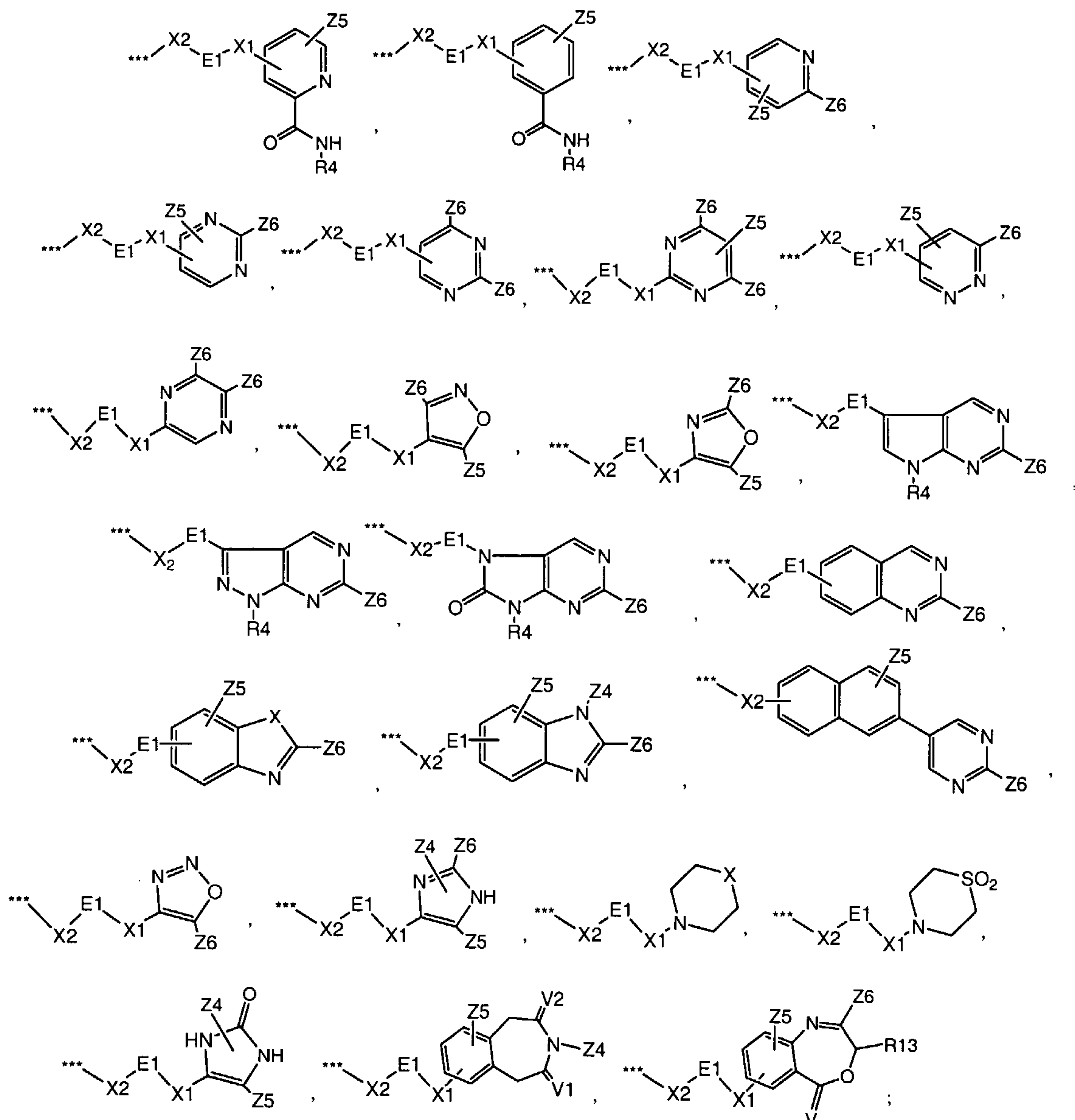


wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR₃;

D comprises a member of 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 3,4,5-trifluorophenyl, 3-phenoxyphenyl, 4-phenoxyphenyl, cyclohexyl,





wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

X1 is selected from the group consisting of O, S, NR3, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR3-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR3-, -N(R3)-(CH₂)_q-N(R3)-, -(CH₂)_n-N(R4)-C(=O)-, -(CH₂)_n-N(R4)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R4)-, -(CH₂)_p-, C2-C5alkenyl, C2-

C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of $-(CH_2)_n$ -, $-(CH_2)_q$ -, $(CH_2)_p$, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

Each R2 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, C1-C6fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, monocyclic heteroaryl, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and C1-C6alkyl;

each R2' is selected from the group consisting of halogen and R2;

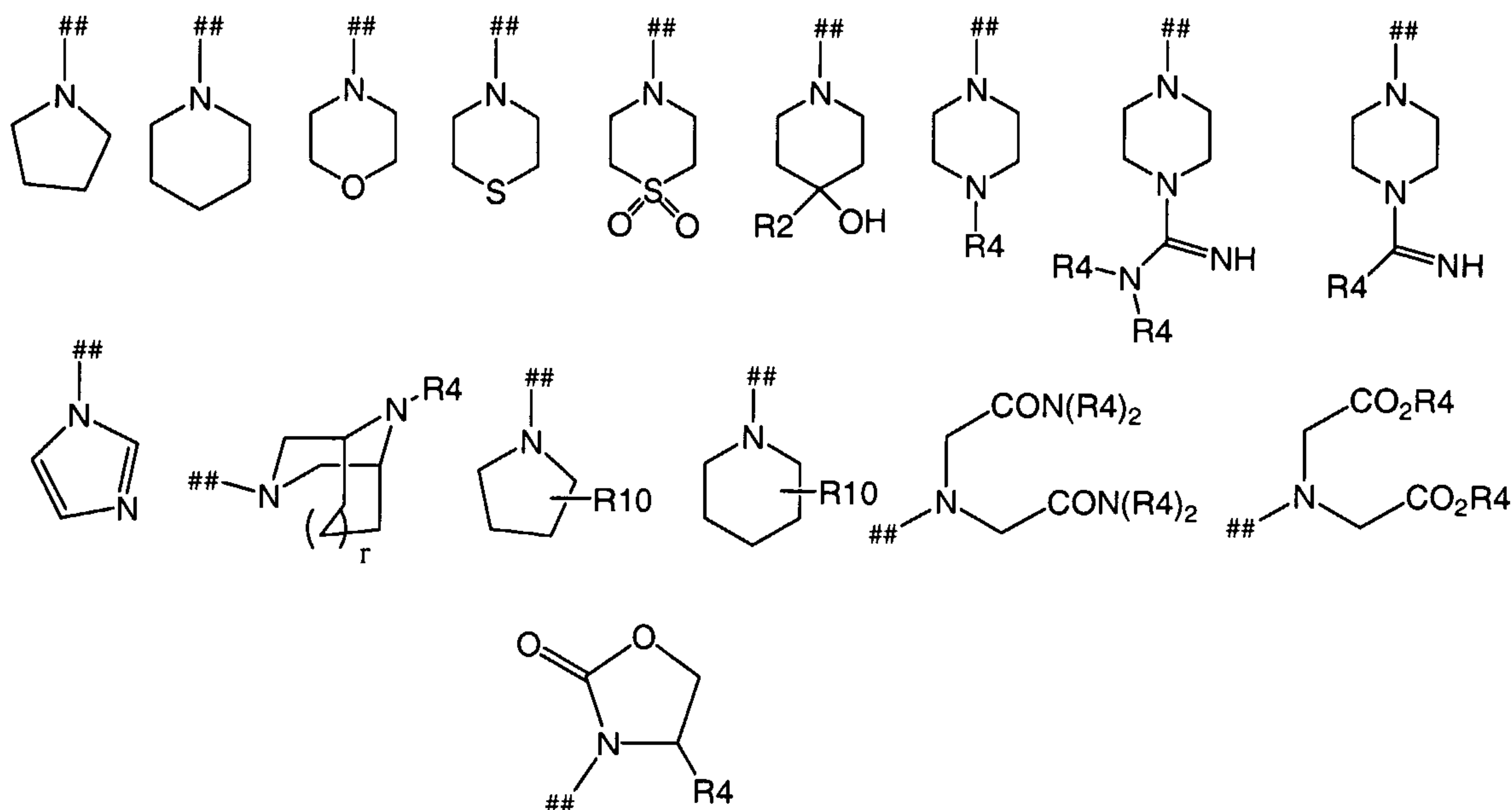
each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocyclyl ring;

each R5 is independently and individually selected from the group consisting of



;

and wherein the symbol (##) is the point of attachment to respective R8, R10, R13, Z2, Z3, Z4, Z5, or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

each R13 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, hydroxyC2-C7alkyl, C1-C6alkoxyC2-C7alkyl, (R4)₂N-CO, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_q, R5-C2-C6alkylN(R4)-(CH₂)_q, (R4)₂N-C2-C6alkylO-(CH₂)_q, R5-C2-C6alkyl-O-(CH₂)_q, - (CH₂)_qN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC2-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoc2-C6alkyl, and heterocyclylaminoc2-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R13 may cyclize to form a C3-C7 heterocyclyl ring;

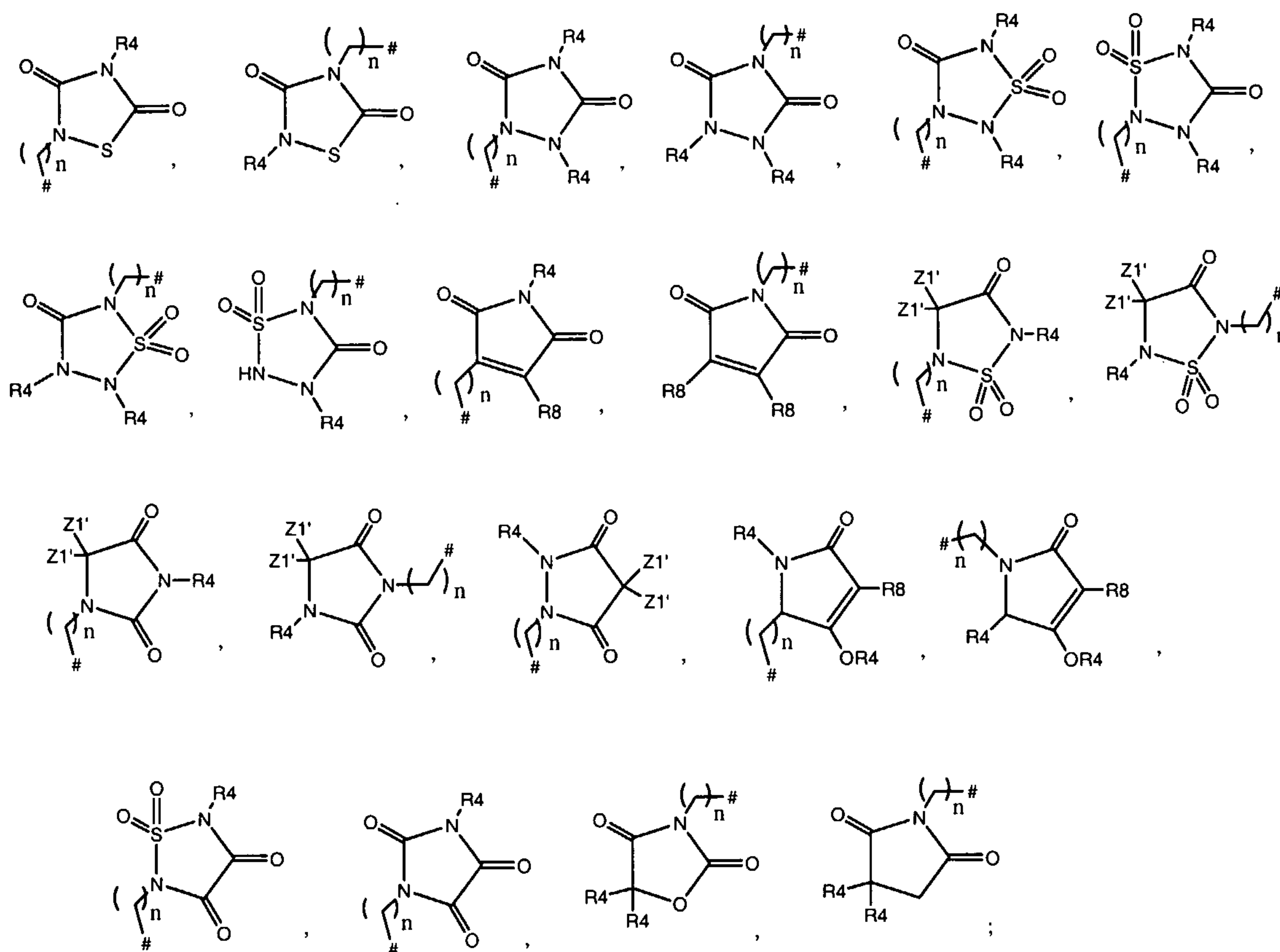
each R14 is independently and respectively selected from the group consisting of H and C1-C6alkyl;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-

C6alkyl, (R₄)₂N-C2-C6alkylN(R₄)-(CH₂)_p, (R₄)₂N-C2-C6alkylO-(CH₂)_p, (R₄)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R₄)C(O)R₈, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, , heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R₄ moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z₃ is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyl, hydroxyC1-C6alkyl, cyano, C1-C6alkoxy, C1-C6alkoxyC1-C6alkyl, halogen, CF₃, (R₃)₂N-, (R₄)₂N-, (R₄)₂NC1-C6alkyl, (R₄)₂NC2-C6alkylN(R₄)-(CH₂)_n, (R₄)₂NC2-C6alkylO-(CH₂)_n, R₈CO-, (R₄)₂N-CO-C1-C6alkyl, carboxyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R₃)₂NSO₂, -SO₂R₃, SOR₃, (R₄)₂NSO₂, -SO₂R₄, -SOR₄, -(CH₂)_nN(R₄)C(O)R₈, -C=(NOH)R₆, -C=(NOR₃)R₆, heteroaryl, heterocyclyl, heteroarylC1-C6alkyl, heterocyclylC1-C6alkyl, heteroaryloxy, heterocycliloxy, heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylamino, heteroarylamino, heterocyclylamino, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocyclylaminoC1-C6alkyl, or moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z3 moiety to the A2 ring of formula I;

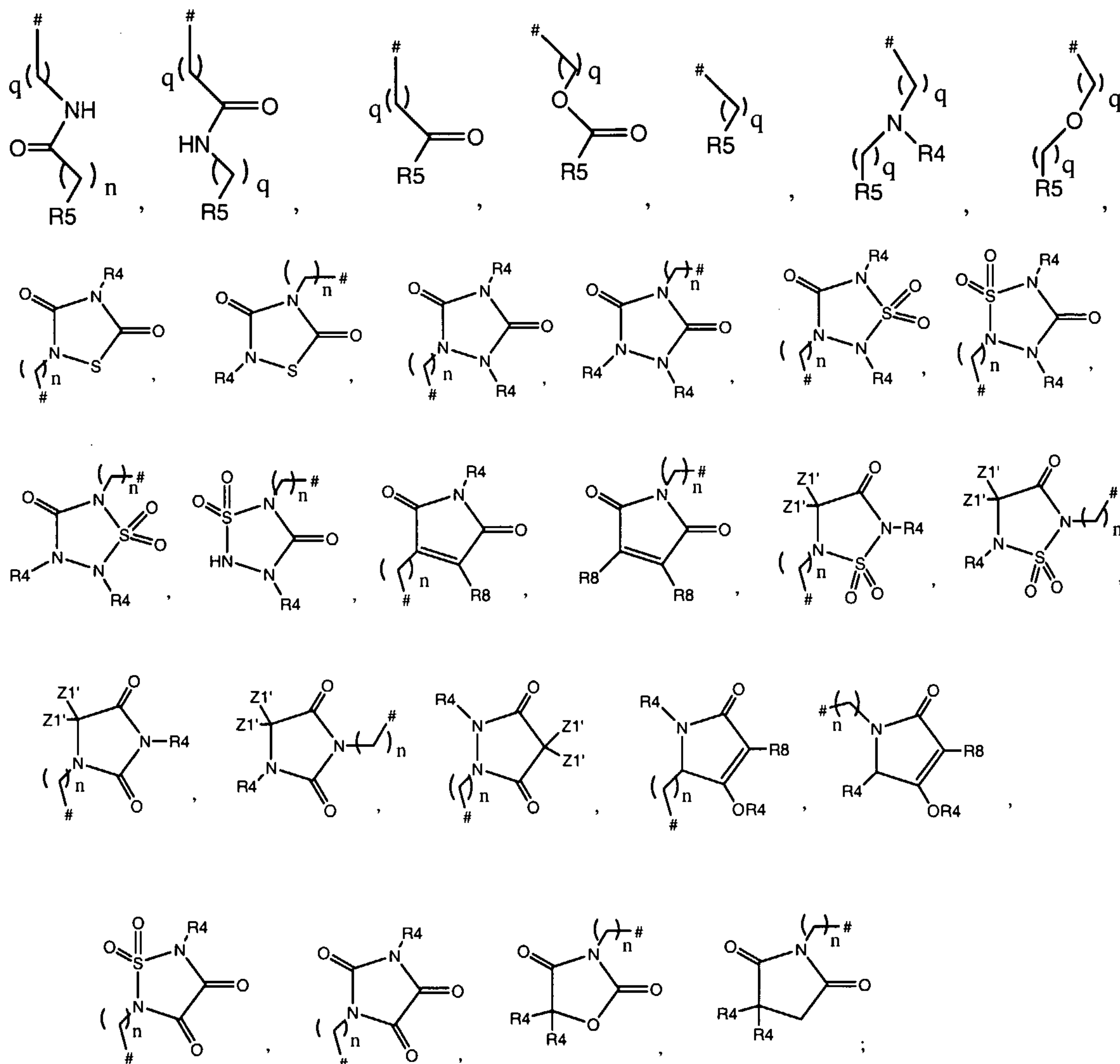
in the event that Z3 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

each Z4 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-

C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R⁴ moieties independently and individually taken from the group consisting of C₁-C₆alkyl, branched C₃-C₆alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z₆ may cyclize to form a C₃-C₇ heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

V, V₁, and V₂ are each independently and respectively selected from the group consisting of O and H₂;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs, and salts of any of the foregoing.

3.1.6b

The following specific compounds are most preferred: 1-(3-t-butyl-1-(3-hydroxy-2,3-dihydro-1H-inden-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(hydroxyimino)-2,3-dihydro-1H-inden-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-methyl-1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1H-indazol-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(indolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(1-acetylindolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(4-((1-methylsulfonylamino-1-oxo-methylamino)methyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 2-(3-(3-t-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)naphthalen-1-yl)acetic acid, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, (3S)-6-(3-t-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)-

1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1-(3-t-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-carbamimidoyl-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(4-oxo-3,4-dihydroquinazolin-7-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3,4-trifluorophenyl)urea, 1-(3-t-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3,4-trifluorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3,4-trifluorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3,4-trifluorophenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-((1-amino-1-oxo-methylamino)methyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-((3S)-3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3,5-trifluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3,4,5-trifluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3,5-difluorophenyl)urea, 1-(3-t-butyl-

1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,3-difluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3-difluorophenyl)urea,
 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-difluorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-difluorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,4-difluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,4-difluorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,4-difluorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-fluorophenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-phenoxyphenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-phenoxyphenyl)urea, 1-(3-t-butyl-1-(1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(4-(aminomethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(5-chloropyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(2-(2-aminoethylamino)quinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-(dimethylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(2-aminoquinolin-6-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-(methylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-

7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-cyclopentyl-1-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea.

3.1.7 Methods

3.1.7a Methods of Protein Modulation

The invention includes methods of modulating kinase activity of RAF kinases and other kinases in the RAS-RAF-MEK-ERK-MAP kinase pathway including, but not limited to, A-Raf, B-Raf, and C-Raf. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 3.1 and 3.1.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

3.1.7b Treatment Methods

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer and hyperproliferative diseases. These methods comprise administering to such individuals compounds of the invention, and especially those of section 3.1 and 3.1.6a. condition being melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney cancers, cervical

carcinomas, metastasis of primary solid tumor secondary sites, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies including diabetic retinopathy and age-related macular degeneration, rheumatoid arthritis characterized by the in-growth of a vascularized pannus, or a disease caused by a mutation in the RAS- RAF- MEK-ERK-MAP kinase pathway. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

3.1.8 *Pharmaceutical Preparations*

The compounds of the invention, especially those of 3.1 and 3.1.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

3.1.9 *Kinase/Compound Adducts*

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 3.1 and 3.1.6a.

3.2 *Generally – Monocyclic A2 Compounds with Polycyclic E2 Rings*

The invention includes compounds of the formula I as defined in section 2.2, wherein each R2 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, C1-C6fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, monocyclic heteroaryl, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and C1-C6alkyl;

3.2.1 *Preferred D Moieties*

3.2.1a

Preferably, the compounds of formula I in 3.2 contain D moieties wherein E1 and E2 are as defined in section 1.2.1

3.2.1b

Additionally preferred D moieties of formula I in 3.2 are as defined in section 1.2.1b

3.2.1c

More preferred D moieties of 3.2.1b are where E2 is defined as in section 1.2.1c

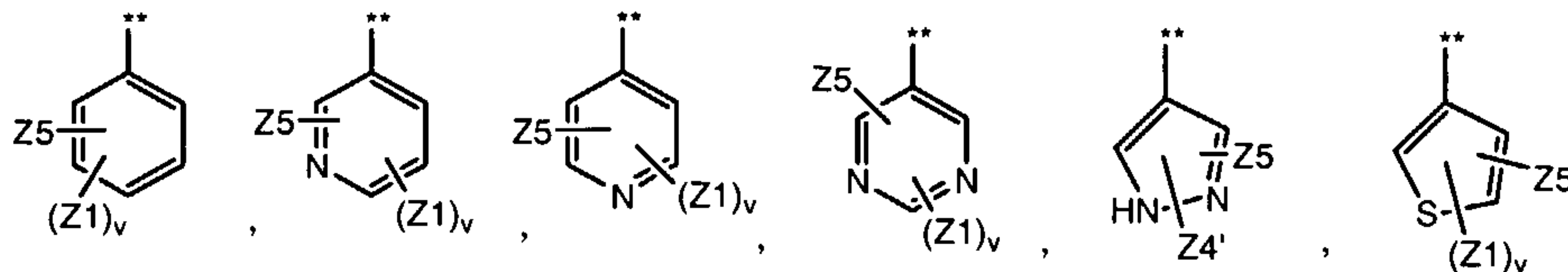
3.2.2 Preferred A2 moieties

3.2.2a

Compounds of Formula I as defined above in section 3.2 have preferred A2 moieties as defined in section 2.2.2a;

3.2.2b

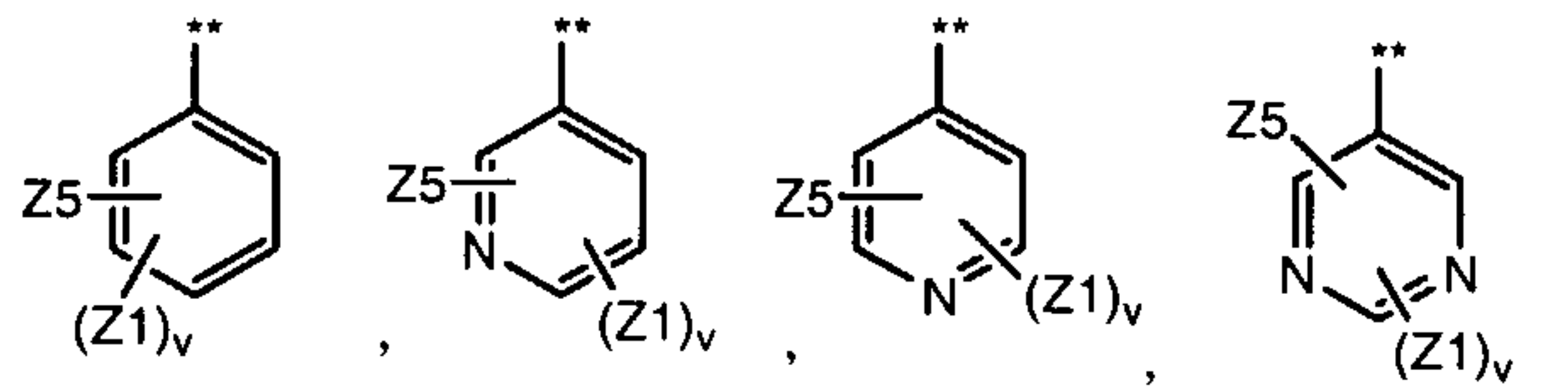
More preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring for formula I.

3.2.2c

Even more preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I.

3.2.3 Preferred Classes of Compounds

3.2.3a

Compounds as defined in 3.2.1a wherein the A2 group is defined in 3.2.2a.

3.2.3b

Compounds as defined in 3.2.3a wherein the A2 group is defined in 3.2.2b.

3.2.3c

Compounds as defined in 3.2.3a wherein the A2 group is defined in 3.2.2c.

3.2.3d

Compounds as defined in 3.2.1b wherein the A2 group is defined in 3.2.2a.

3.2.3e

Compounds as defined in 3.2.3c wherein the A2 group is defined in 3.2.2b.

3.2.3f

Compounds as defined in 3.2.3c wherein the A2 group is defined in 3.2.2c.

3.2.4 Preferred A1 Moieties

3.2.4a

These preferred A1 moieties are defined in 3.1.4a.

3.2.4b

These more preferred A1 moieties are defined in 3.1.4b.

3.2.4c

These even more preferred A1 moieties are defined in 3.1.4c.

3.2.5 Preferred W and Y Moieties

3.2.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR₄ and X=O; or (3) W=CHR₄, Y=NH, and X=O.

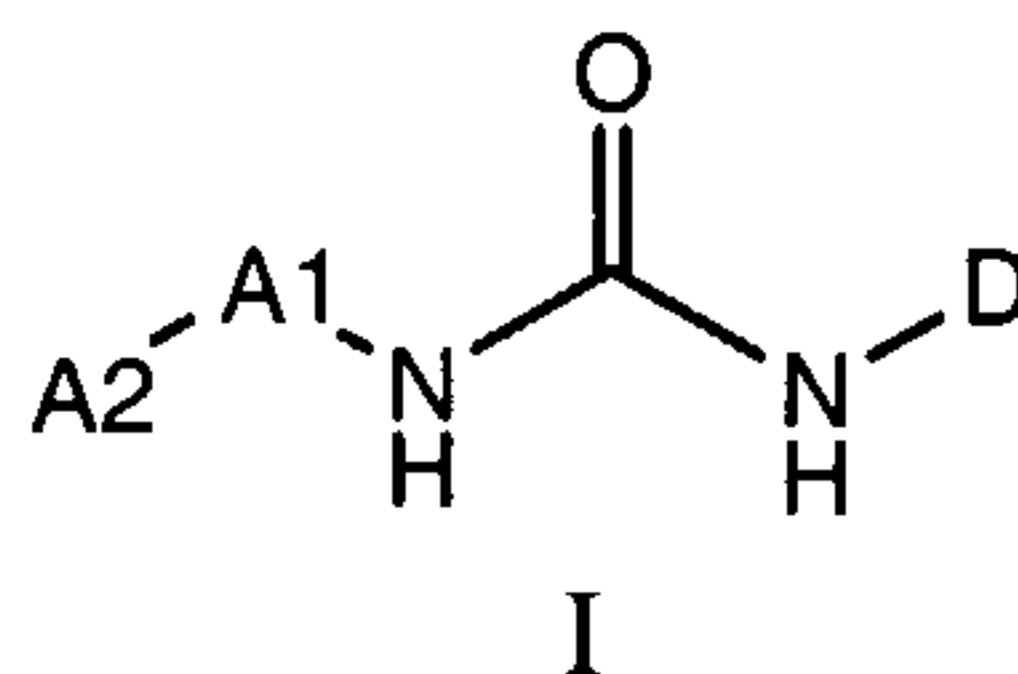
3.2.5b

W and Y are each NH and X=O.

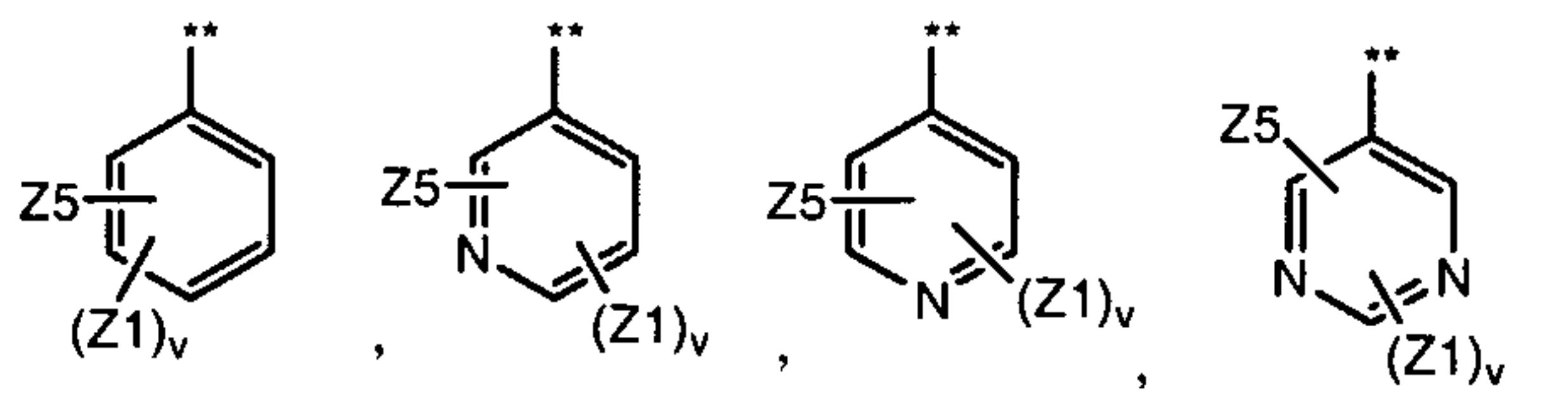
3.2.6 Further Preferred Compounds

3.2.6a

Further preferred compounds are of the formula

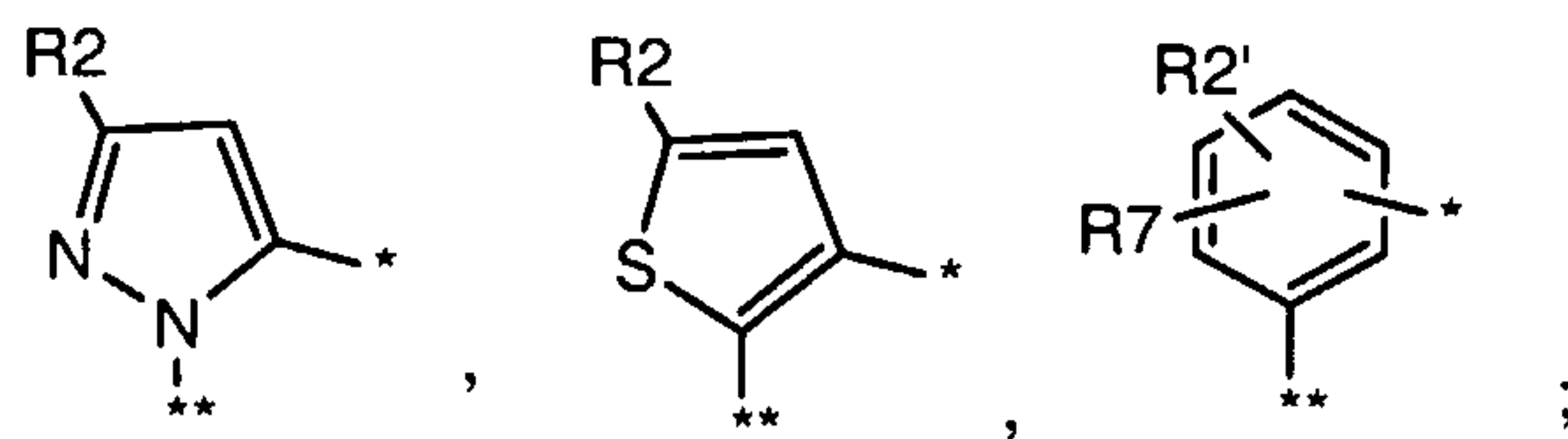


wherein A2 is selected from the group consisting of



wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

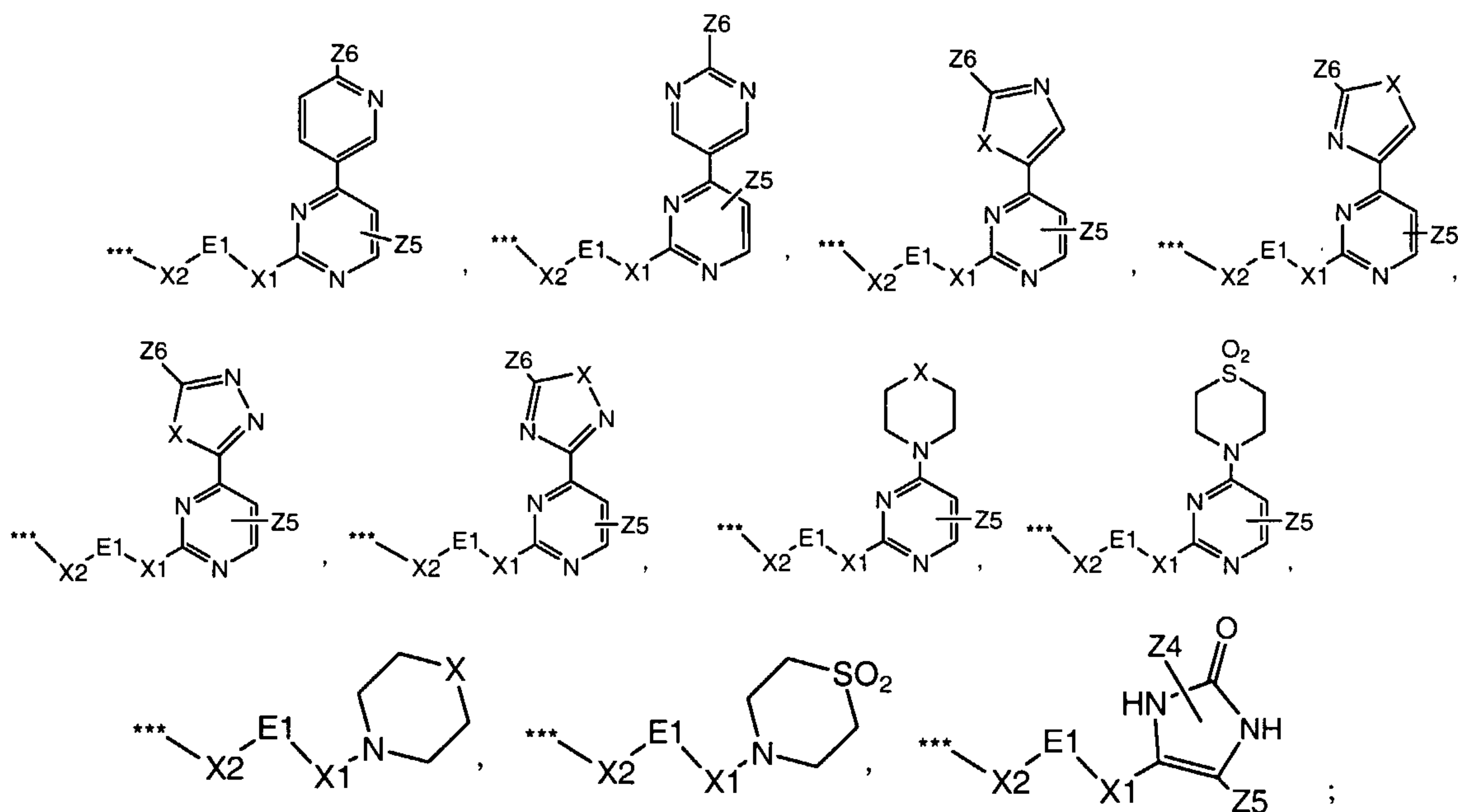
A1 is selected from the group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR₃;

D comprises a member of



wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of $-(CH_2)_n$ -, $-(CH_2)_q$ -, $(CH_2)_p$, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

Each R2 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, C1-C6fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, monocyclic heteroaryl, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and C1-C6alkyl;

each R2' is selected from the group consisting of halogen and R2;

each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocyclyl ring;

each R5 is independently and individually selected from the group consisting of

each R⁸ is independently and individually selected from the group consisting of C₁-C₆alkyl, C₁-C₆ fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C₄-C₇alkyl, carbocyclyl, phenyl, C₁-C₆phenylalkyl, heteroaryl or heteroarylC₁-C₆alkyl, heterocyclyl, heterocyclylC₁-C₆alkyl, OH, C₁-C₆alkoxy, N(R³)₂, N(R⁴)₂, or R⁵;

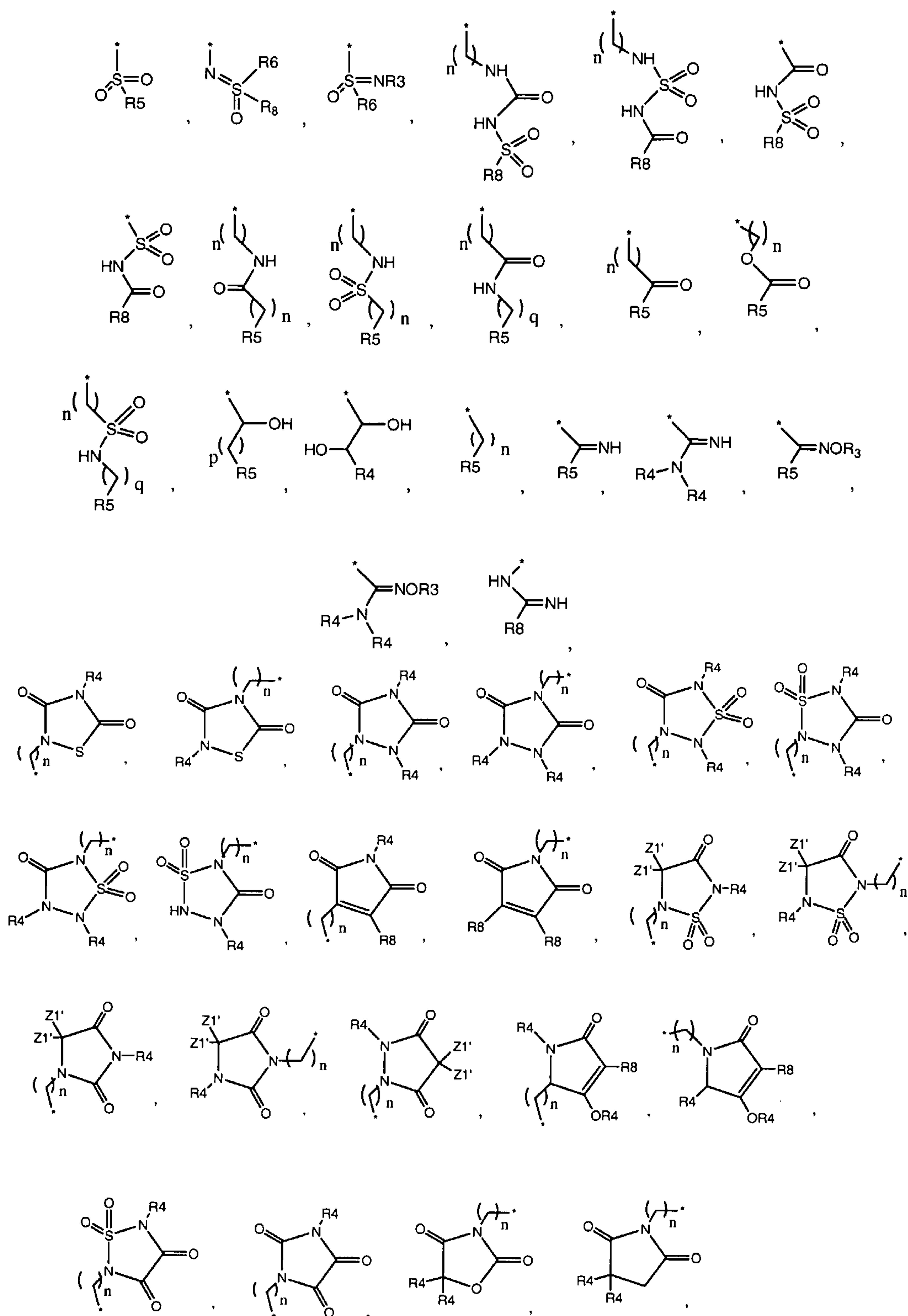
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

each Z1 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC1-C6alkyl, C2-C6alkoxy, C1-C6alkoxyC1-C6alkyl, (R4)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, (R3)₂N-C(=O)-, (R4)₂N-C(=O)-, (R4)₂N-CO-C1-C6alkyl, C1-C6alkoxycarbonyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)₂NSO₂, SOR3, (R4)₂NSO₂, -SO₂R3', -SOR4, -C(=O)R6, -C(=NOH)R6, -C(=NOR3)R6, -(CH₂)_nN(R4)C(O)R8, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocycliloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocycliloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

In the foregoing definition of Z1, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

In the foregoing definition of Z1, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

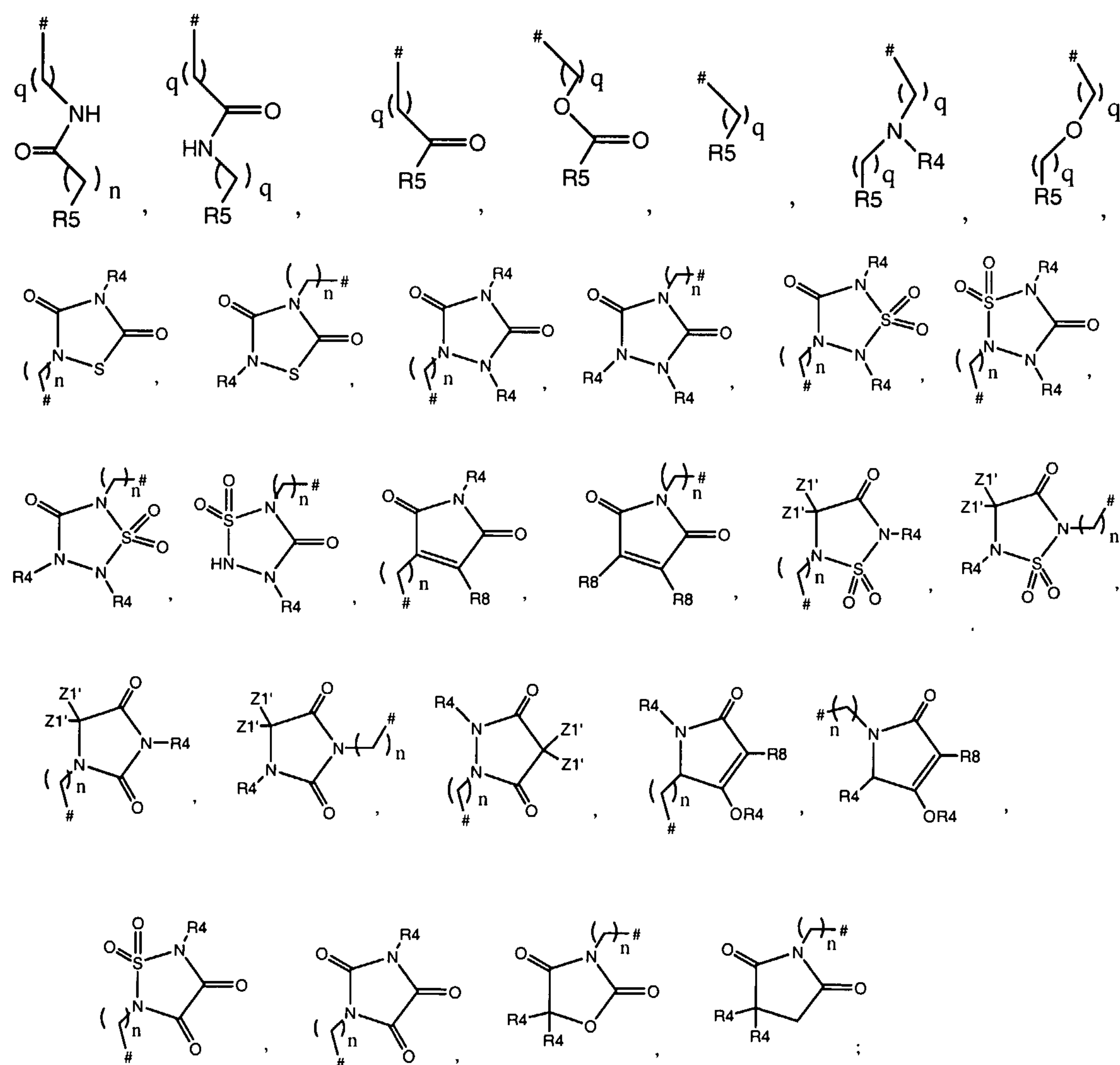
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_p, (R4)₂N-C2-C6alkylO-(CH₂)_p, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, , heteroaryloxyC1-C6alkyl, heterocyclyloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R⁴ moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z⁴ is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R⁴)₂N-C2-C6alkyl, (R⁴)₂N-C2-C6alkylN(R⁴)-C2-C6alkyl, (R⁴)₂N-C2-C6alkyl-O-C2-C6alkyl, (R⁴)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R⁴)C(O)R⁸, R⁸-C(=NR³)-, -SO₂R⁸, -COR⁸, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



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wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

3.2.6b

The following specific compounds of Formula I are more preferred: 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea, 1-(3-t-butyl-1-(3-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea, 1-(2-(3-(2-amino-2-oxoethyl)phenyl)-5-t-butylthiophen-3-yl)-3-(4-(4-(pyridin-3-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-t-butyl-1-(3-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(4-(6-(thiazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(4-(pyridin-3-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(4-(isoxazol-4-yl)pyrimidin-2-ylamino)phenyl)urea

3.2.7 Methods

3.2.7a Methods of Protein Modulation

The invention includes methods of modulating kinase activity of RAF kinases and other kinases in the RAS-RAF-MEK-ERK-MAP kinase pathway including, but not limited to, A-Raf, B-Raf, and C-Raf. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 3.2 and 3.2.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid

acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

3.2.7b Treatment Methods

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer and hyperproliferative diseases. These methods comprise administering to such individuals compounds of the invention, and especially those of section 3.2 and 3.2.6a. condition being melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary solid tumor secondary sites, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies including diabetic retinopathy and age-related macular degeneration, rheumatoid arthritis characterized by the in-growth of a vascularized pannus, or a disease caused by a mutation in the RAS- RAF-MEK-ERK-MAP kinase pathway. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

3.2.8 Pharmaceutical Preparations

The compounds of the invention, especially those of 3.2 and 3.2.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

3.2.9 Kinase/Compound Adducts

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 3.2 and 3.2.6a.

3.3 Generally – Monocyclic A2 Compounds with Monocyclic E2 Rings

The invention includes compounds of the formula I as defined in section 2.3 wherein each R2 is independently and individually selected from the group consisting of C1-C6alkyl, branched

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C3-C7alkyl, C1-C6fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, monocyclic heteroaryl, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and C1-C6alkyl.

3.3.1 Preferred D Moieties

3.3.1a

Preferably, the compounds of formula I in 3.3 contain D moieties wherein E1 and E2 are as defined in section 1.3.1a.

3.3.1b

Additionally preferred D moieties of formula I in 3.3 are as defined in section 1.3.1b.

3.3.1c

More preferred D moieties of 3.2.1b are wherein E2 is defined as in section 1.3.1c.

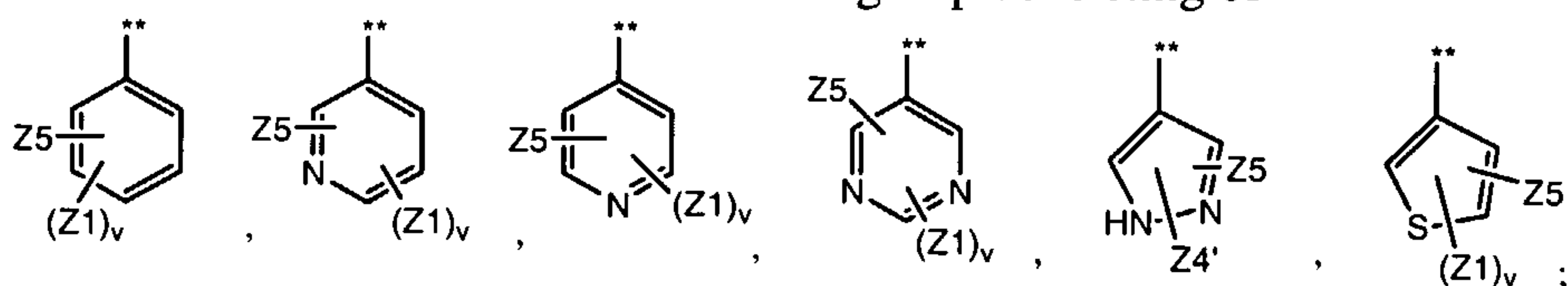
3.3.2 Preferred A2 moieties

3.3.2a

Compounds of Formula I as defined above in section 3.3 have preferred A2 moieties as defined in section 2.2.2a.

3.3.2b

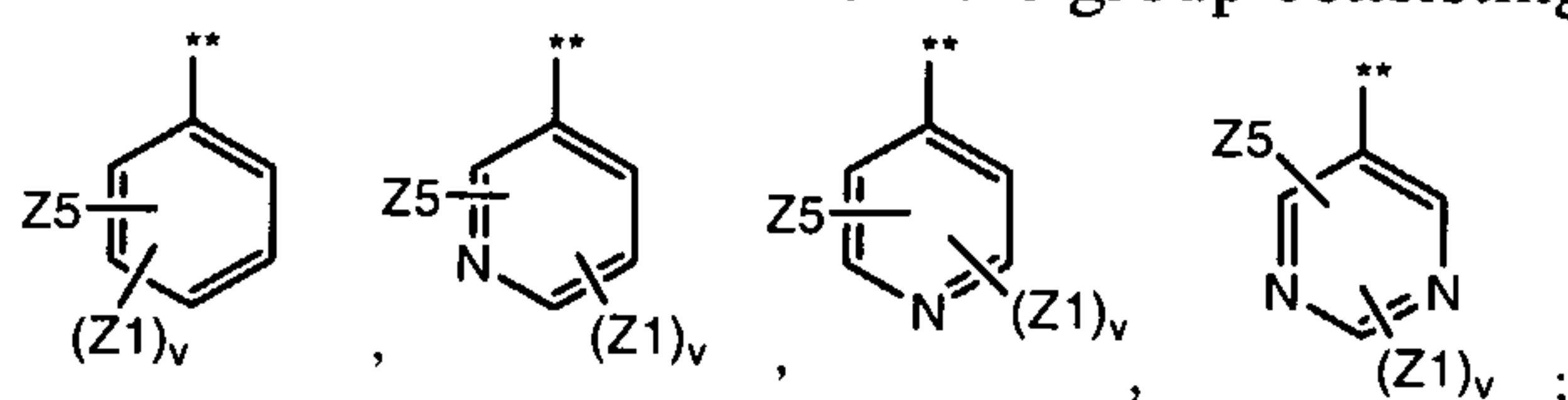
More preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring for formula I.

3.3.2c

Even more preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I.

3.3.3 Preferred Classes of Compounds

3.3.3a

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Compounds as defined in 3.3.1a wherein the A2 group is defined in 3.3.2a.

3.3.3b

Compounds as defined in 3.3.3a wherein the A2 group is defined in 3.3.2b.

3.3.3c

Compounds as defined in 3.3.3a wherein the A2 group is defined in 3.3.2c.

3.3.3d

Compounds as defined in 3.3.1b wherein the A2 group is defined in 3.3.2a.

3.3.3e

Compounds as defined in 3.3.3c wherein the A2 group is defined in 3.3.2b.

3.3.3f

Compounds as defined in 3.3.3c wherein the A2 group is defined in 3.3.2c.

3.3.4 Preferred A1 Moieties

3.3.4a

These preferred A1 moieties are defined in 3.1.4a.

3.3.4b

These more preferred A1 moieties are defined in 3.1.4b.

3.3.4c

These even more preferred A1 moieties are defined in 3.1.4c.

3.3.5 Preferred W and Y Moieties

3.3.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR₄ and X=O; or (3) W=CHR₄, Y=NH, and X=O.

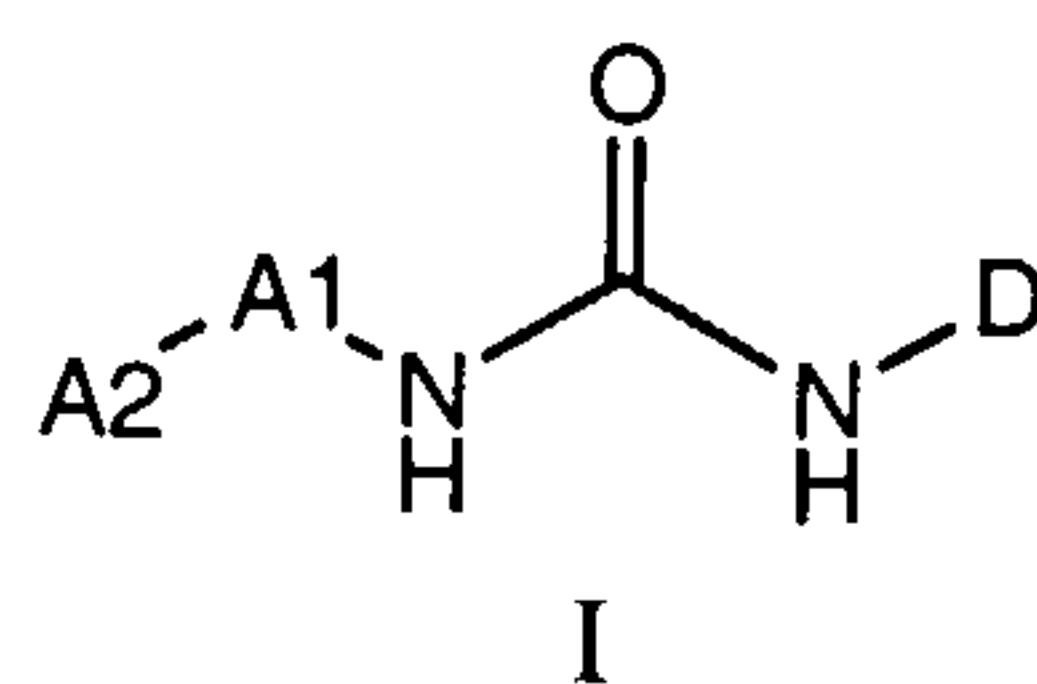
3.3.5b

W and Y are each NH and X=O.

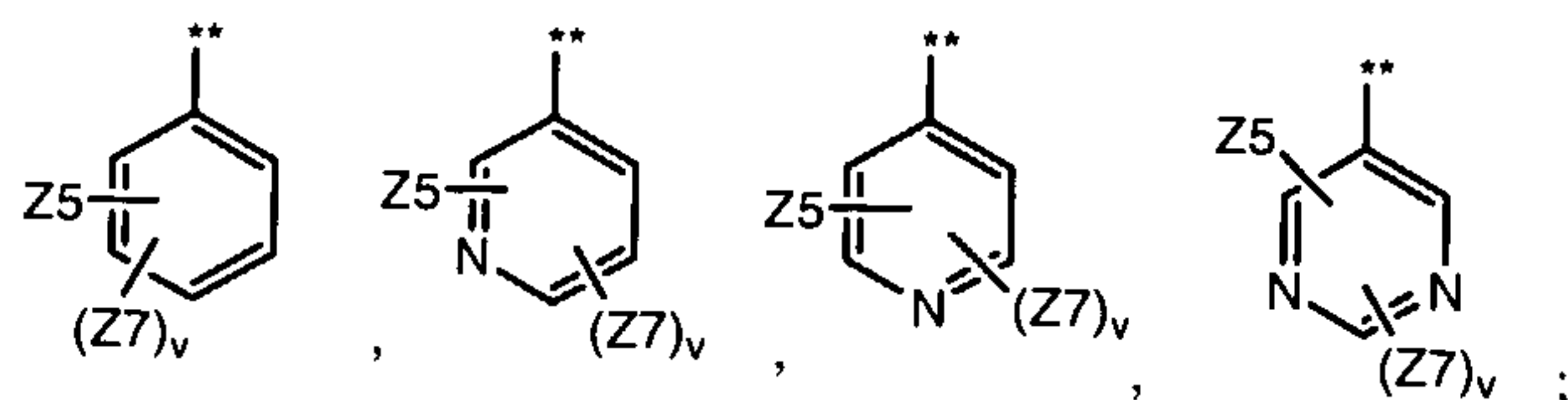
3.3.6 Further Preferred Compounds

3.3.6a

Further preferred compounds are of the formula

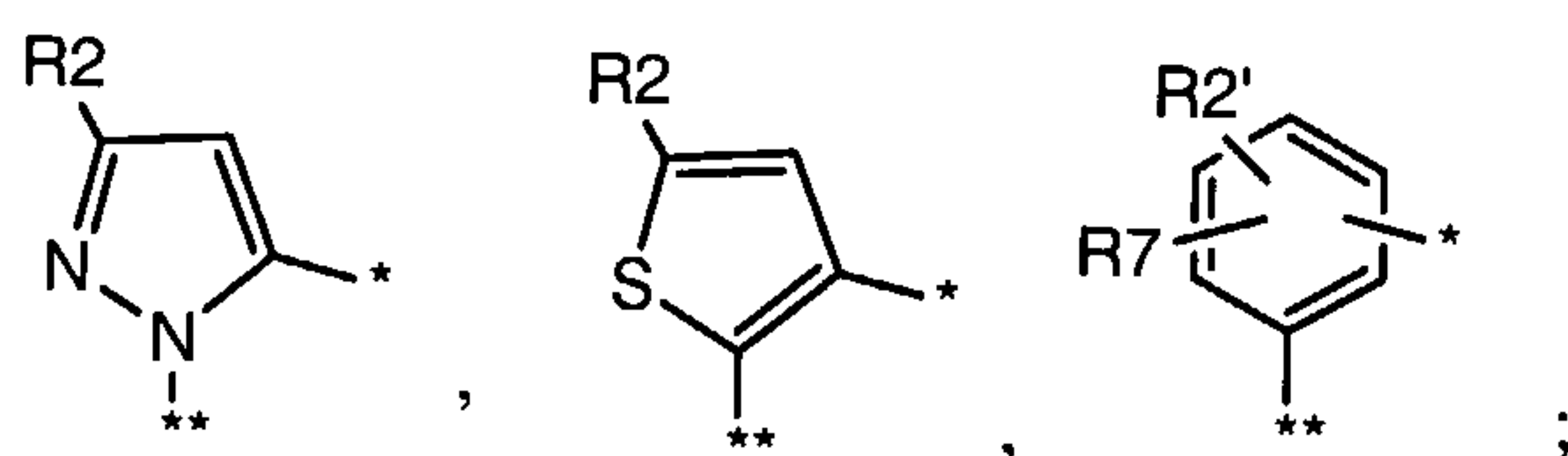


wherein A2 is selected from the group consisting of



wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

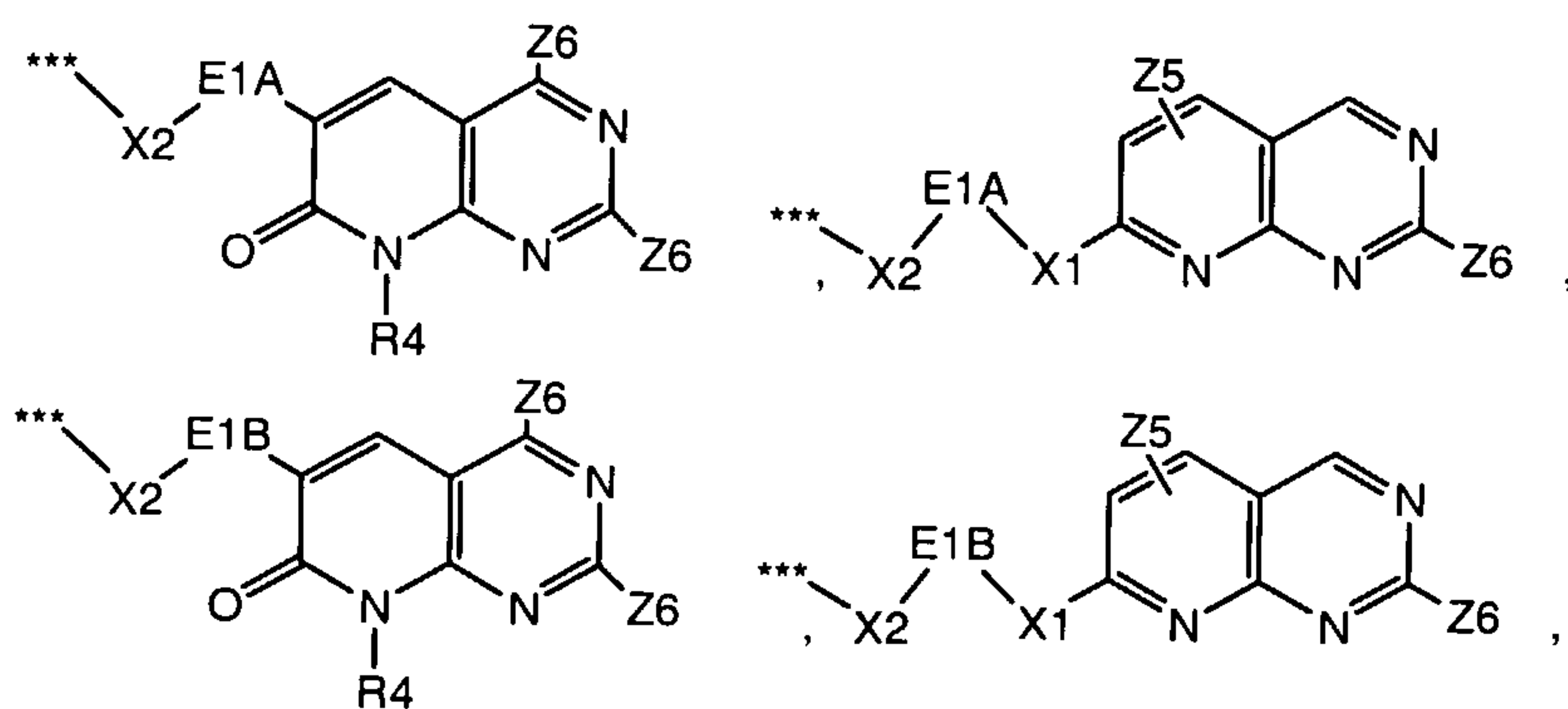
A1 is selected from the group consisting of

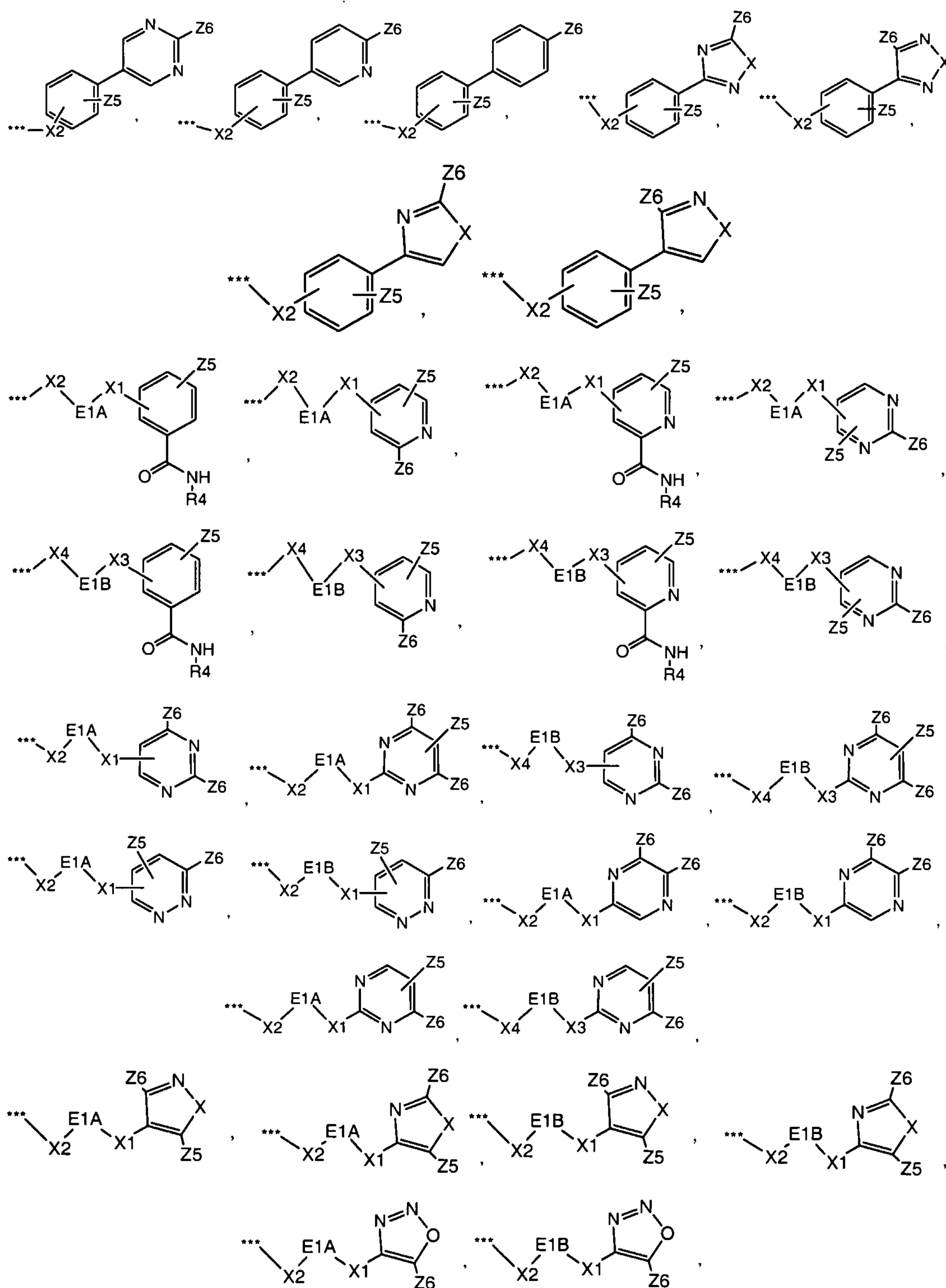


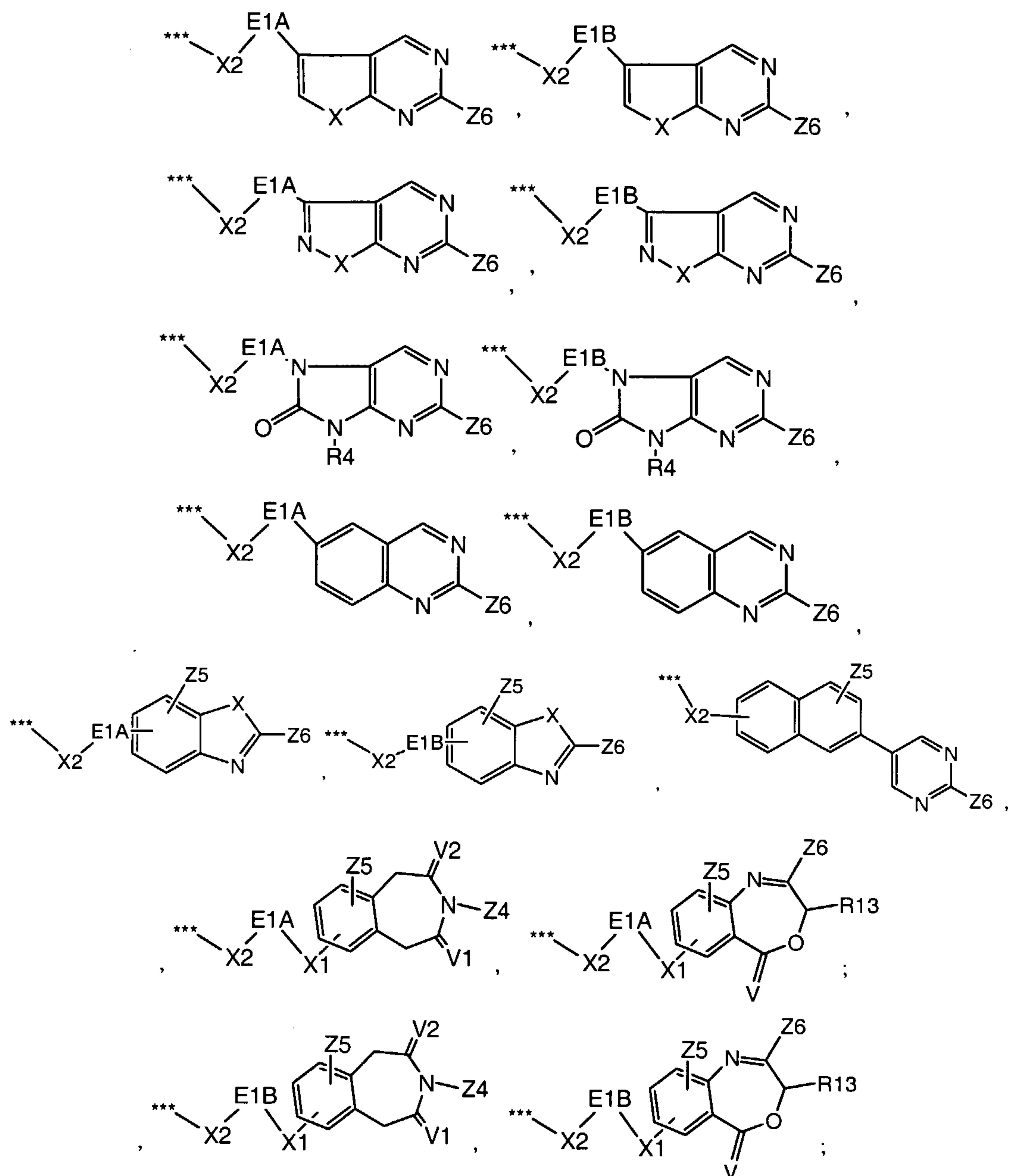
wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR₃;

D comprises a member of 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,4-trifluorophenyl, 3,4,5-trifluorophenyl, 3-phenoxyphenyl, 4-phenoxyphenyl, cyclohexyl,







wherein E1A is taken from the groups consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, and pyrimidinyl;

wherein E1B is taken from the groups consisting of phenyl and naphthyl;

wherein E2A is taken from the group comprising naphthyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, triazinyl and fused bicyclic rings selected from the group

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comprising indolyl, isoindolyl, isoindolinyl, isoindolonyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, imidazopyrimidinyl, imidazolonopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, furylopyrimidinyl, thienopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl, phthalazinyl, benzodioxyl, indolinyl, benzisothiazoline-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzoxapinyl, benzoxazepinyl;

wherein E2B is taken from the group consisting of phenyl, pyridyl, and pyrimidyl;

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, (CH₂)_p, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

X3 is selected from the group consisting of NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_q-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the either the E1B ring or E2B ring are directly linked by a covalent bond;

and wherein the carbon atoms of $-(CH_2)_q-$, C2-C5alkenyl, and C2-C5alkynyl moieties of X3 may be further substituted by one or more C1-C6alkyl;

X4 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl;

Each R2 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, C1-C6fluoroalkyl, wherein the alkyl group is partially or fully fluorinated, monocyclic heteroaryl, and R19 substituted C3-C8carbocyclyl wherein R19 is H, and C1-C6alkyl;

each R2' is selected from the group consisting of halogen and R2;

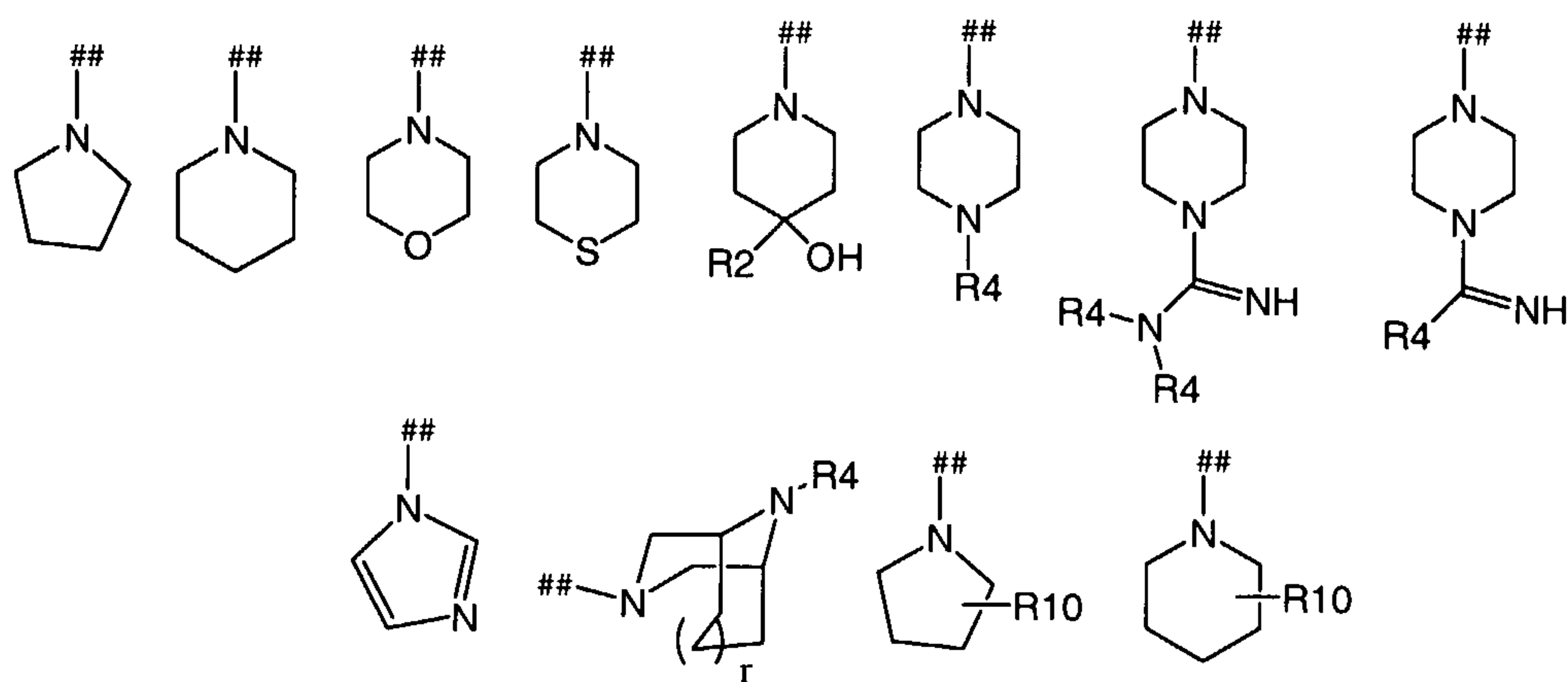
each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocyclyl ring;

each R5 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R8, R10, Z4, Z5, Z6 or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

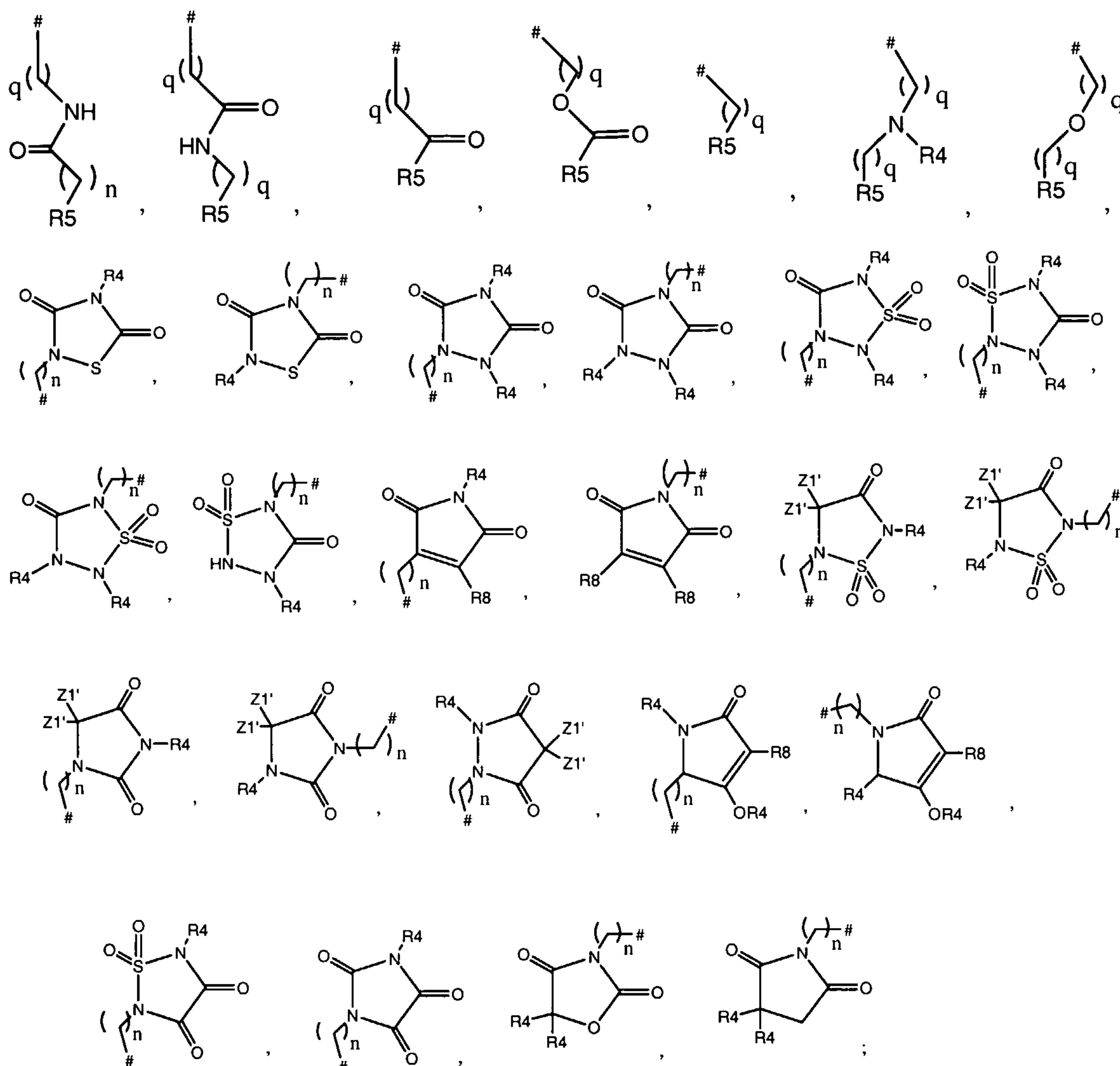
each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_p, (R4)₂N-C2-C6alkylO-(CH₂)_p, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, , heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

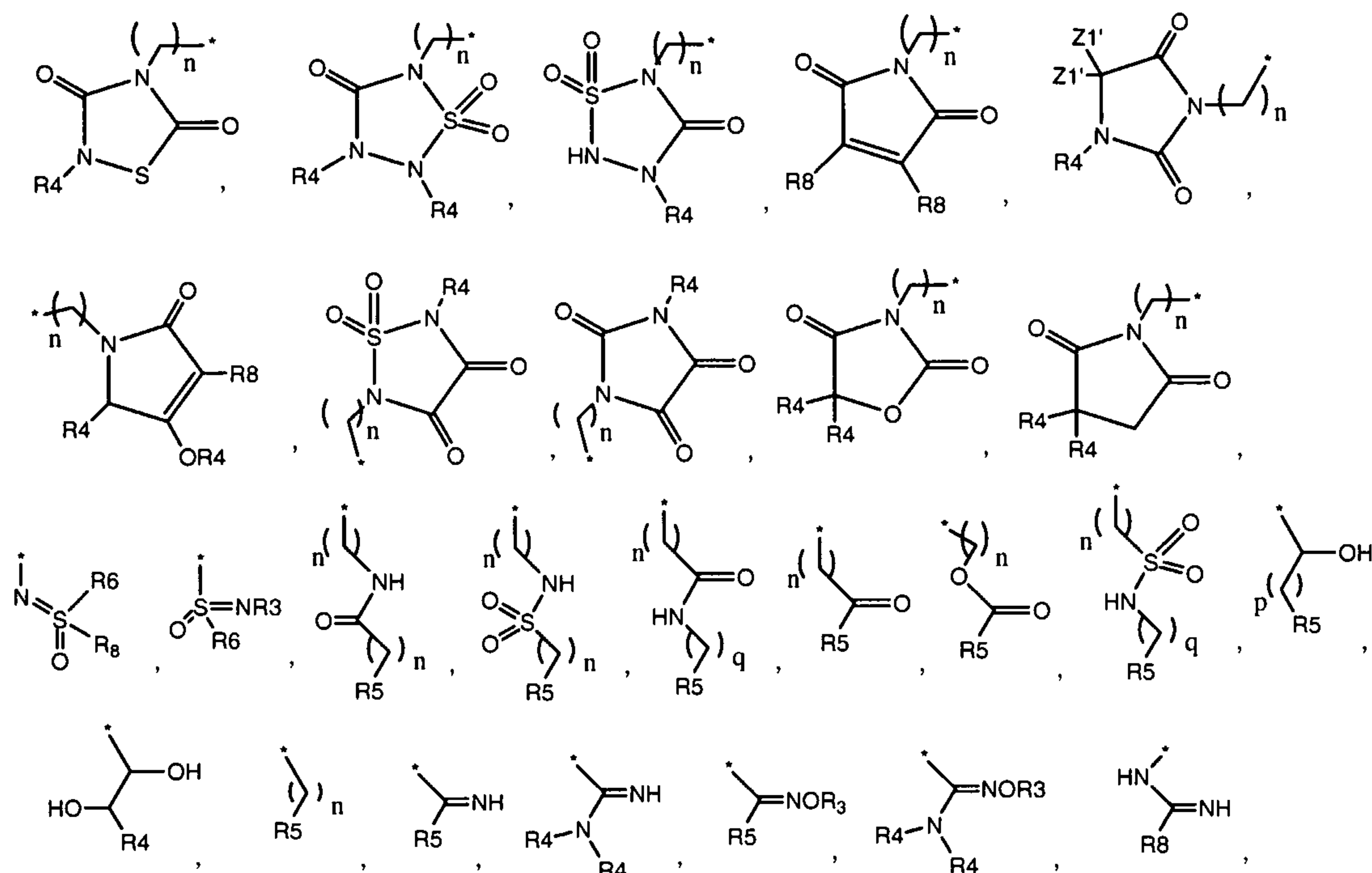
Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocycliloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

each Z7 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC1-C6alkyl,

(R₆)₂NC1-C6alkyl, (R₄)₂NC2-C6alkylN(R₄)-(CH₂)_n, (R₄)₂NC2-C6alkylO-(CH₂)_n, (R₃)₂N-CO, (R₄)₂N-CO, -SO₂R₃', SOR₃, -SOR₄, -C(=O)R₆, -C(=NOH)R₆, -C(=NOR₃)R₆, (CH₂)_nN(R₄)C(O)N(R₄)₂, (CH₂)_nN(R₄)C(O)R₅, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocycliloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocycliloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

In the foregoing definition of Z7, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z7 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R³ moieties are independently and individually taken from the group consisting of C₁-C₆alkyl and branched C₃-C₆alkyl and are attached to the same nitrogen heteroatom of Z⁷ may cyclize to form a C₃-C₇ heterocyclyl ring;

wherein two R⁴ moieties independently and individually taken from the group consisting of C₁-C₆alkyl, branched C₃-C₆alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z⁷ may cyclize to form a C₃-C₇ heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

3.3.6b

The following specific compounds of Formula I are more preferred: 1-(3-t-butyl-1-(3-(pyridin-3-yl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(3-(1H-pyrazol-4-yl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-cyclopentyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(3-(1-amino-1-oxopropan-2-yl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(2-(2-hydroxyethylamino)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(2-((S)-3-(dimethylamino)pyrrolidin-1-yl)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-((2,4,5-trioxoimidazolidin-1-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-((4,5-dioxo-2,2-dioxo-2,1,3-thiadiazol-yl)methyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-carbamimidoyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(3-(N-hydroxycarbamimidoyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(4-(N-hydroxycarbamimidoyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(2-hydroxyethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-cyanophenyl)-1H-pyrazol-5-yl)-3-(2,3,4-trifluorophenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,4,5-trifluorophenyl)urea, 2-(3-(3-t-butyl-5-(3-(2,3-difluorophenyl)ureido)-1H-

pyrazol-1-yl)phenyl)acetic acid, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-cyclopentyl-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea.

3.3.7 *Methods*

3.3.7a *Methods of Protein Modulation*

The invention includes methods of modulating kinase activity of RAF kinases and other kinases in the RAS-RAF-MEK-ERK-MAP kinase pathway including, but not limited to, A-Raf, B-Raf, and C-Raf. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 3.3 and 3.3.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

3.3.7b *Treatment Methods*

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer and hyperproliferative diseases. These methods comprise administering to such individuals compounds of the invention, and especially those of section 3.3 and 3.3.6a. condition being melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary solid tumor secondary sites, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies including diabetic retinopathy and age-related macular degeneration, rheumatoid arthritis characterized by the in-growth of a vascularized pannus, or a disease caused by a mutation in the RAS-RAF-MEK-ERK-MAP kinase pathway. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

3.3.8 *Pharmaceutical Preparations*

The compounds of the invention, especially those of 3.3 and 3.3.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

3.3.9 *Kinase/Compound Adducts*

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 3.3 and 3.3.6a.

4. *First aspect of the invention – P38 Kinase Modulator Compounds, Methods, Preparations and Adducts*

4.1 *Generally – A2 Bicyclic Compounds*

The invention includes compounds of formula I as defined in section 2.1, wherein R2 is selected from the group consisting of monocyclic heteroaryl, C1-C6alkyl, branched C3-C7alkyl, a R19-substituted C3-C8carbocyclyl wherein R19 is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, and phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents or chlorine;

4.1.1 *Preferred D Moieties*

4.1.1a

Preferred compounds of Formula I as defined above in section 4.1 contain D moieties as defined in section 1.1.1a.

4.1.1b

Additionally preferred compounds of Formula I as defined above in section 4.1 contain D moieties as defined in section 1.1.1b.

4.1.1c

More preferred compounds of Formula I as defined above in section 4.1.1b contain D moieties as defined in section 1.1.1c.

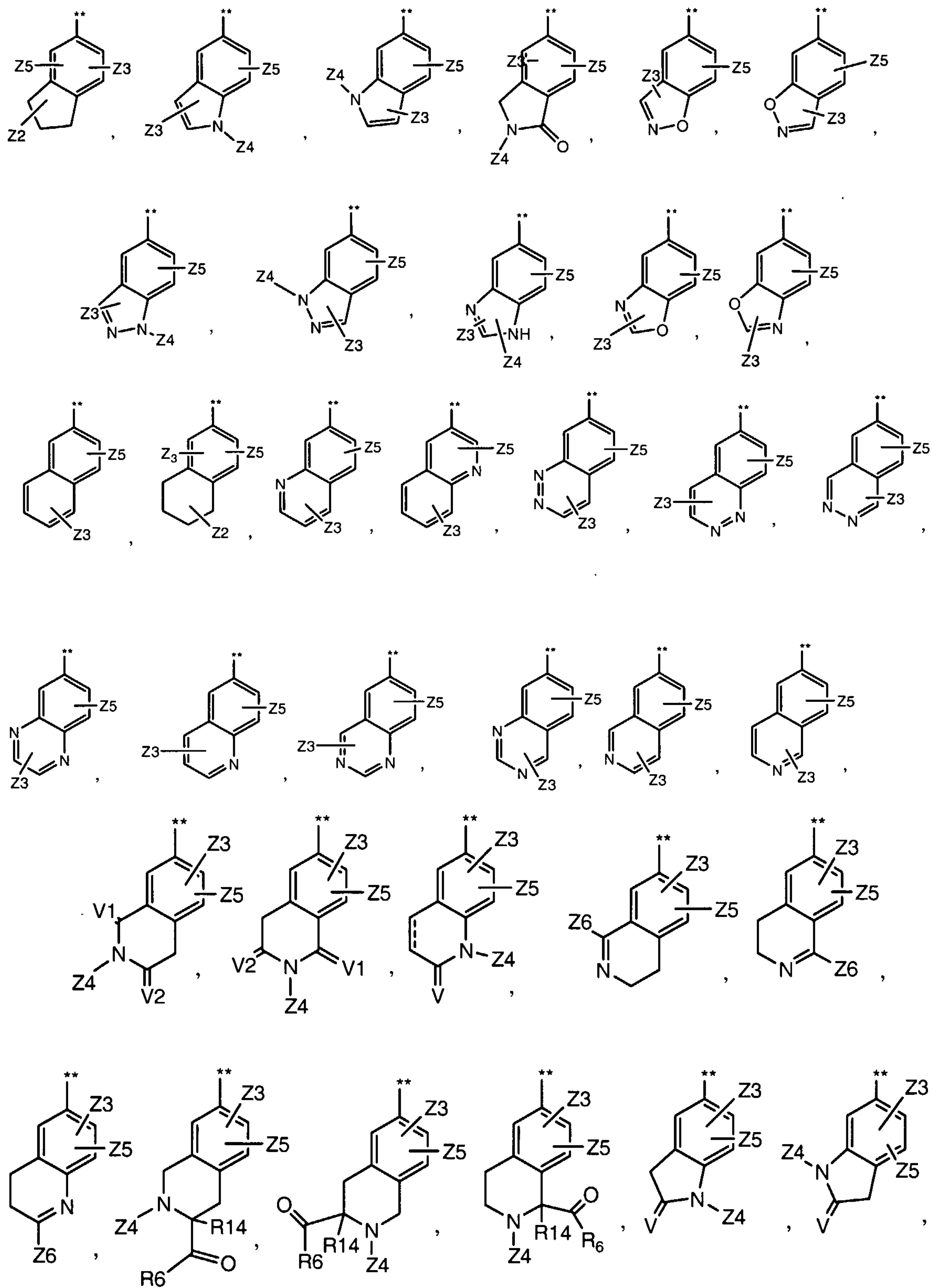
4.1.2 *Preferred A2 moieties*

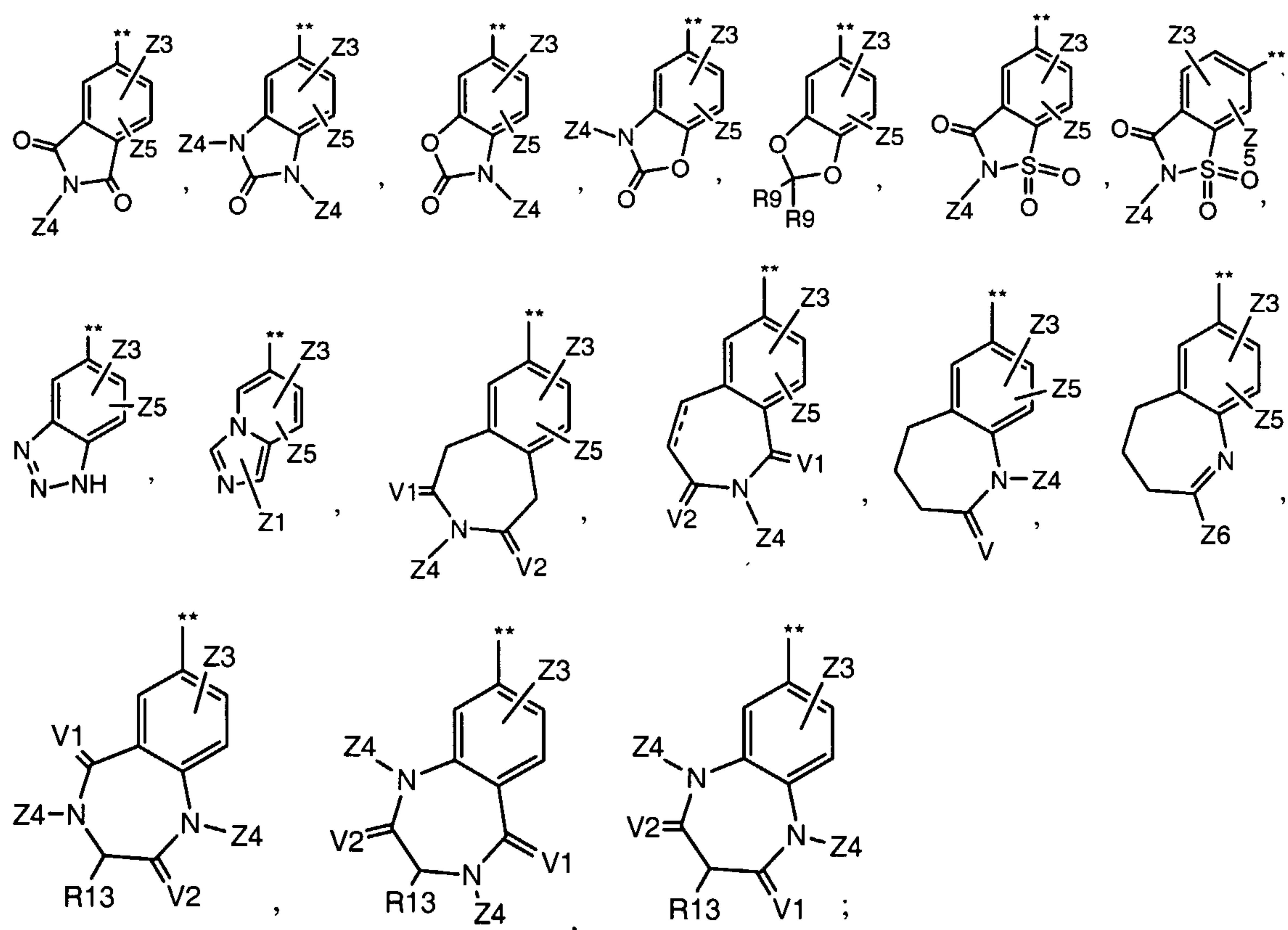
4.1.2a

Compounds of Formula I as defined above in section 4.1 have preferred A2 moieties as defined in section 1.1.2a.

4.1.2b *More preferred A2 moieties*

Compounds of Formula I as defined above in section 4.1 have more preferred A2 moieties selected from group consisting of





and wherein the symbol (**) is the point of attachment to the A1 ring for formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring.

4.1.2c

Still more preferred compounds of Formula I as defined above in section 4.1 have A2 moieties selected from group consisting of

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Compounds as defined in 4.1.1a wherein the A2 group is defined in 4.1.2a.

4.1.3b

Compounds as defined in 4.1.3a wherein the A2 group is defined in 4.1.2b.

4.1.3c

Compounds as defined in 4.1.3a wherein the A2 group is defined in 4.1.2c.

4.1.3d

Compounds as defined in 4.1.1b wherein the A2 group is defined in 4.1.2a.

4.1.3e

Compounds as defined in 4.1.3c wherein the A2 group is defined in 4.1.2b.

4.1.3f

Compounds as defined in 4.1.3c wherein the A2 group is defined in 4.1.2c.

4.1.4 Preferred A1 Moieties

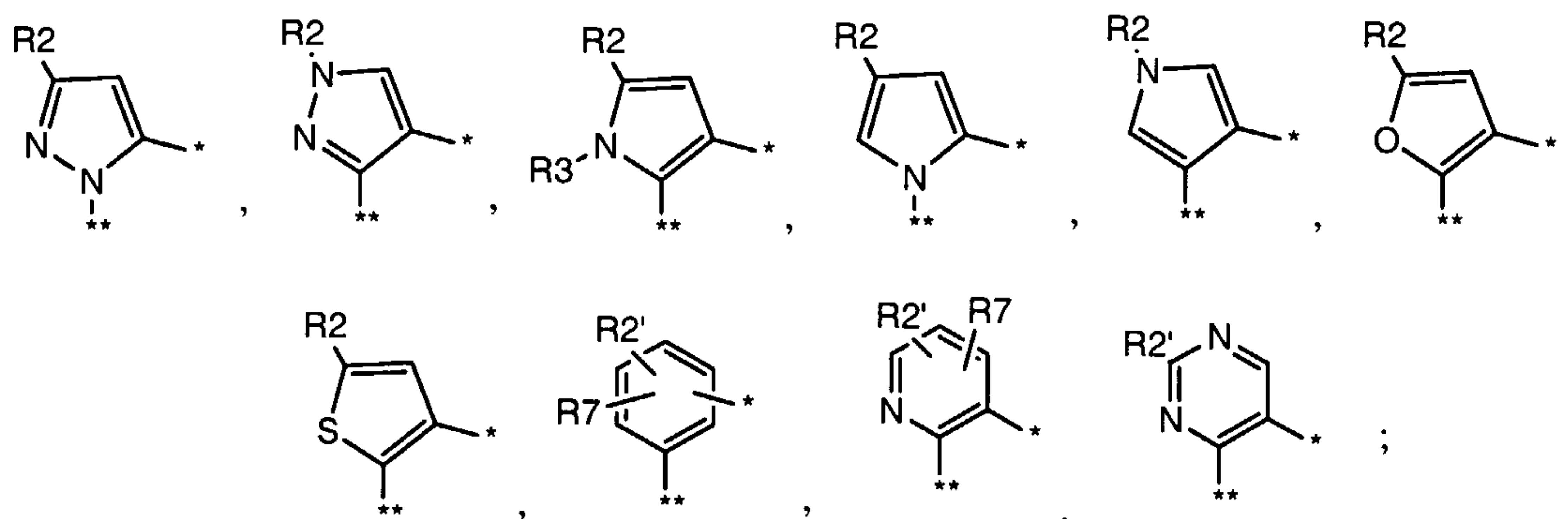
4.1.4a

Compounds of Formula I as defined above in section 4.1 have preferred A1 moieties selected from group defined in section 4.1.4a;

wherein each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

4.1.4b

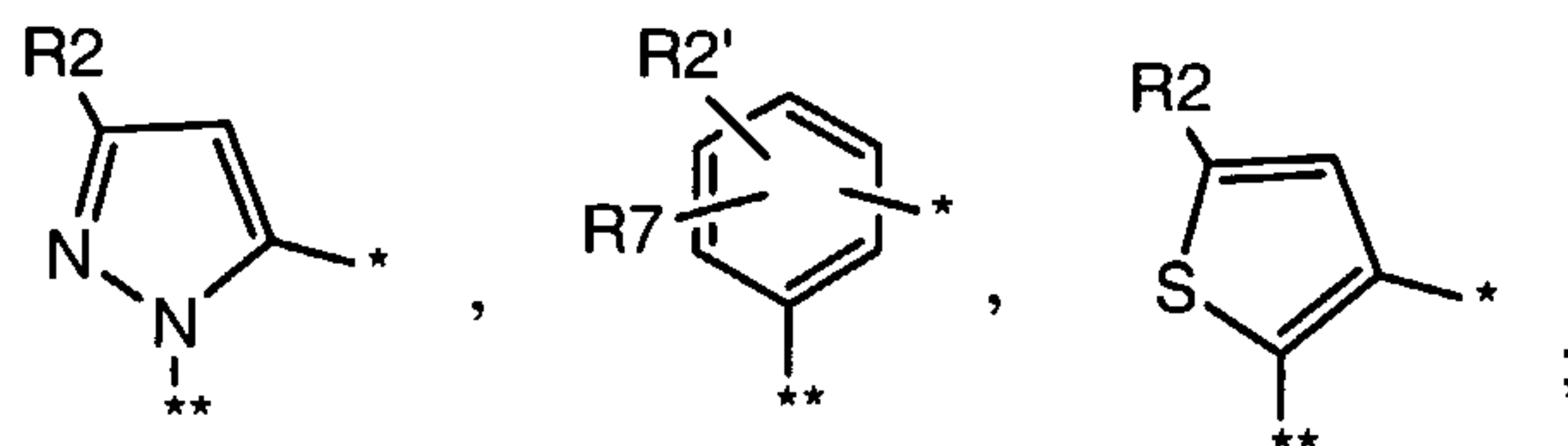
Compounds of Formula I as defined above in section 4.1 have more preferred A1 moieties selected from group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I.

4.1.4c

Compounds of Formula I as defined above in section 4.1 have even more preferred A1 moieties selected from group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I.

4.1.5 Preferred W and Y Moieties

4.1.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR₄ and X=O; or (3) W=CHR₄, Y=NH, and X=O.

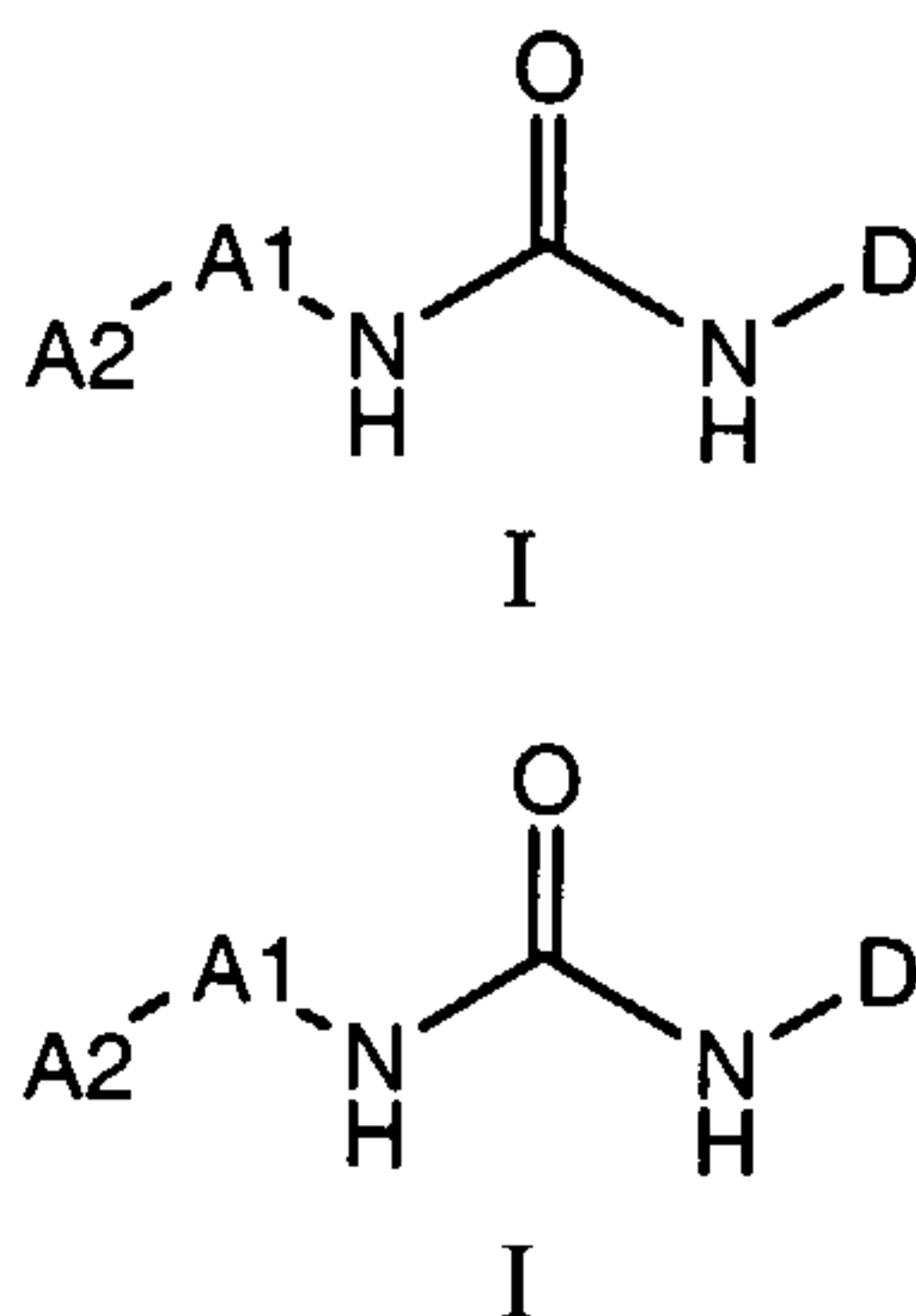
4.1.5b

W and Y are each NH and X=O.

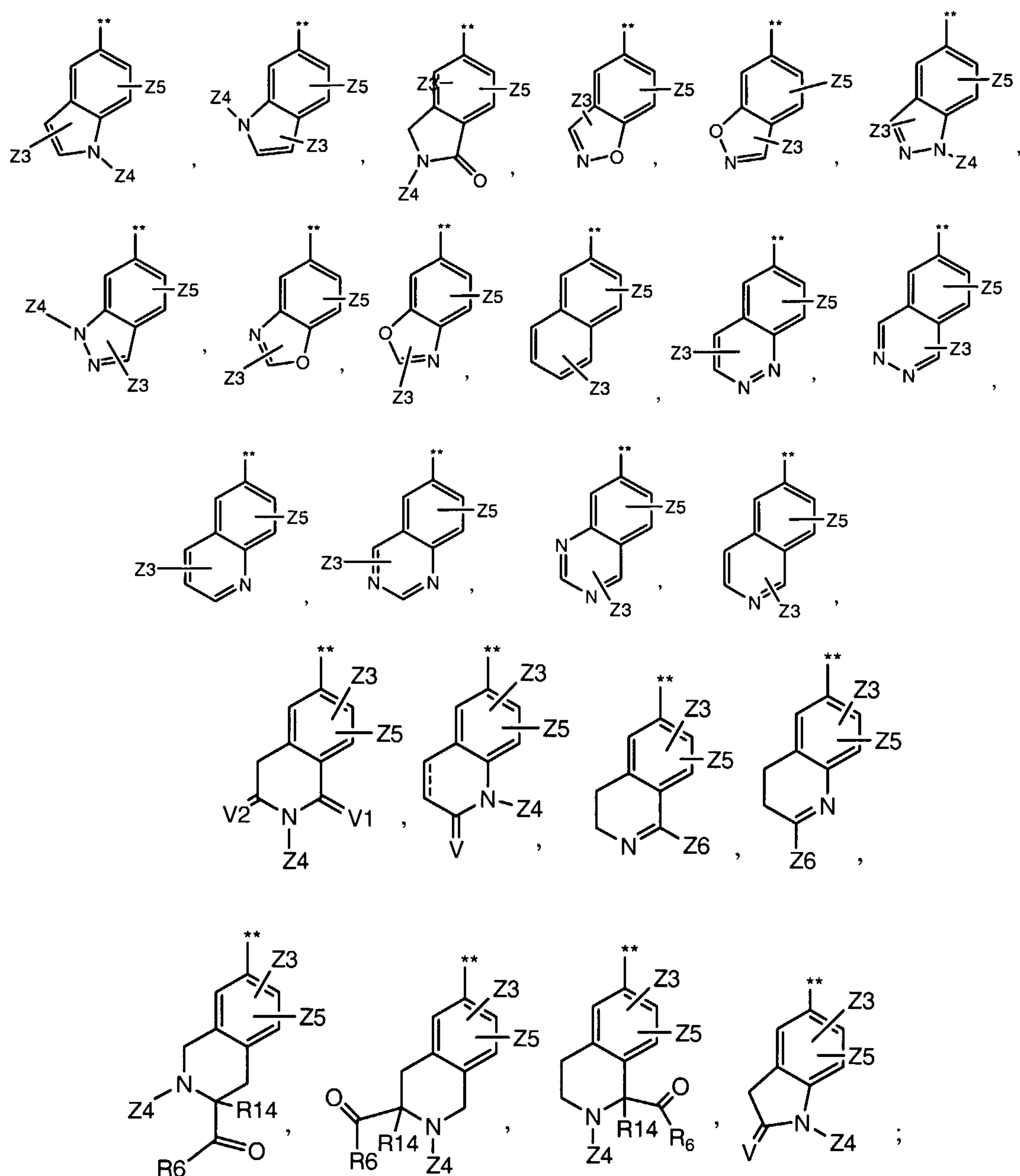
4.1.6 Further Preferred Compounds

4.1.6a

Further preferred compounds are of the formula



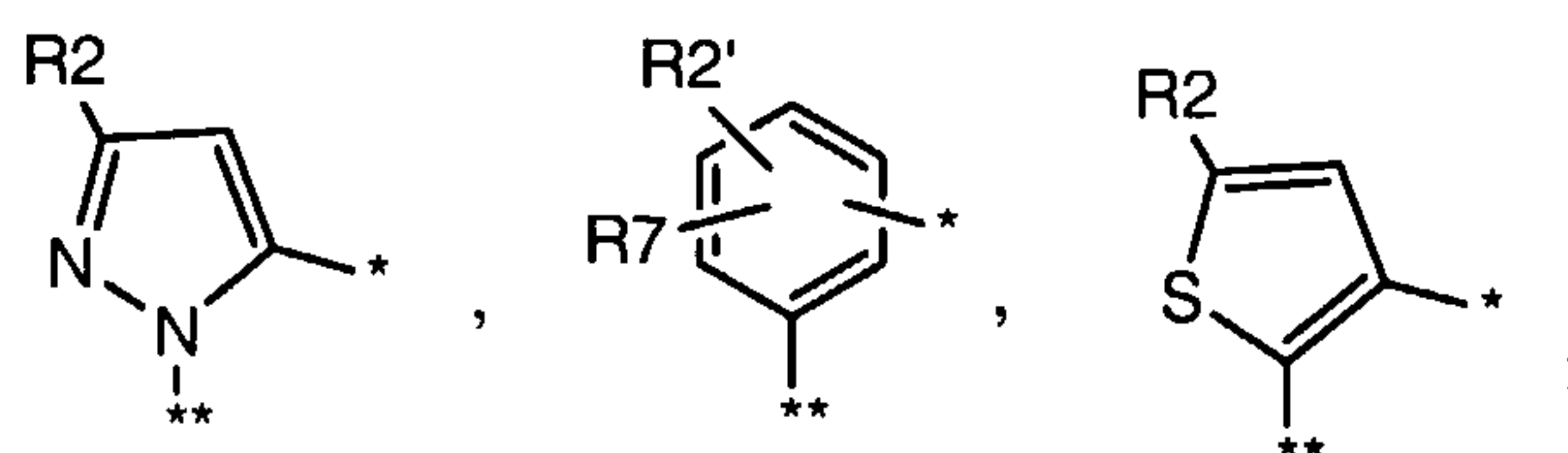
wherein A2 is selected from the group consisting of



wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring;

wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

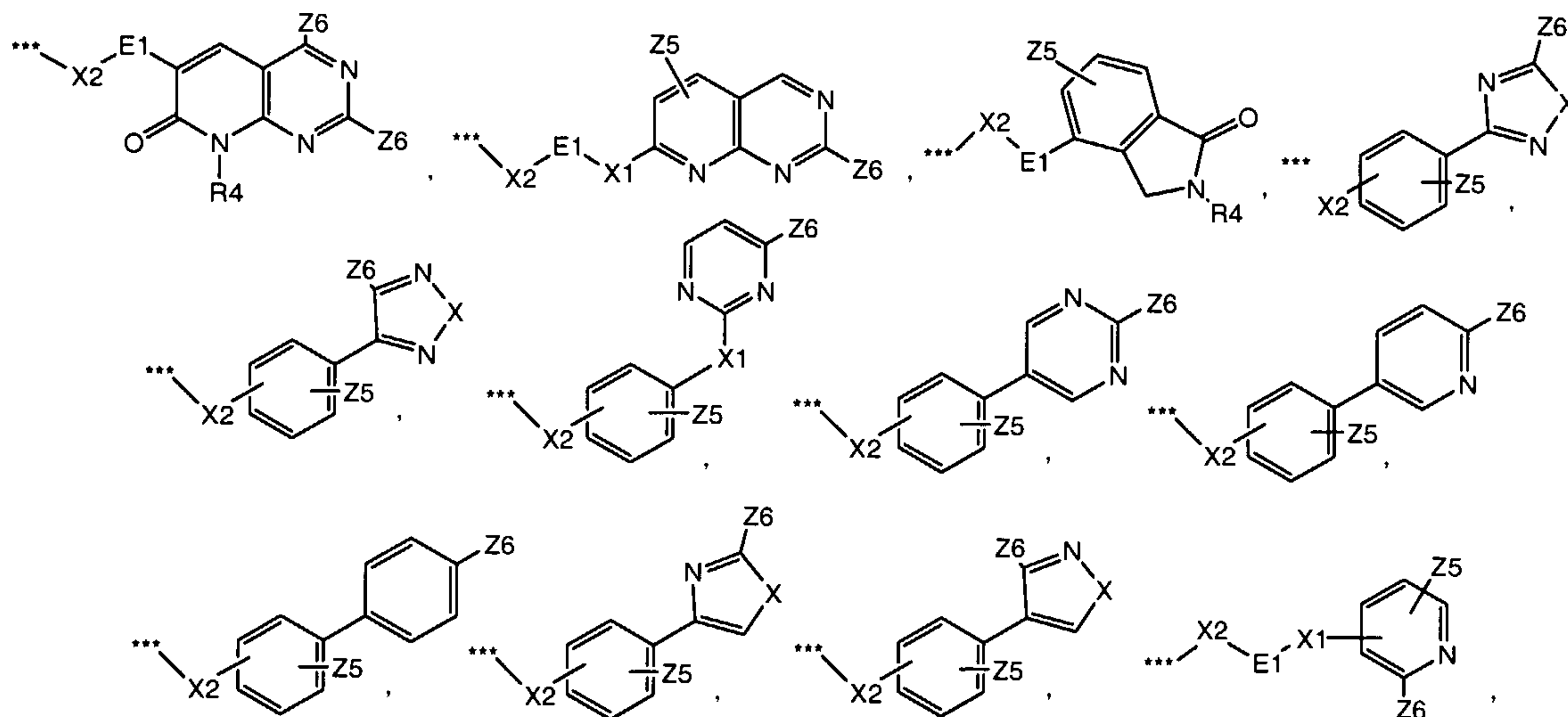
A1 is selected from the group consisting of

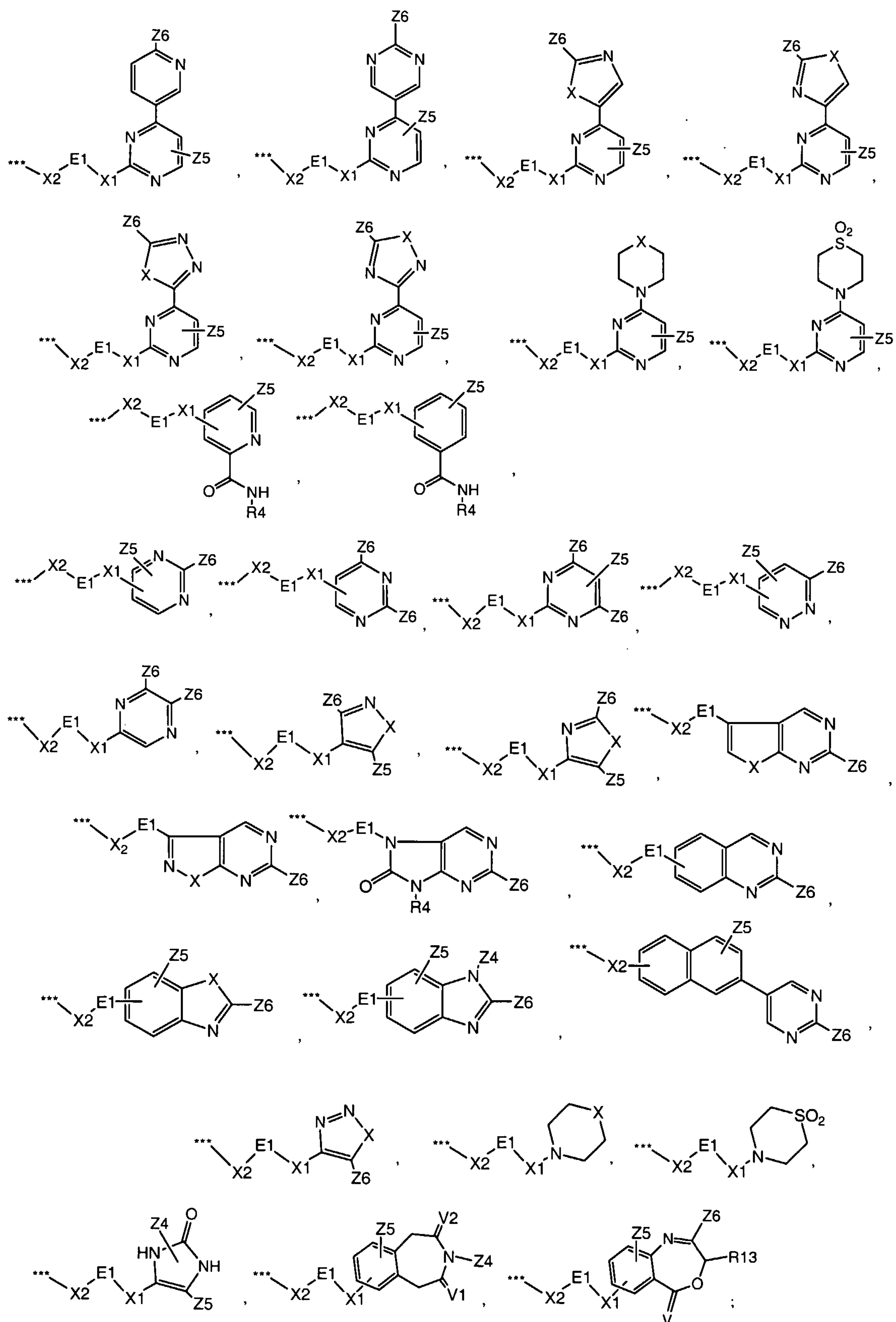


wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR₃;

D comprises a member of 2,3-dichlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3-trifluoromethylphenyl, 3-trifluoromethyl-4-chlorophenyl, 2,3,4-trifluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,5-trifluorophenyl, 3,4,5-trifluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-cyanophenyl, 3-phenoxyphenyl, 4 phenoxyphenyl, 1-naphthyl-2,3-dihydro-1H-inden-1-yl, 1,2,3,4-tetrahydronaphthalen-1-yl, benzo[d][1,3]dioxol-5-yl or benzo[d][1,3]dioxol-4-yl,





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wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, (CH₂)_p, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

each R₂ is selected from the group consisting of monocyclic heteroaryl, C1-C6alkyl, branched C3-C7alkyl, a R₁₉-substituted C3-C8carbocyclyl wherein R₁₉ is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, and phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents or chlorine;

each R₂' is selected from the group consisting of halogen and R₂;

each R₃ is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

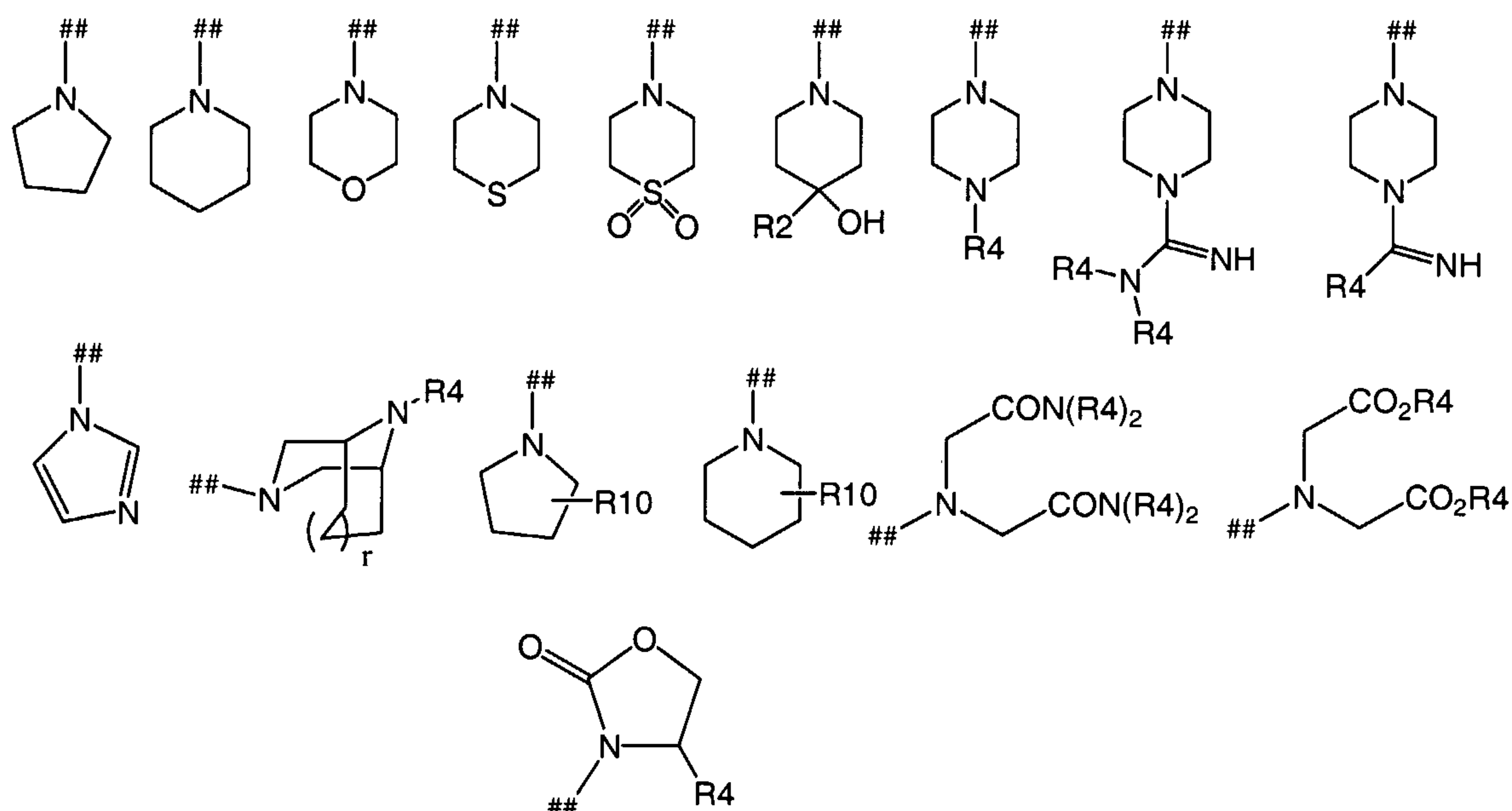
wherein two R₃ moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R₃ moieties may cyclize to form a C3-C7 heterocyclyl ring;

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each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocyclyl ring;

each R5 is independently and individually selected from the group consisting of



;

and wherein the symbol (##) is the point of attachment to respective R8, R10, R13, Z2, Z3, Z4, Z5, or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

each R13 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, hydroxyC2-C7alkyl, C1-C6alkoxyC2-C7alkyl, (R4)₂N-CO, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_q, R5-C2-C6alkylN(R4)-(CH₂)_q, (R4)₂N-C2-C6alkylO-(CH₂)_q, R5-C2-C6alkyl-O-(CH₂)_q, -(CH₂)_qN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC2-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, and heterocyclylaminoC2-C6alkyl;

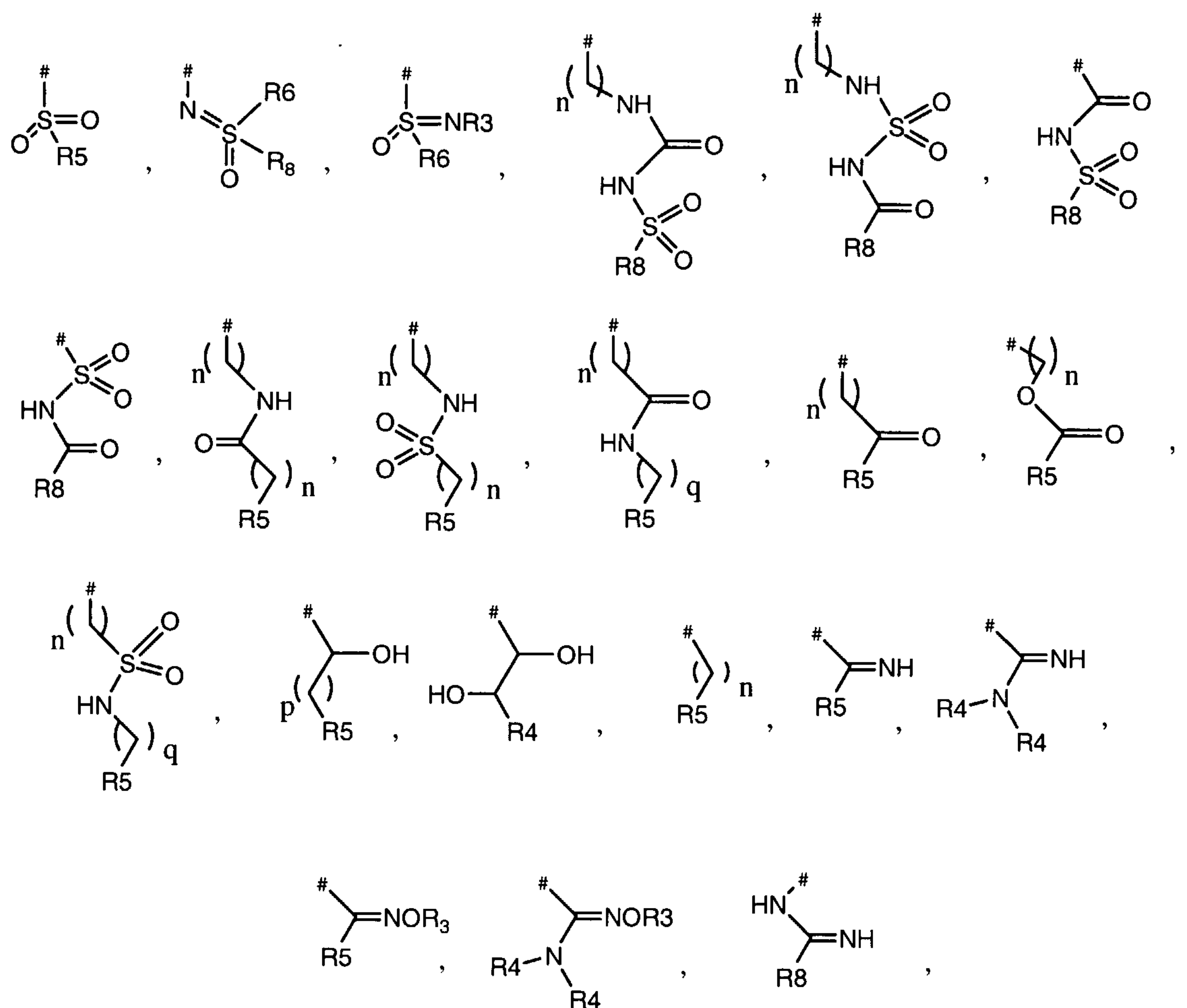
wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R13 may cyclize to form a C3-C7 heterocyclyl ring;

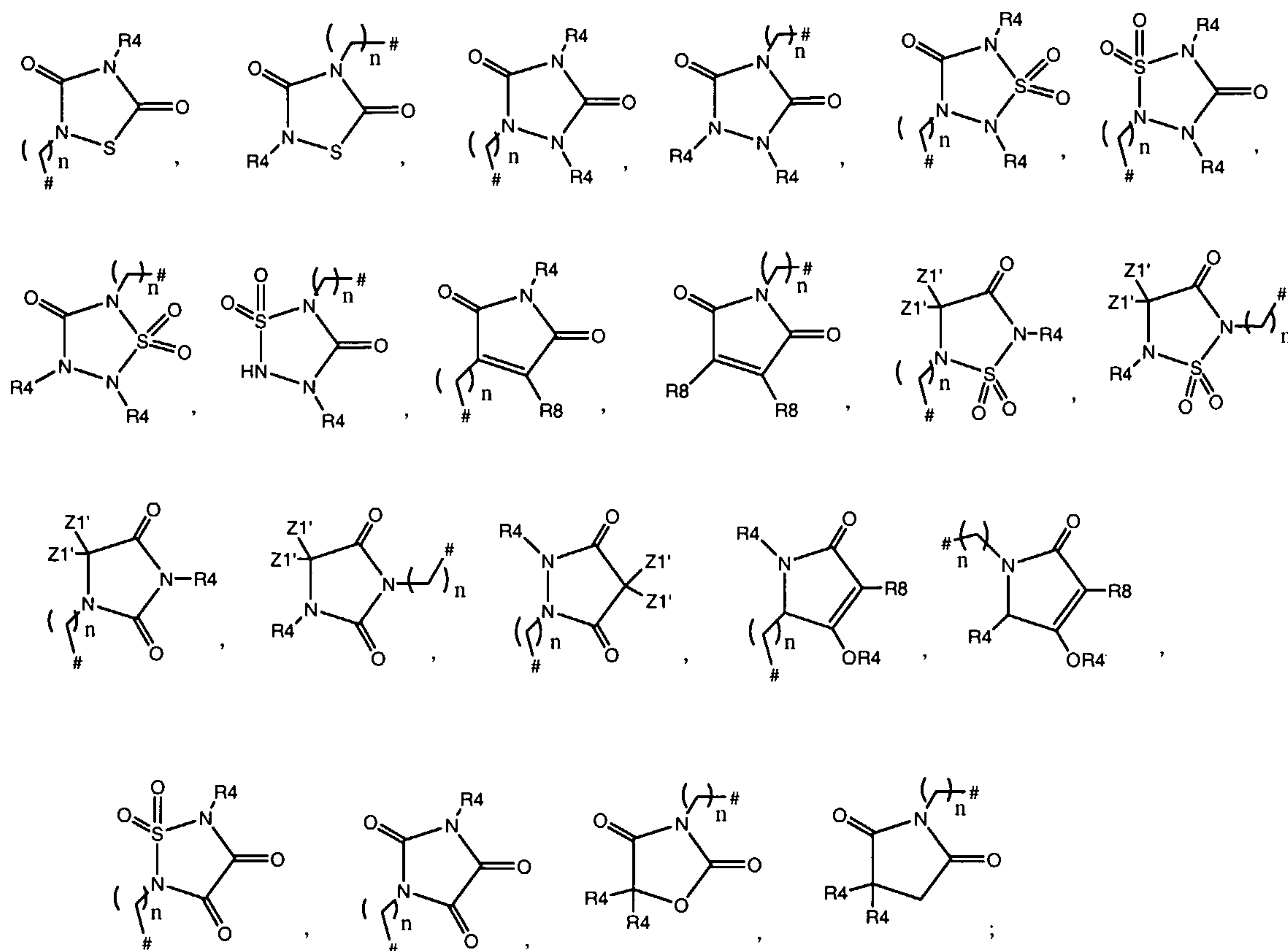
each R14 is independently and respectively selected from the group consisting of H and C1-C6alkyl;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_p, (R4)₂N-C2-C6alkylO-(CH₂)_p, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyl, hydroxyC1-C6alkyl, cyano, C1-C6alkoxy, C1-C6alkoxyC1-C6alkyl, halogen, CF₃, (R3)₂N-, (R4)₂N-, (R4)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, R8CO-, (R4)₂N-CO-C1-C6alkyl, carboxyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)₂NSO₂, -SO₂R3, SOR3, (R4)₂NSO₂, -SO₂R4, -SOR4, -(CH₂)_nN(R4)C(O)R8, -C=(NOH)R6, -C=(NOR3)R6, heteroaryl, heterocyclyl, heteroarylC1-C6alkyl, heterocyclylC1-C6alkyl, heteroaryloxy, heterocycliloxy, heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylamino, heteroarylamino, heterocyclylamino, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocyclylaminoC1-C6alkyl, or moieties of the formulae





wherein the symbol (#) indicates the point of attachment of the Z3 moiety to the A2 ring of formula I;

in the event that Z3 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

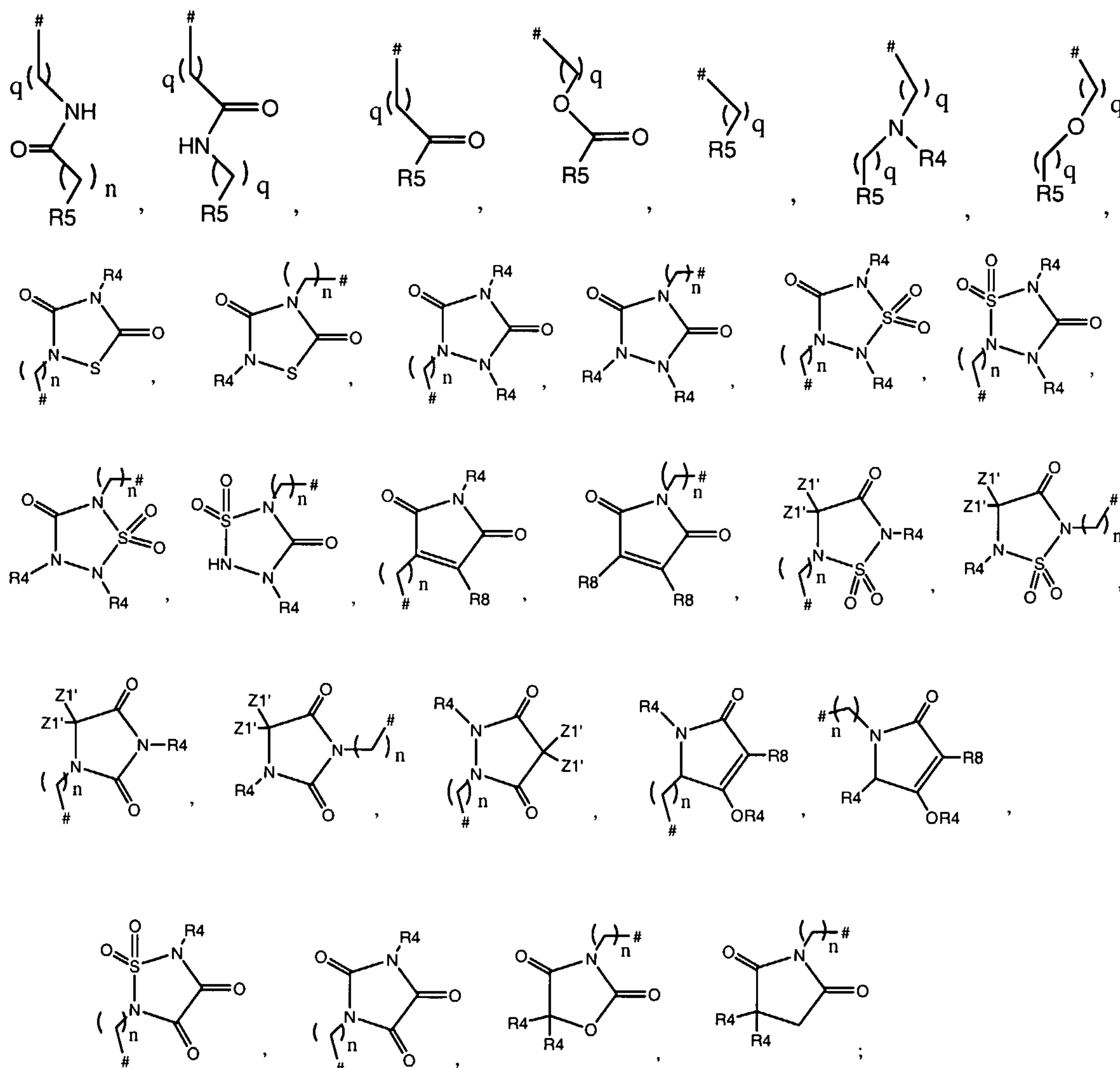
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z3 may cyclize to form a C3-C7 heterocyclyl ring;

each Z4 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-

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C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoc2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R⁴ moieties independently and individually taken from the group consisting of C₁-C₆alkyl, branched C₃-C₆alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z₆ may cyclize to form a C₃-C₇ heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

V, V₁, and V₂ are each independently and respectively selected from the group consisting of O and H₂;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs, and salts of any of the foregoing.

4.1.6b

The following specific compounds are most preferred: 1-(3-t-butyl-1-(3-hydroxy-2,3-dihydro-1H-inden-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-oxo-2,3-dihydro-1H-inden-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(hydroxyimino)-2,3-dihydro-1H-inden-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(indolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-(methylsulfonyl)indolin-5-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 2-(3-(3-t-butyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)naphthalen-1-yl)acetic acid, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(4-(hydroxymethyl)naphthalen-2-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(1-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(2-oxo-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(3-carbamoyl-2,3-dihydro-1H-inden-5-yl)-3-cyclopentyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(indolin-6-yl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea, 1-(3-t-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea, 1-(1-(4-(2-amino-2-oxoethyl)naphthalen-2-yl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-

(3-t-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(3-t-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea,

4.1.7 *Methods*

4.1.7a *Methods of Protein Modulation*

The invention includes methods of modulating kinase activity of the p38 family of kinases including, but not limited to p38-alpha and other MAP kinases. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 4.1 and 4.1.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

4.1.7b *Treatment Methods*

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of inflammation, osteoarthritis, respiratory diseases, stroke, systemic shock, immunological diseases, and cardiovascular disease. These methods comprise administering to such individuals compounds of the invention, and especially those of section 4.1 and 4.1.6a, said condition being human inflammation, rheumatoid arthritis, rheumatoid spondylitis, osteo-arthritis, asthma, gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic pulmonary inflammatory disease, bone resorptive diseases, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, and combinations thereof. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

4.1.8 *Pharmaceutical Preparations*

The compounds of the invention, especially those of 4.1 and 4.1.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

4.1.9 Kinase/Compound Adducts

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 4.1 and 4.1.6a.

4.2 Generally – Monocyclic A2 Compounds with Polycyclic E2 Rings

The invention includes compounds of the formula I as defined in section 2.2, wherein R2 is selected from the group consisting of monocyclic heteroaryl, C1-C6alkyl, branched C3-C7alkyl, a R19-substituted C3-C8carbocyclyl wherein R19 is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, and phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents or chlorine;

4.2.1 Preferred D Moieties

4.2.1a

Preferably, the compounds of formula I in 4.2 contain D moieties wherein E1 and E2 are as defined in section 1.2.1

4.2.1b

Additionally preferred D moieties of formula I in 4.2 are as defined in section 1.2.1b

4.2.1c

More preferred D moieties of 4.2.1b are where E2 is defined as in section 1.2.1c

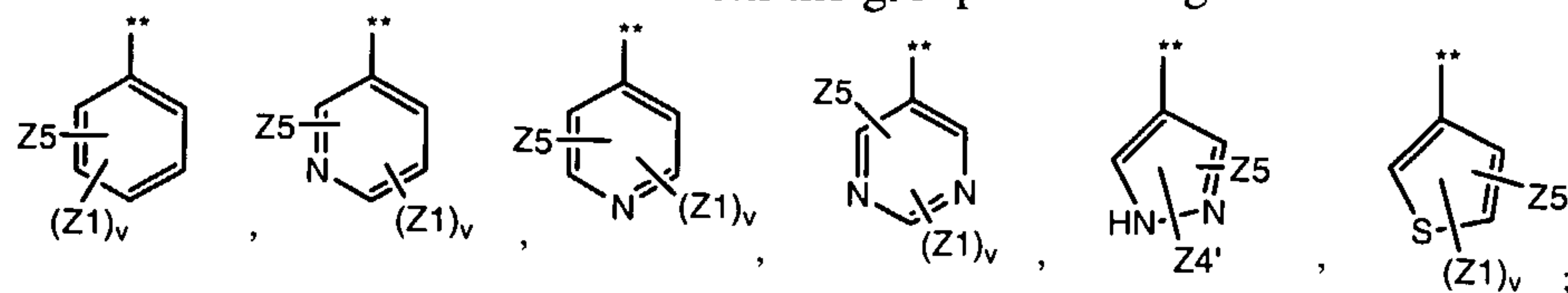
4.2.2 Preferred A2 moieties

4.2.2a

Compounds of Formula I as defined above in section 4.2 have preferred A2 moieties as defined in section 2.2.2a;

4.2.2b

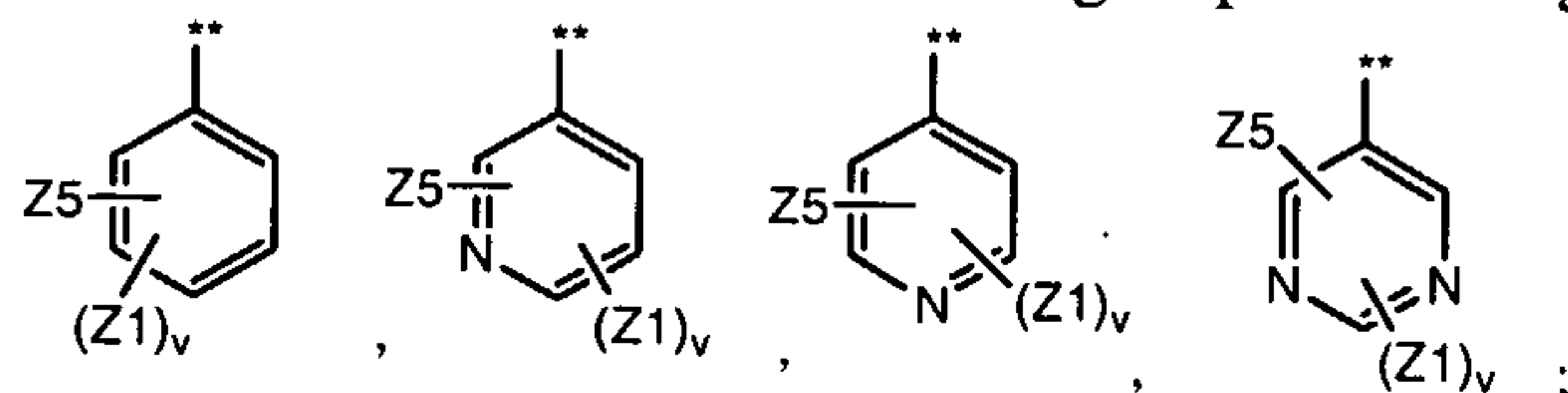
More preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring for formula I.

4.2.2c

Even more preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I.

4.2.3 Preferred Classes of Compounds

4.2.3a

Compounds as defined in 4.2.1a wherein the A2 group is defined in 4.2.2a.

4.2.3b

Compounds as defined in 4.2.3a wherein the A2 group is defined in 4.2.2b.

4.2.3c

Compounds as defined in 4.2.3a wherein the A2 group is defined in 4.2.2c.

4.2.3d

Compounds as defined in 4.2.1b wherein the A2 group is defined in 4.2.2a.

4.2.3e

Compounds as defined in 4.2.3c wherein the A2 group is defined in 4.2.2b.

4.2.3f

Compounds as defined in 4.2.3c wherein the A2 group is defined in 4.2.2c.

4.2.4 Preferred A1 Moieties

4.2.4a

These preferred A1 moieties are defined in 4.1.4a.

4.2.4b

These more preferred A1 moieties are defined in 4.1.4b.

4.2.4c

These even more preferred A1 moieties are defined in 4.1.4c.

4.2.5 Preferred W and Y Moieties

4.2.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR₄ and X=O; or (3) W=CHR₄, Y=NH, and X=O.

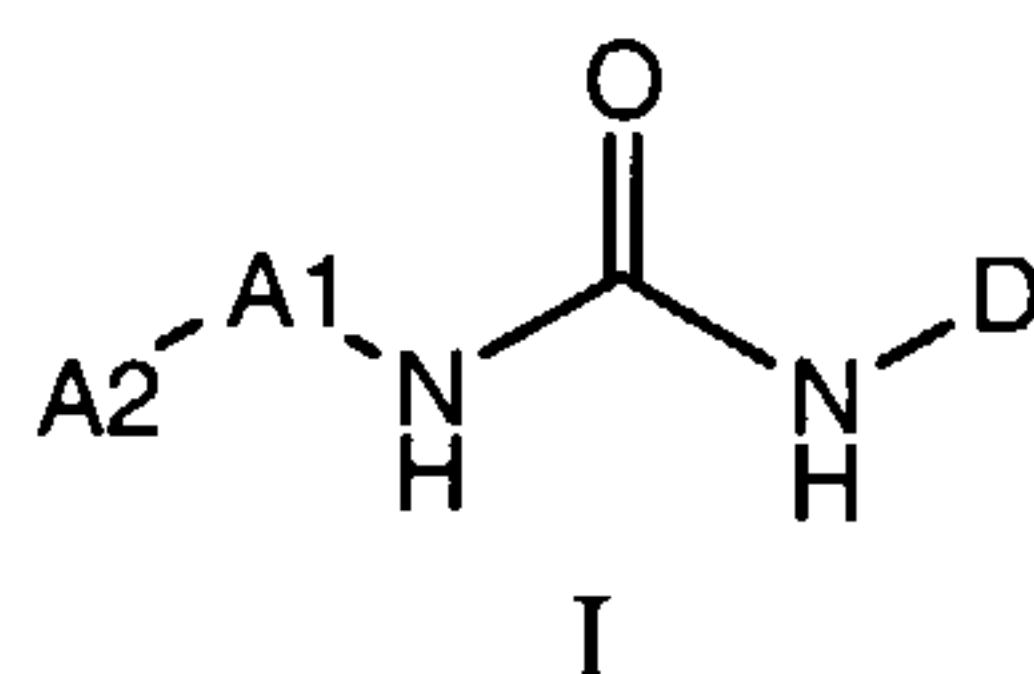
4.2.5b

W and Y are each NH and X=O.

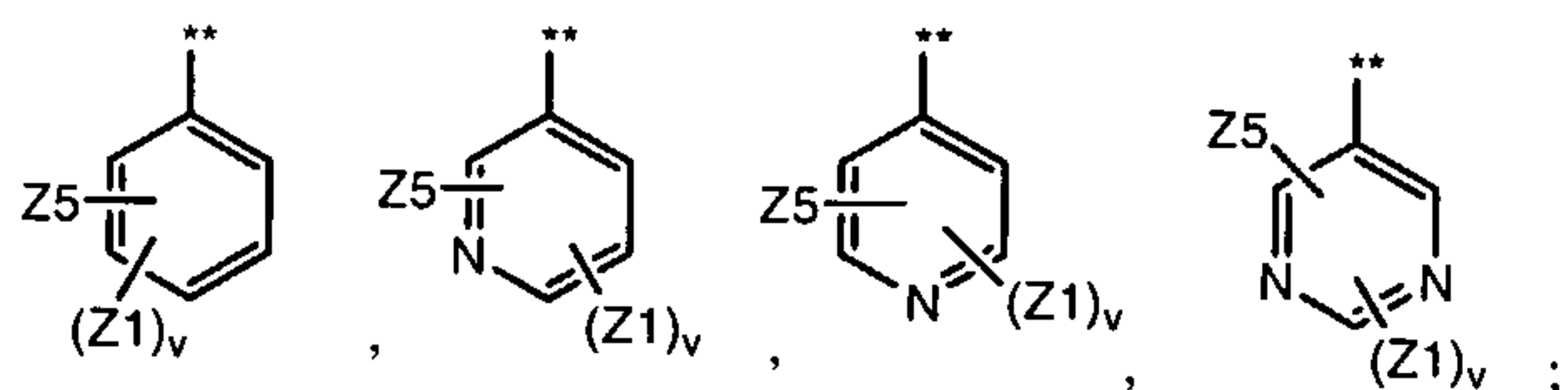
4.2.6 Further Preferred Compounds

4.2.6a

Further preferred compounds are of the formula

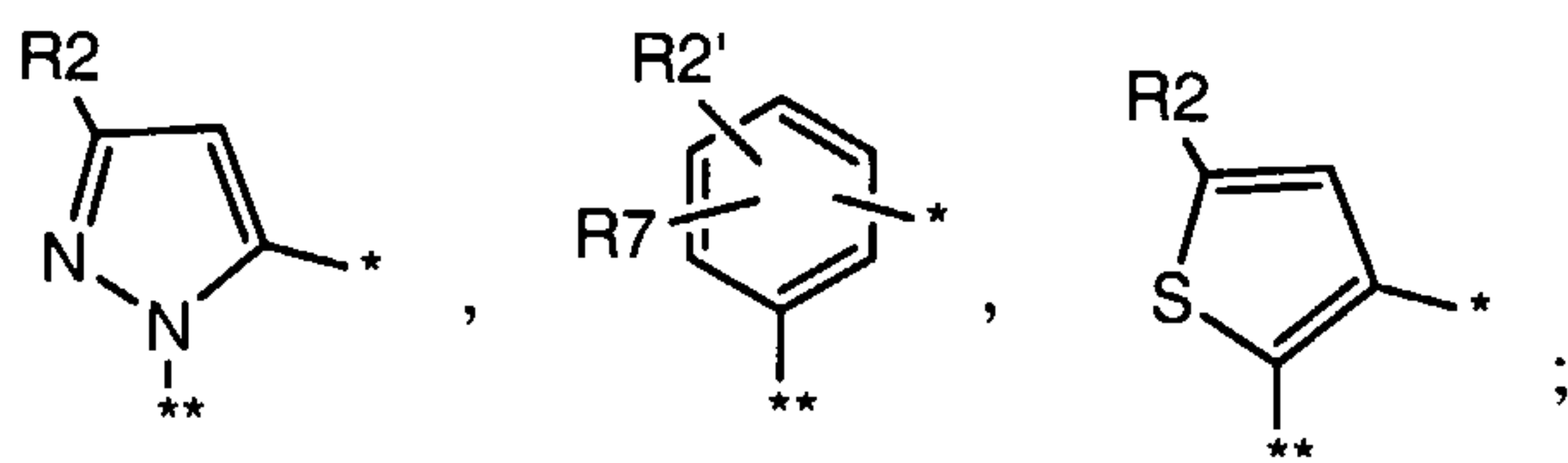


wherein A2 is selected from the group consisting of



wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

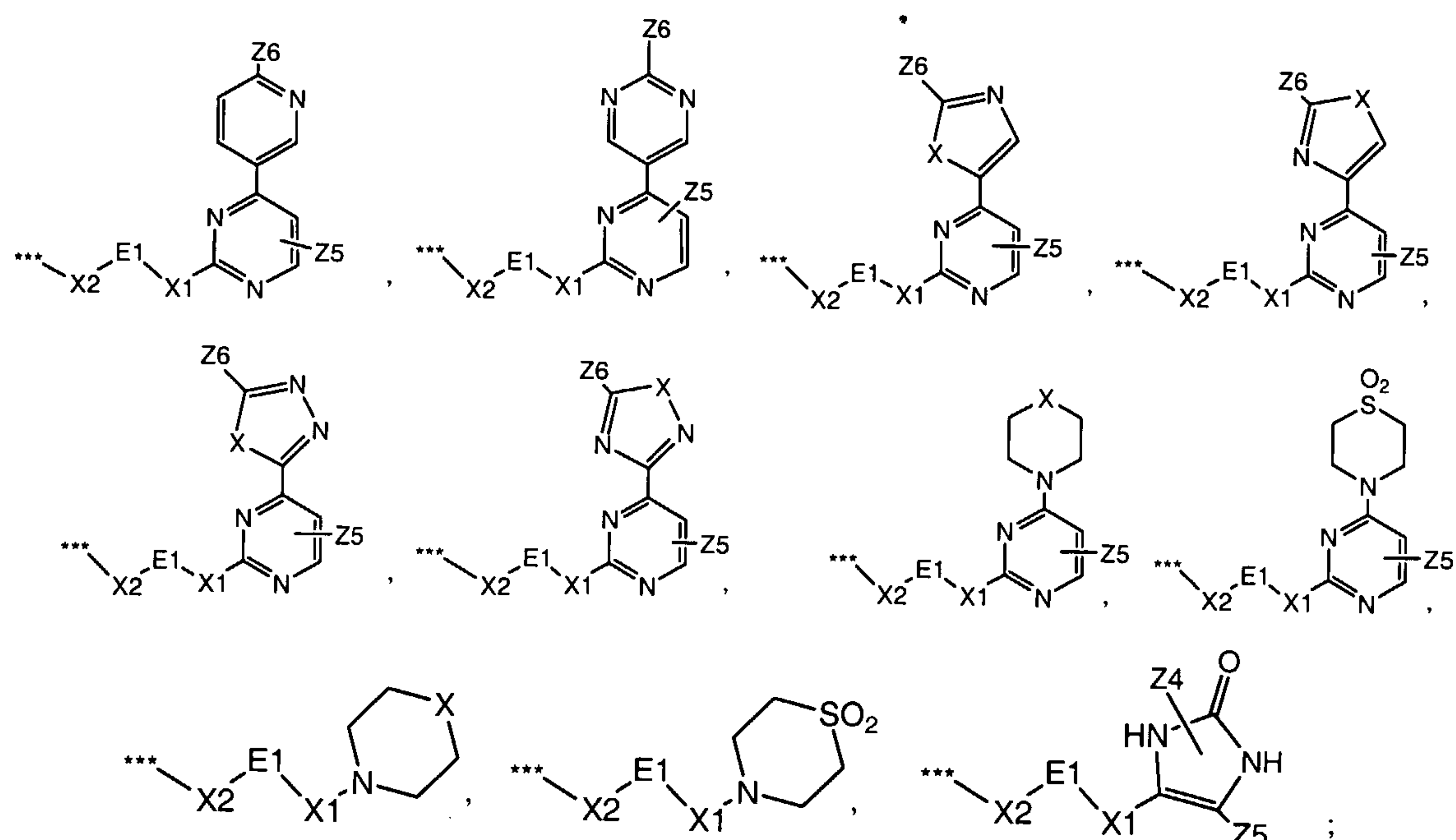
A1 is selected from the group consisting of



wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR₃;

D comprises a member of



wherein E1 is selected from the group consisting cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, phenyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl and naphthyl;

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, (CH₂)_p, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

each R2 is selected from the group consisting of monocyclic heteroaryl, C1-C6alkyl, branched C3-C7alkyl, a R19-substituted C3-C8carbocyclyl wherein R19 is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, and phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents or chlorine;

each R2' is selected from the group consisting of halogen and R2;

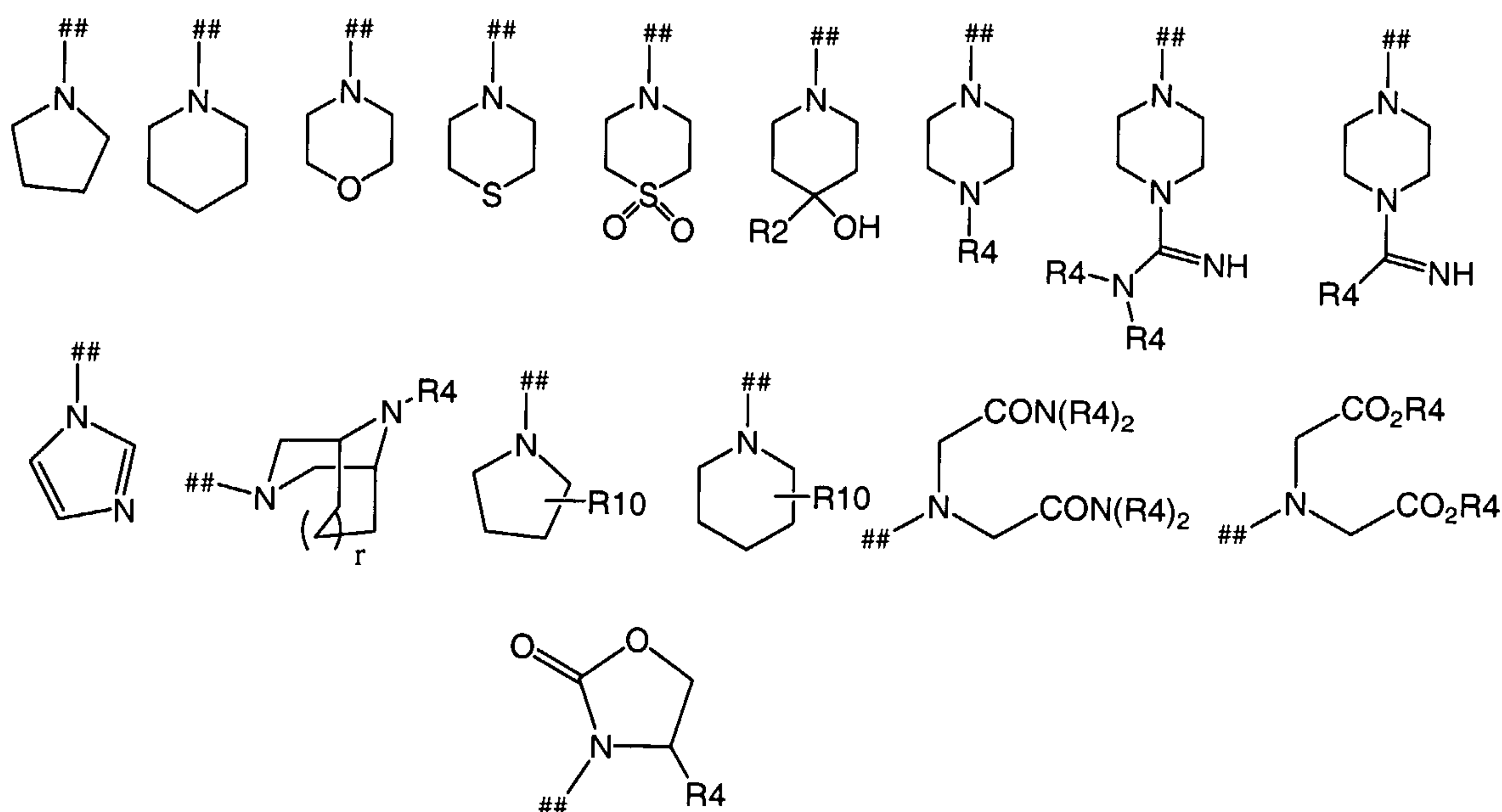
each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocyclyl ring;

each R5 is independently and individually selected from the group consisting of



;

and wherein the symbol (##) is the point of attachment to respective R8, R10, Z1, Z4, Z5, Z6 or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

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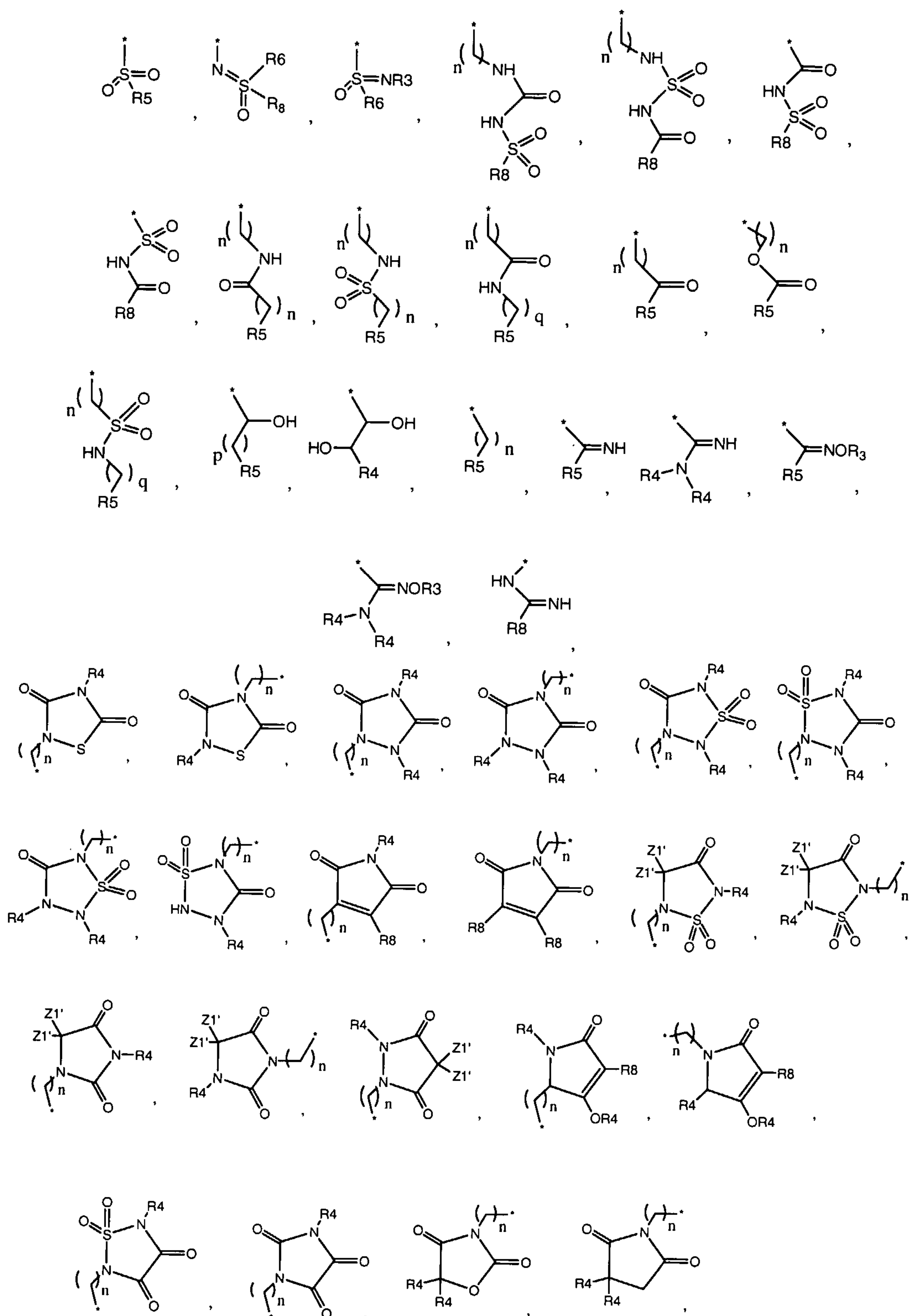
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

each Z1 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC1-C6alkyl, C2-C6alkoxy, C1-C6alkoxyC1-C6alkyl, (R4)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, (R3)₂N-C(=O)-, (R4)₂N-C(=O)-, (R4)₂N-CO-C1-C6alkyl, C1-C6alkoxycarbonyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)₂NSO₂, SOR3, (R4)₂NSO₂, -SO₂R3', -SOR4, -C(=O)R6, -C(=NOH)R6, -C(=NOR3)R6, -(CH₂)_nN(R4)C(O)R8, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocycliloxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocycliloxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



cyano wherein the site of attachment to the A2 ring is meta to the point of attachment to the A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

In the foregoing definition of Z1, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

In the foregoing definition of Z1, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

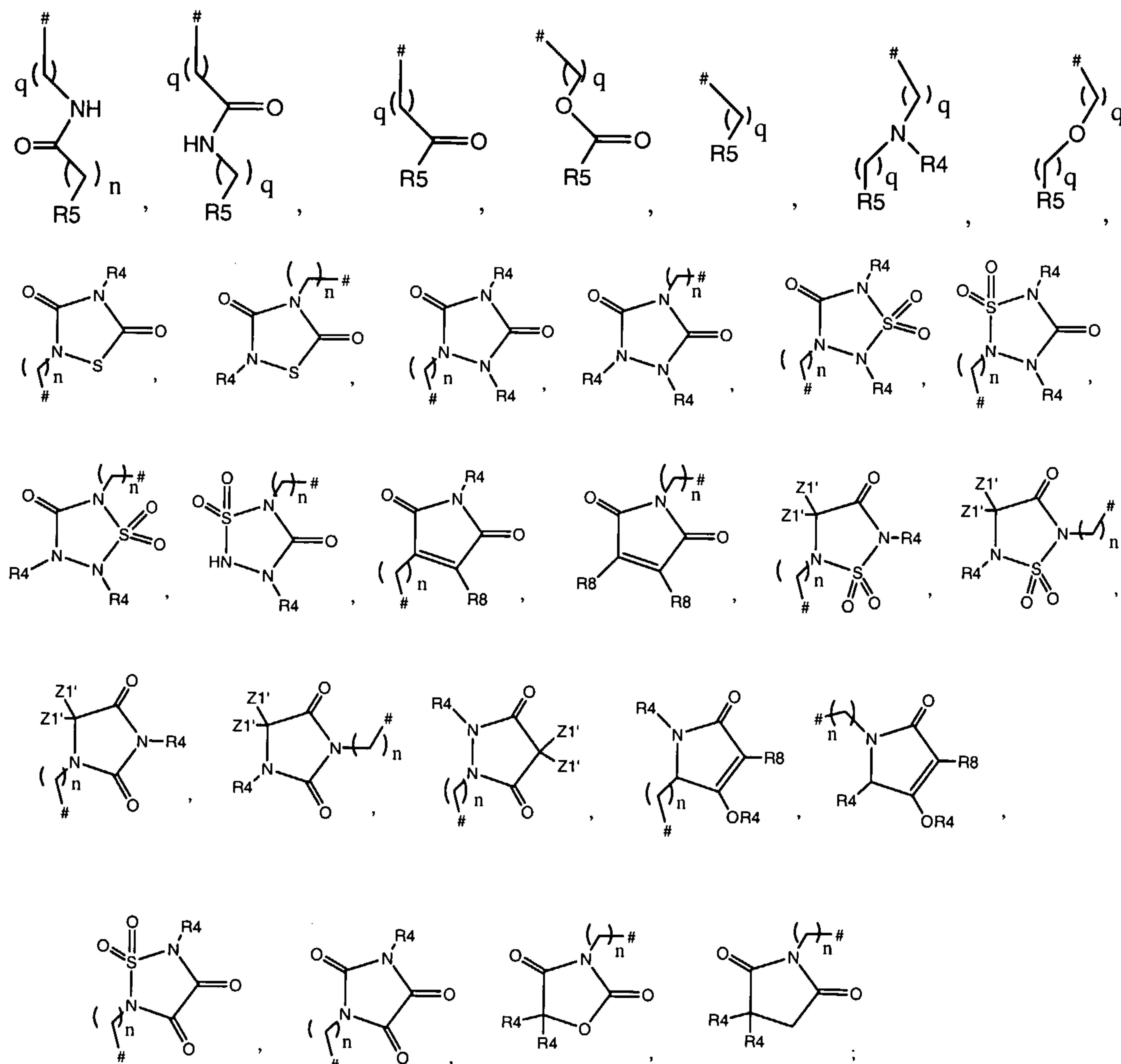
wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1 may cyclize to form a C3-C7 heterocyclyl ring;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_p, (R4)₂N-C2-C6alkylO-(CH₂)_p, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, , heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl; arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, arylamino, heteroarylamino, and heterocyclylamino;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z6 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

4.2.6b

The following specific compounds of Formula I are more preferred: 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea, 1-(3-t-butyl-1-(3-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl)urea

4.2.7 Methods

4.2.7a Methods of Protein Modulation

The invention includes methods of modulating kinase activity of the p38 family of kinases including, but not limited to p38-alpha and other MAP kinases. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 4.2 and 4.2.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

4.2.7b Treatment Methods

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of inflammation, osteoarthritis, respiratory diseases, stroke, systemic shock, immunological diseases, and cardiovascular disease. These methods comprise administering to such individuals compounds of the invention, and especially those of section 4.2 and 4.2.6a, said condition being human inflammation, rheumatoid arthritis, rheumatoid spondylitis, osteo-arthritis, asthma, gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic pulmonary inflammatory disease, bone resorptive diseases, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, and combinations thereof. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

4.2.8 *Pharmaceutical Preparations*

The compounds of the invention, especially those of 4.2 and 4.2.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

4.2.9 *Kinase/Compound Adducts*

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 4.2 and 4.2.6a.

4.3 *Generally – Monocyclic A2 Compounds with Monocyclic E2 Rings*

The invention includes compounds of the formula I as defined in section 2.3 wherein R2 is selected from the group consisting of monocyclic heteroaryl, C1-C6alkyl, branched C3-C7alkyl, a R19-substituted C3-C8carbocyclyl wherein R19 is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, and phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents or chlorine;

4.3.1 *Preferred D Moieties*

4.3.1a

Preferably, the compounds of formula I in 4.3 contain D moieties wherein E1 and E2 are as defined in section 1.3.1a.

4.3.1b

Additionally preferred D moieties of formula I in 4.3 are as defined in section 1.3.1b.

4.3.1c

More preferred D moieties of 3.2.1b are wherein E2 is defined as in section 1.3.1c.

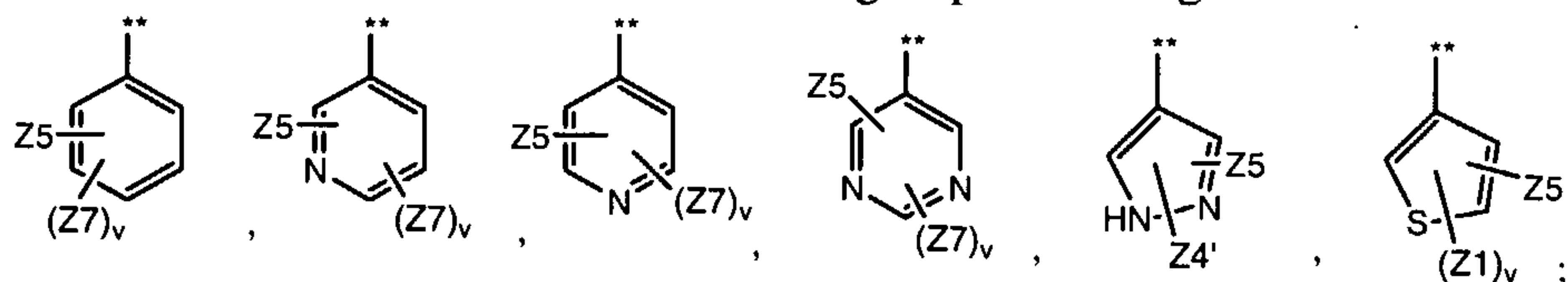
4.3.2 Preferred A2 moieties

4.3.2a

Compounds of Formula I as defined above in section 4.3 have preferred A2 moieties as defined in section 2.2.2a.

4.3.2b

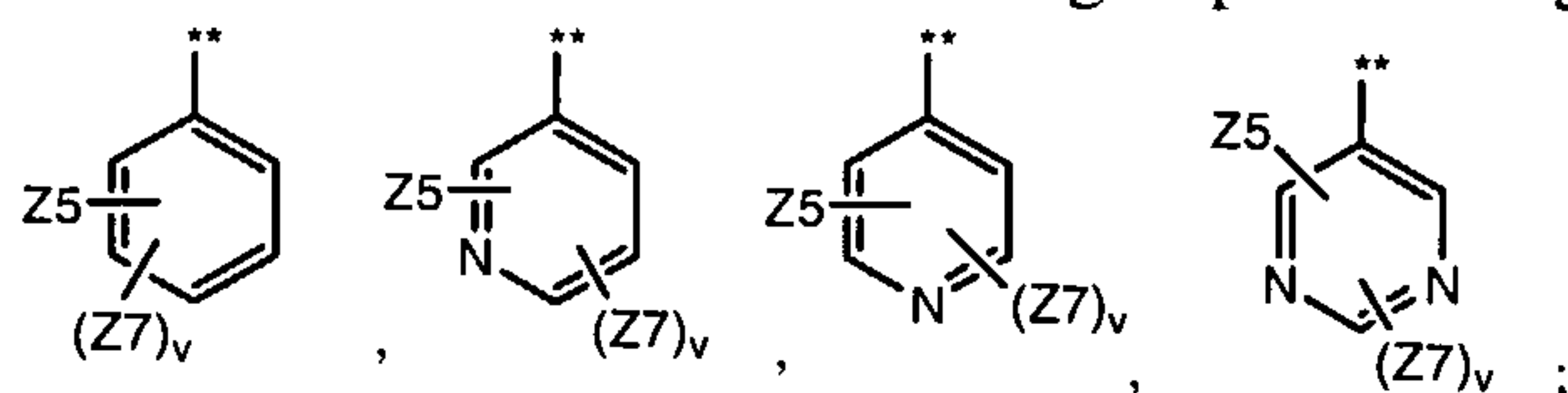
More preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring for formula I.

4.3.2c

Even more preferred A2 moieties are selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the A1 ring of formula I.

4.3.3 Preferred Classes of Compounds

4.3.3a

Compounds as defined in 4.3.1a wherein the A2 group is defined in 4.3.2a.

4.3.3b

Compounds as defined in 4.3.3a wherein the A2 group is defined in 4.3.2b.

4.3.3c

Compounds as defined in 4.3.3a wherein the A2 group is defined in 4.3.2c.

4.3.3d

Compounds as defined in 4.3.1b wherein the A2 group is defined in 4.3.2a.

4.3.3e

Compounds as defined in 4.3.3c wherein the A2 group is defined in 4.3.2b.

4.3.3f

Compounds as defined in 4.3.3c wherein the A2 group is defined in 4.3.2c.

4.3.4 Preferred A1 Moieties

4.3.4a

These preferred A1 moieties are defined in 4.1.4a.

4.3.4b

These more preferred A1 moieties are defined in 4.1.4b.

4.3.4c

These even more preferred A1 moieties are defined in 4.1.4c.

4.3.5 Preferred W and Y Moieties

4.3.5a

(1) W and Y are each NH, and X=O; (2) W=NH, Y=CHR⁴ and X=O; or (3) W=CHR⁴, Y=NH, and X=O.

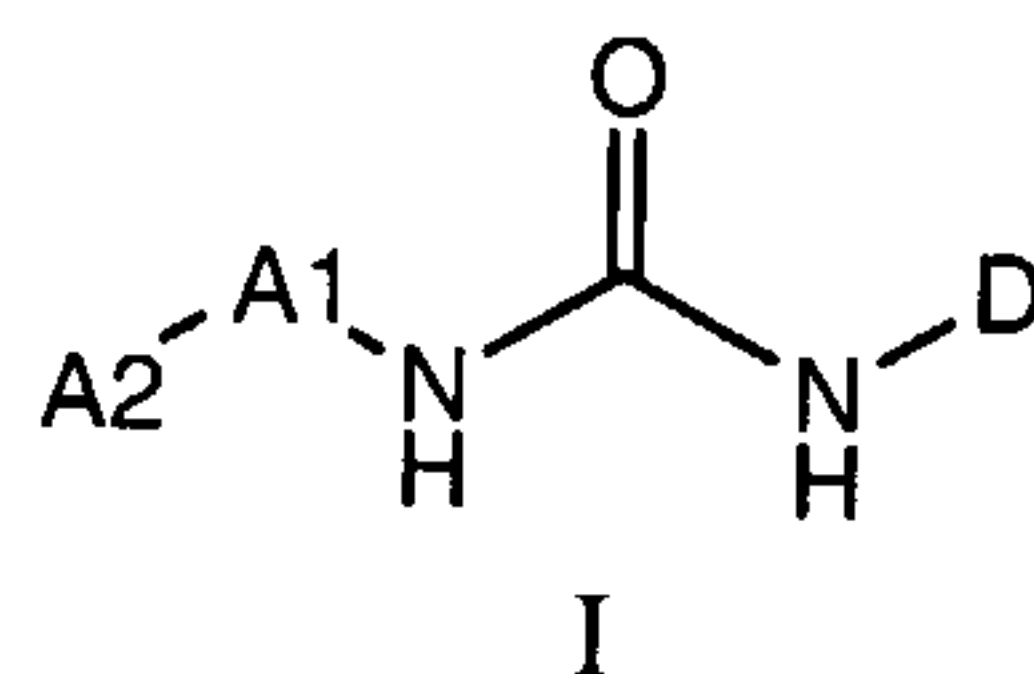
4.3.5b

W and Y are each NH and X=O.

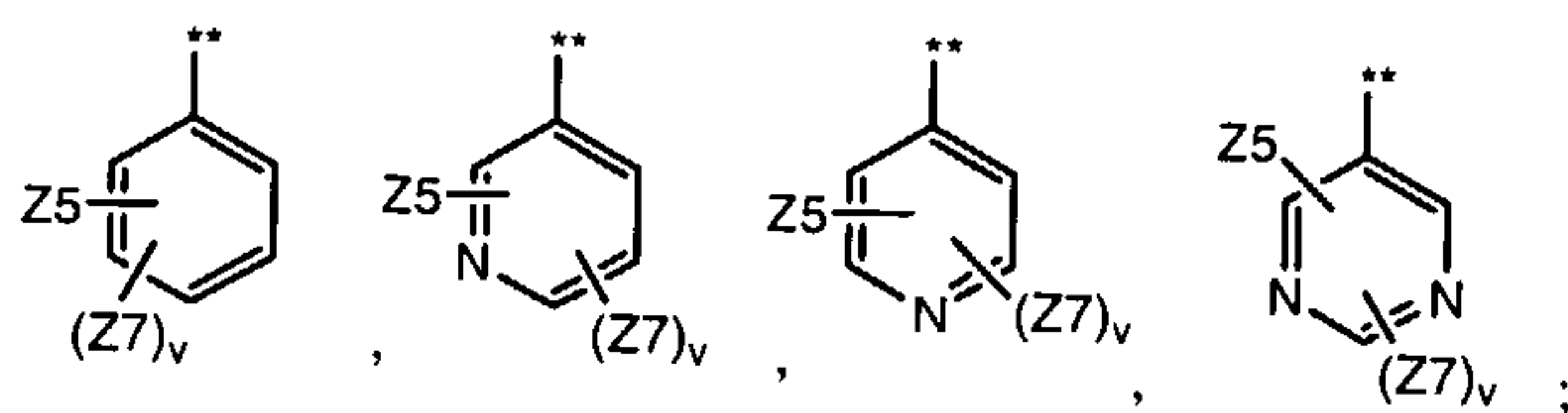
4.3.6 Further Preferred Compounds

4.3.6a

Further preferred compounds are of the formula

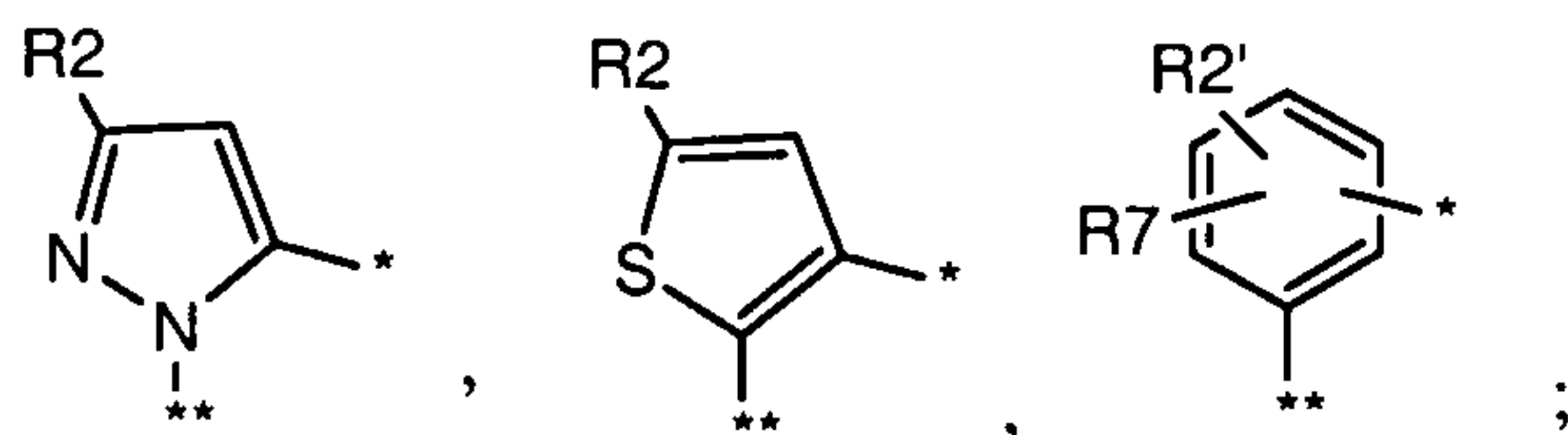


wherein A2 is selected from the group consisting of



wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

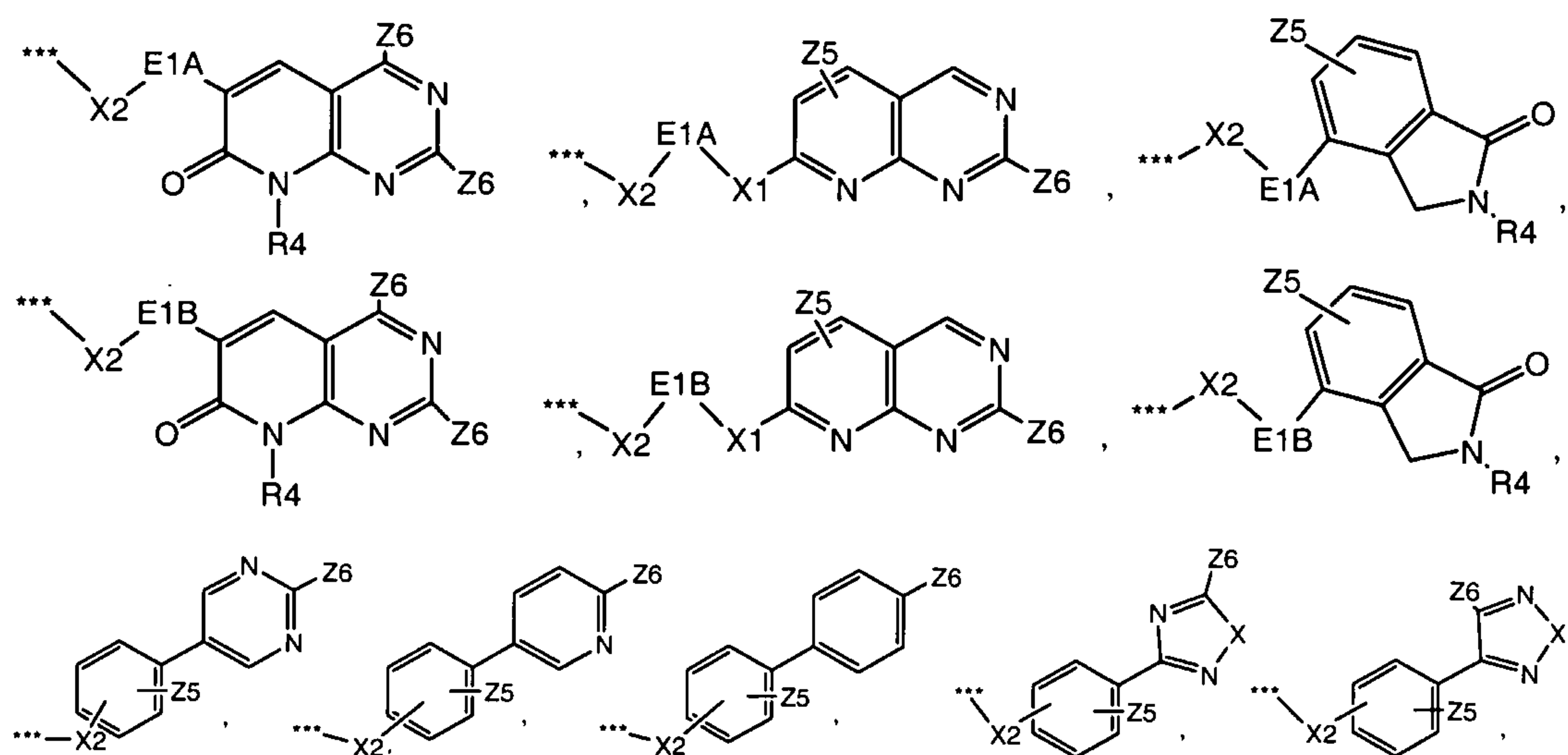
A1 is selected from the group consisting of

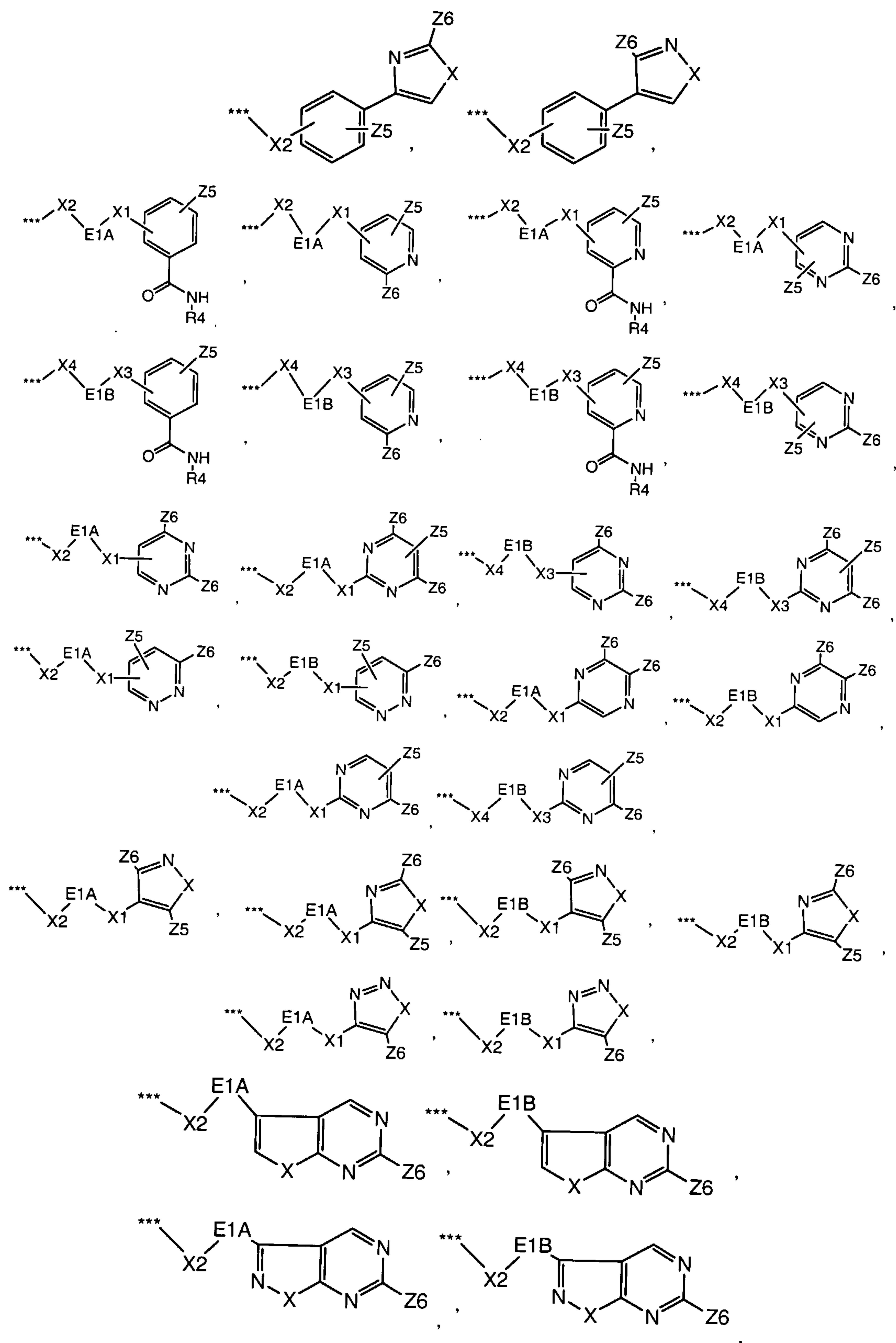


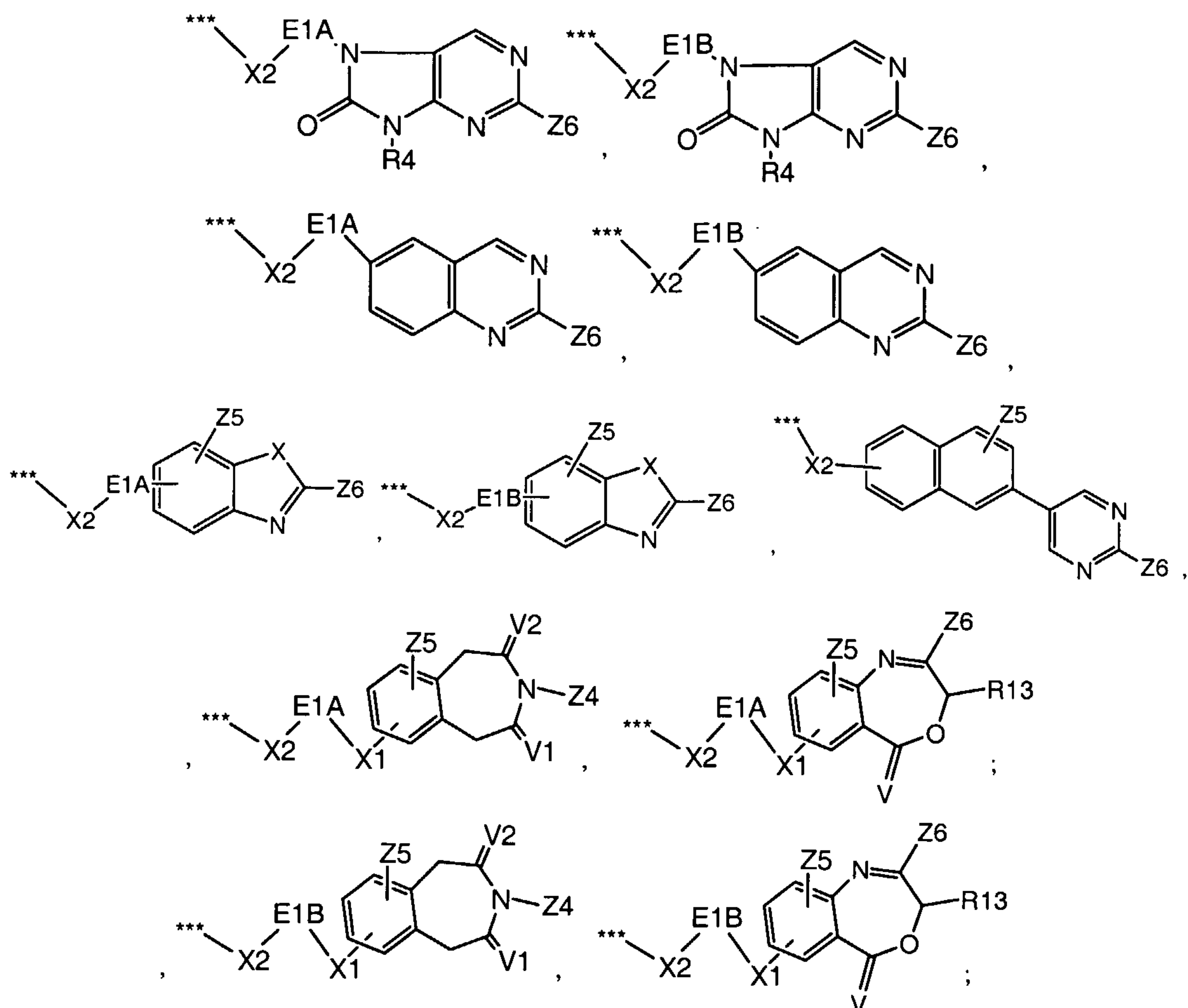
wherein the symbol (*) denotes the attachment to the W moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I;

X is O, S, or NR3;

D comprises a member of 2,3-dichlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3-trifluoromethylphenyl, 3-trifluoromethyl-4-chlorophenyl, 2,3,4-trifluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,5-trifluorophenyl, 3,4,5-trifluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-cyanophenyl, 3-phenoxyphenyl, 4 phenoxyphenyl, 1-naphthyl-2,3-dihydro-1H-inden-1-yl, 1,2,3,4-tetrahydronaphthalen-1-yl, benzo[d][1,3]dioxol-5-yl or benzo[d][1,3]dioxol-4-yl,







wherein E1A is taken from the groups consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl piperidinyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, and pyrimidinyl;

wherein E1B is taken from the groups consisting of phenyl and naphthyl;

wherein E2A is taken from the group comprising naphthyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, triazinyl and fused bicyclic rings selected from the group comprising indolyl, isoindolyl, isoindolinyl, isoindolonyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, imidazopyrimidinyl, imidazolonopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, furylopyrimidinyl, thienopyrimidinyl, phthalimidyl, phthalimidinyl,

pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnoliny, quinoxaliny, quinazoliny, quinoliny, isoquinoliny, phthalaziny, benzodioxyl, indoliny, benzisothiazoline-1,1,3-trionyl, dihydroquinoliny, tetrahydroquinoliny, dihydroisoquinolyl, tetrahydroisoquinoliny, benzoazepiny, benzodiazepiny, benzoxapiny, benzoxazepiny;

wherein E2B is taken from the group consisting of phenyl, pyridyl, and pyrimidyl;

wherein the symbol (***) denotes the attachment to the Y moiety of formula I;

X1 is selected from the group consisting of O, S, NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_p-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the E1 ring and the E2 ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_n-, -(CH₂)_q-, (CH₂)_p, C2-C5alkenyl, and C2-C5alkynyl moieties of X1 may be further substituted by one or more C1-C6alkyl;

X2 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl, or a direct bond wherein E1 is directly linked to the Y group of formula I;

X3 is selected from the group consisting of NR₃, -C(=O)-, -O-(CH₂)_n-, -S-(CH₂)_n-, -NR₃-(CH₂)_n-, -O-(CH₂)_q-O-, -O-(CH₂)_q-NR₃-, -N(R₃)-(CH₂)_q-N(R₃)-, -(CH₂)_n-N(R₄)-C(=O)-, -(CH₂)_n-N(R₄)-C(=O)(CH₂)_n-, -(CH₂)_n-CO-N(R₄)-, -(CH₂)_q-, C2-C5alkenyl, C2-C5alkynyl, C3-C6cycloalkyl, and a direct bond wherein the either the E1B ring or E2B ring are directly linked by a covalent bond;

and wherein the carbon atoms of -(CH₂)_q-, C2-C5alkenyl, and C2-C5alkynyl moieties of X3 may be further substituted by one or more C1-C6alkyl;

X4 is selected from the group consisting of C1-C6 alkyl, C3-C6 branched alkyl;

each R2 is selected from the group consisting of monocyclic heteroaryl, C1-C6alkyl, branched C3-C7alkyl, a R19-substituted C3-C8carbocyclyl wherein R19 is H, or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, and phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents or chlorine;

each R2' is selected from the group consisting of halogen and R2;

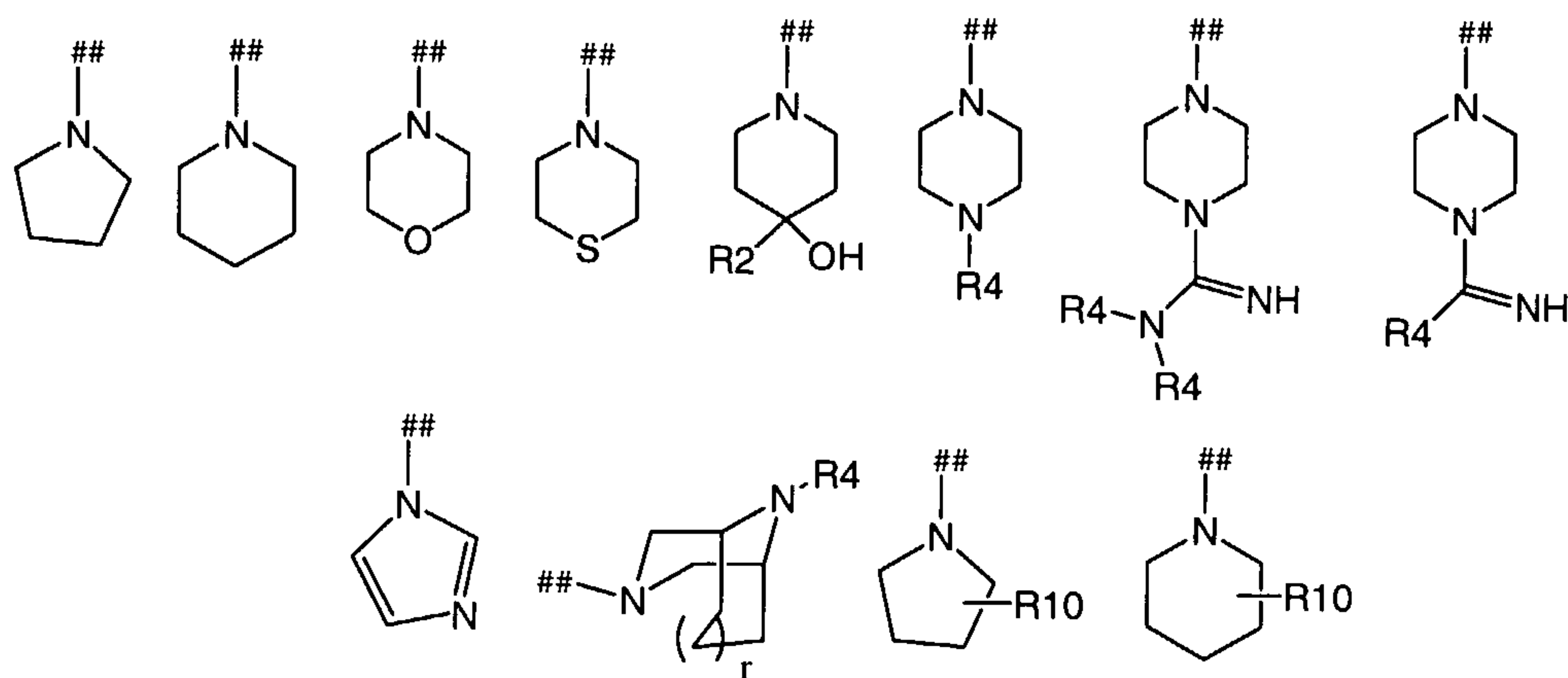
each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, or phenyl;

wherein two R3 moieties independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C7alkyl are attached to the same nitrogen heteroatom, the two R3 moieties may cyclize to form a C3-C7 heterocyclyl ring;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6 alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocyclyl ring;

each R5 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R8, R10, Z4, Z5, Z6 or A2 ring moieties containing a R5 moiety;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R7 is selected from the group consisting of H, halogen, C1-C3fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, C1-C3alkyl, cyclopropyl, cyano, or C1-C3alkoxy;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, C1-C6 fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, branched C4-C7alkyl, carbocyclyl, phenyl, C1-C6phenylalkyl, heteroaryl or heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, or R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R8 may cyclize to form a C3-C7 heterocyclyl ring;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, -N(R4)₂;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R10 may cyclize to form a C3-C7 heterocyclyl ring;

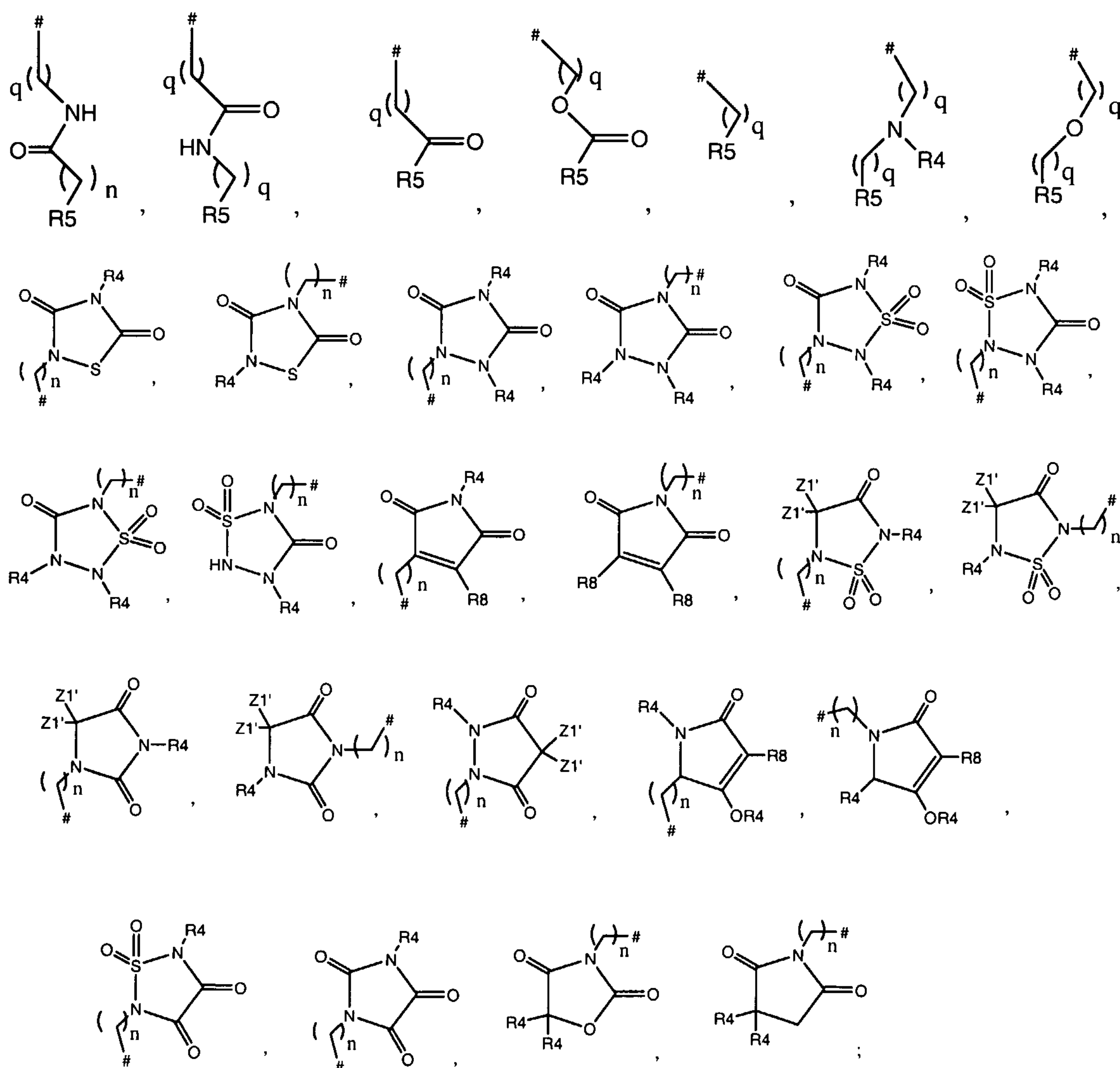
each R13 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, hydroxyC2-C7alkyl, C1-C6alkoxyC2-C7alkyl, (R4)₂N-CO, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_q, R5-C2-C6alkylN(R4)-(CH₂)_q, (R4)₂N-C2-C6alkylO-(CH₂)_q, R5-C2-C6alkyl-O-(CH₂)_q, -(CH₂)_qN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC2-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, and heterocyclylaminoC2-C6alkyl;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of R13 may cyclize to form a C3-C7 heterocyclyl ring;

wherein Z1' is independently and individually selected from the group consisting of H, C1-C6alkyl, C3-C7cycloalkyl, hydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R4)₂N-C1-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-(CH₂)_p, (R4)₂N-C2-C6alkylO-(CH₂)_p, (R4)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl, -(CH₂)_pN(R4)C(O)R8, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC1-C6alkyl, , heteroaryloxyC1-C6alkyl, heterocycliloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, or heterocyclylaminoC1-C6alkyl;

wherein two R⁴ moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z1' may cyclize to form a C3-C7 heterocyclyl ring;

each Z⁴ is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R⁴)₂N-C2-C6alkyl, (R⁴)₂N-C2-C6alkylN(R⁴)-C2-C6alkyl, (R⁴)₂N-C2-C6alkyl-O-C2-C6alkyl, (R⁴)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R⁴)C(O)R⁸, R⁸-C(=NR³)-, -SO₂R⁸, -COR⁸, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocycliloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z4 may cyclize to form a C3-C7 heterocyclyl ring;

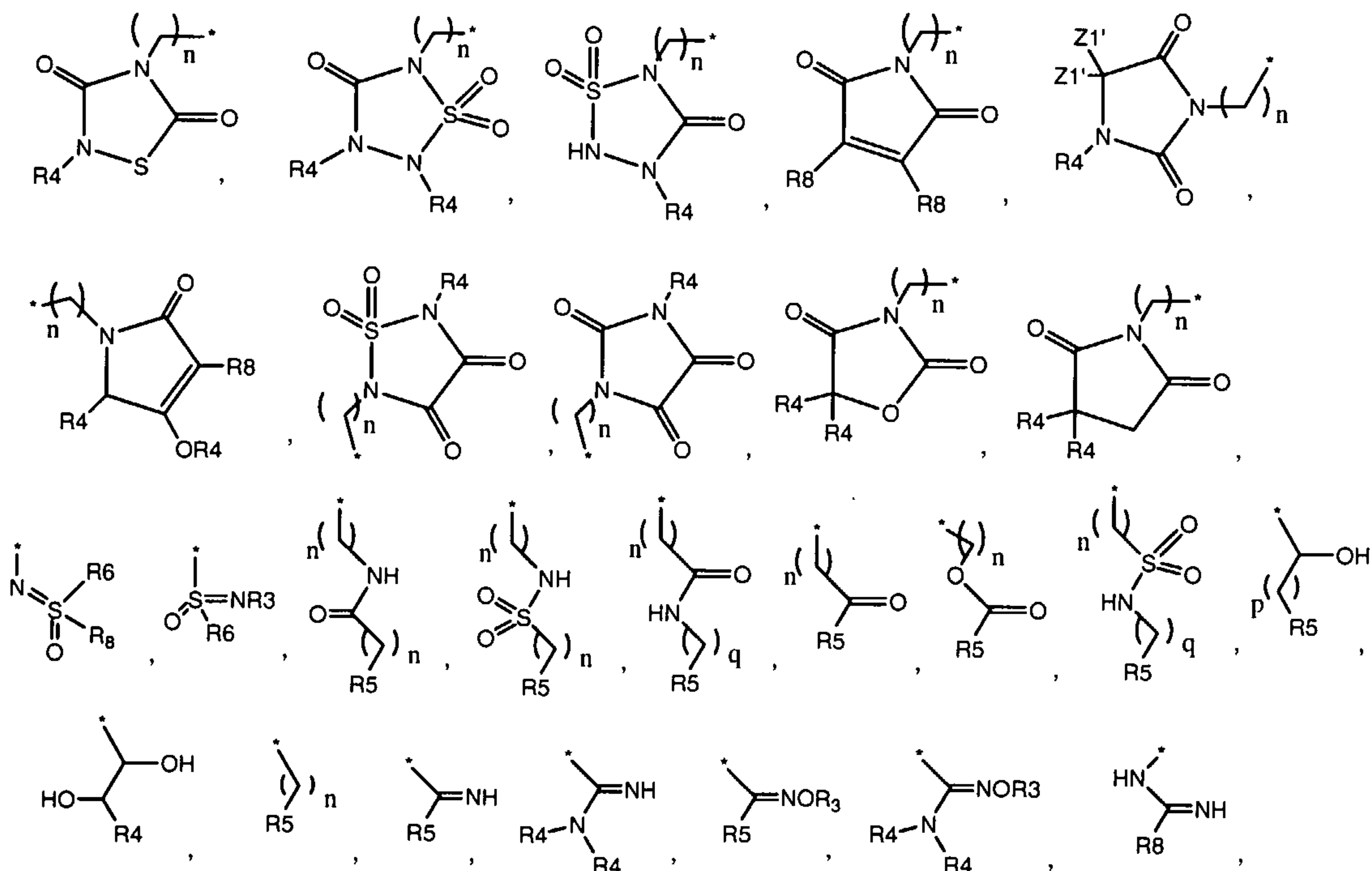
Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z5 may cyclize to form a C3-C7 heterocyclyl ring;

Each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, -SO₂NHR4, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, arylamino, heteroarylamino, and heterocyclylamino;

each Z7 is a substituent attached to a ring carbon and is independently and individually selected from the group consisting of hydroxyC2-C6alkyl, C1-C6alkoxyC1-C6alkyl, (R6)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, (R3)₂N-CO, (R4)₂N-CO, -SO₂R3', SOR3, -SOR4, -C(=O)R6, -C(=NOH)R6, -C(=NOR3)R6, (CH₂)_nN(R4)C(O)N(R4)₂, (CH₂)_nN(R4)C(O)R5, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic heteroarylC1-C6alkyl, monocyclic heterocyclylC1-C6alkyl, monocyclic heteroaryloxy, monocyclic heterocyclyoxy, monocyclic heteroaryloxyC1-C6alkyl, monocyclic heterocyclyoxyC1-C6alkyl, arylamino, monocyclic heteroarylamino, monocyclic heterocyclylamino, arylaminoC1-C6alkyl, monocyclic heteroarylaminoC1-C6alkyl, monocyclic heterocyclylaminoC1-C6alkyl, or moieties of the formulae



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A1 ring and wherein A2 is phenyl, and cyano wherein the site of attachment is to a substitutable position when A2 is pyridyl, pyrimidinyl or a five-membered ring;

In the foregoing definition of Z7, alkyl moieties may optionally be substituted by one or more C1-C6alkyl;

Wherein the asterisk (*) indicates the point of attachment of the Z1 moiety to the A2 ring;

in the event that Z7 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

wherein two R3 moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl and are attached to the same nitrogen heteroatom of Z7 may cyclize to form a C3-C7 heterocyclyl ring;

wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen heteroatom of Z7 may cyclize to form a C3-C7 heterocyclyl ring;

and n is 0-4; p is 1-4; q is 2-6; r is 0 or 1; v is 1 or 2;

and tautomers, diastereomers, geometric isomers, enantiomers, hydrates, prodrugs and salts of any of the foregoing.

4.3.6b

The following specific compounds of Formula I are more preferred: 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-cyclopentyl-1H-pyrazol-5-yl)-3-(3-(8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl)phenyl)urea, 1-(1-(3-(1H-pyrazol-4-yl)phenyl)-3-t-butyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 2-(3-(5-(3-(2,3-dichlorophenyl)ureido)-3-(3-fluorophenyl)-1H-pyrazol-1-yl)phenyl)acetic acid, 2-(3-(5-(3-(2,3-dichlorophenyl)ureido)-3-

(2-fluorophenyl)-1H-pyrazol-1-yl)phenyl)acetic acid, 2-(4-(5-(3-(2,3-dichlorophenyl)ureido)-3-(3-fluorophenyl)-1H-pyrazol-1-yl)phenyl)acetic acid, 2-(4-(5-(3-(2,3-dichlorophenyl)ureido)-3-(2-fluorophenyl)-1H-pyrazol-1-yl)phenyl)acetic acid, 2-(4-(3-cyclopentyl-5-(3-(2,3-dichlorophenyl)ureido)-1H-pyrazol-1-yl)phenyl)acetic acid, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-cyclopentyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-(3-fluorophenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-(2-fluorophenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(2,3-dichlorophenyl)-3-(3-(2-fluorophenyl)-1-(3-(2-(2-hydroxyethylamino)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)urea, 1-(2,3-dichlorophenyl)-3-(1-(3-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)phenyl)-3-(2-fluorophenyl)-1H-pyrazol-5-yl)urea, 1-(3-t-butyl-1-(3-(2-((S)-3-hydroxypyrrolidin-1-yl)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(2-((R)-3-(dimethylamino)pyrrolidin-1-yl)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(1-(4-(2-amino-2-oxoethyl)phenyl)-3-cyclopentyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(2,3-dichlorophenyl)-3-(1-(4-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)phenyl)-3-(2-fluorophenyl)-1H-pyrazol-5-yl)urea, (R)-1-(3-t-butyl-1-(4-(2-(3-hydroxypyrrolidin-1-yl)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, (R)-1-(3-t-butyl-1-(4-(2-(3-methoxypyrrolidin-1-yl)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, (R)-1-(3-t-butyl-1-(4-(2-(3-(dimethylamino)pyrrolidin-1-yl)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(2,3-dichlorophenyl)-3-(3-(2-fluorophenyl)-1-(3-(hydroxymethyl)phenyl)-1H-pyrazol-5-yl)urea, 1-(3-cyclopentyl-1-(3-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-cyclopentyl-1-(3-(2-(2-hydroxyethylamino)-2-oxoethyl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea, 1-(3-t-butyl-1-(3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea. 1-(1-(3-(2-(2,3-dihydroxypropylamino)-2-oxoethyl)phenyl)-3-(2-fluorophenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea, 1-(1-(3-(2-amino-2-oxoethyl)phenyl)-3-(2-fluorophenyl)-1H-pyrazol-5-yl)-3-(naphthalen-1-yl)urea, 2-(3-(3-(2-fluorophenyl)-5-(3-(naphthalen-1-yl)ureido)-1H-pyrazol-1-yl)phenyl)acetic acid,

4.3.7 Methods

4.3.7a Methods of Protein Modulation

The invention includes methods of modulating kinase activity of the p38 family of kinases including, but not limited to p38-alpha and other MAP kinases. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of

the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections 4.3 and 4.3.6a. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

4.3.7b *Treatment Methods*

The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of inflammation, osteoarthritis, respiratory diseases, stroke, systemic shock, immunological diseases, and cardiovascular disease. These methods comprise administering to such individuals compounds of the invention, and especially those of section 4.3 and 4.3.6a, said condition being human inflammation, rheumatoid arthritis, rheumatoid spondylitis, osteo-arthritis, asthma, gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic pulmonary inflammatory disease, bone resorptive diseases, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, and combinations thereof. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

4.3.8 *Pharmaceutical Preparations*

The compounds of the invention, especially those of 4.3 and 4.3.6a may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

4.3.9 *Kinase/Compound Adducts*

The invention also provides adducts in the form of compounds of the invention bound with a species of kinase such as a wild-type kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing. The compounds are advantageously selected from the groups defined in sections 4.3 and 4.3.6a.

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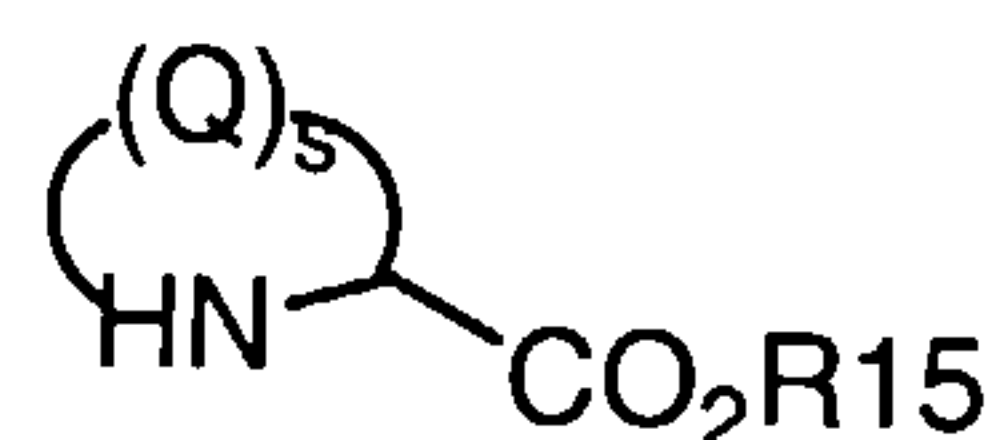
5. Fifth aspect of the invention – Compound Synthesis

Recently, Cu(II)-catalyzed cross coupling reactions have been described for Cu(II) catalyzed cross coupling reactions of aryl or heteroaryl metal reactants with NH-containing heterocycles. These methods have been described by P.Y.S. Lam *et al*, *Tetrahedron Letters* (1998) 39: 2941), P.Y.S. Lam *et al*, *Journal of the American Chemical Society* (2000) 122: 7600; D. M. T. Chan *et al*, *Tetrahedron Letters* (2003) 44: 3863; D. M. T. Chan *et al*, *Tetrahedron Letters* (1998) 39: 2933; D. A. Evans *et al*, *Tetrahedron Letters* (1998) 39: 2937.

5.1 Novel Syntheses

The present invention further provides novel methods for synthesizing the useful compounds. Broadly speaking, the synthesis method comprises the steps:

providing a ring compound of the formula



wherein s is 3 or 4,

the ring compound has two double bonds and one reactable ring NH moiety,

Q is independently and individually selected from the group consisting of N and CR₂, and

R₁₅ is selected from the group consisting of lower alkyl, branched lower alkyl, benzyl, substituted benzyl, or other suitable carboxylic acid protecting group;

each R₂ is selected from the group consisting of C₁-C₆alkyl, branched C₃-C₇alkyl, carbocyclyl, C₁-C₆fluoroalkyl wherein the alkyl group is partially or fully fluorinated;

reacting said ring compound with a compound of the formula

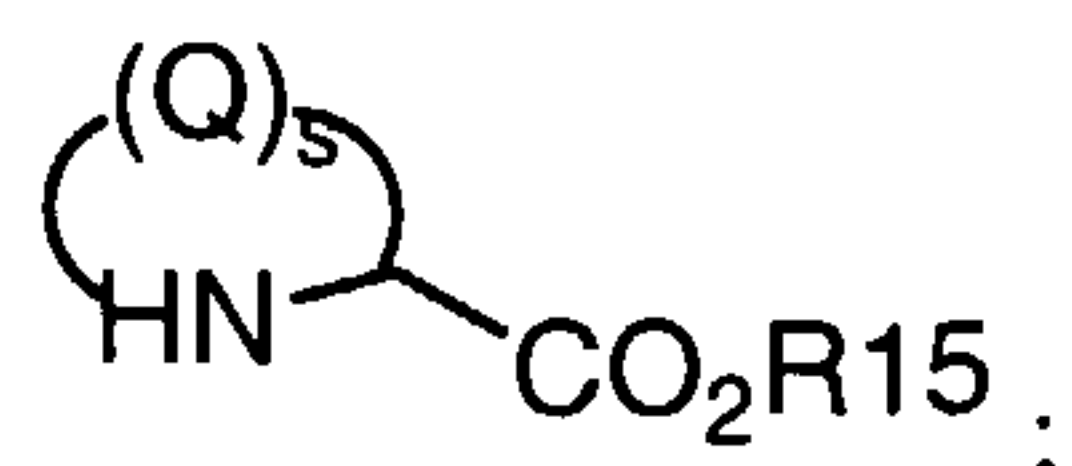
A₃P-M

In the presence of a transition metal catalyst;

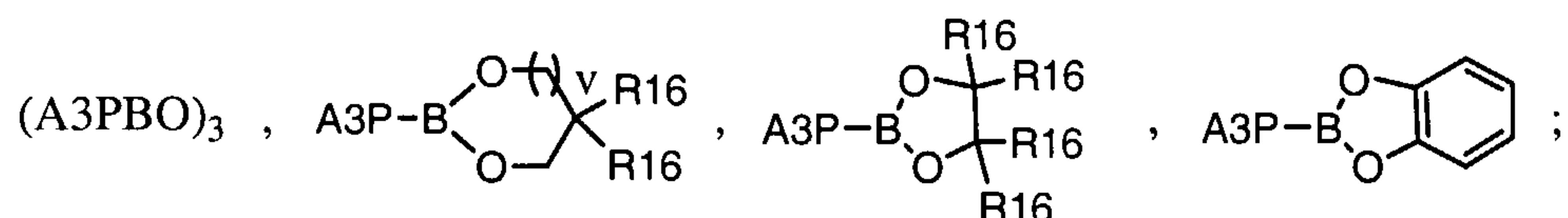
wherein A₃P is a protected form of A₃;

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wherein A3 comprises a member of the group consisting of mono- and poly-aryl, mono- and poly-heteroaryl, mono- and poly-heterocyclyl moieties, P is a protective group wherein A3 is chemically protected so as not to interfere with the reaction of A3P-M with

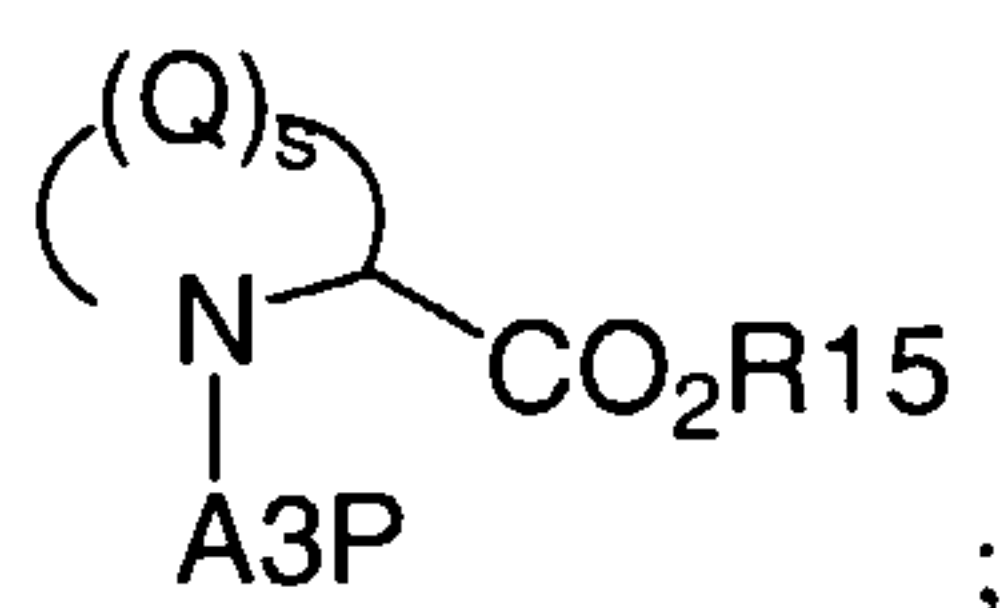


wherein A3P-M is taken from the group consisting of A3P -B(OH)₂, - A3P -B(OR16)₂, - A3P -B(R17)₃M2, - A3P -Si(R18)₃, or A3P -Sn(R16)₃, wherein R16 is taken from lower alkyl or branched lower alkyl, R17 is halogen, R18 is lower alkoxy, and M2 is Li, K, or Na, and from the formulae

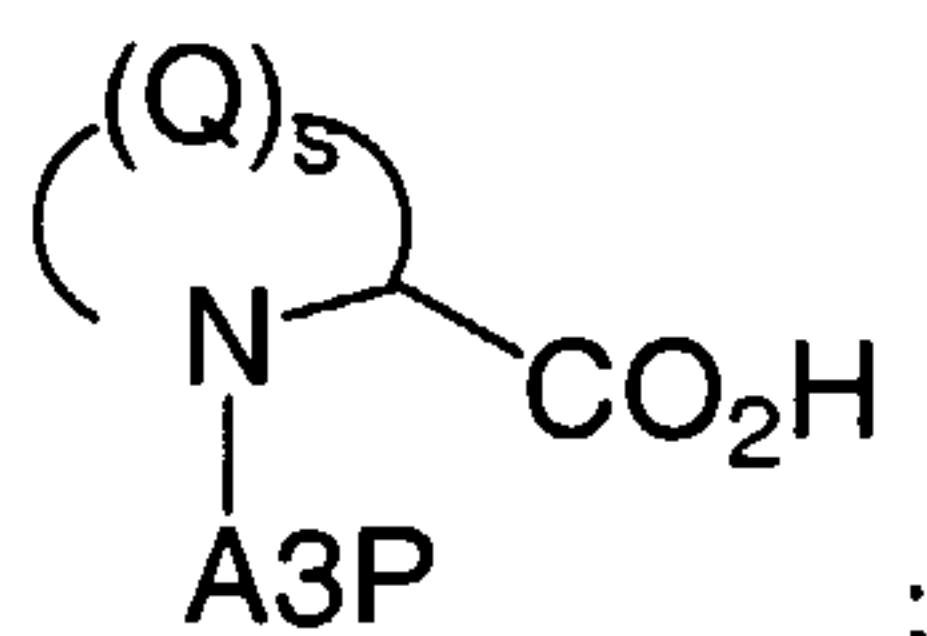


wherein v is 1 or 2;

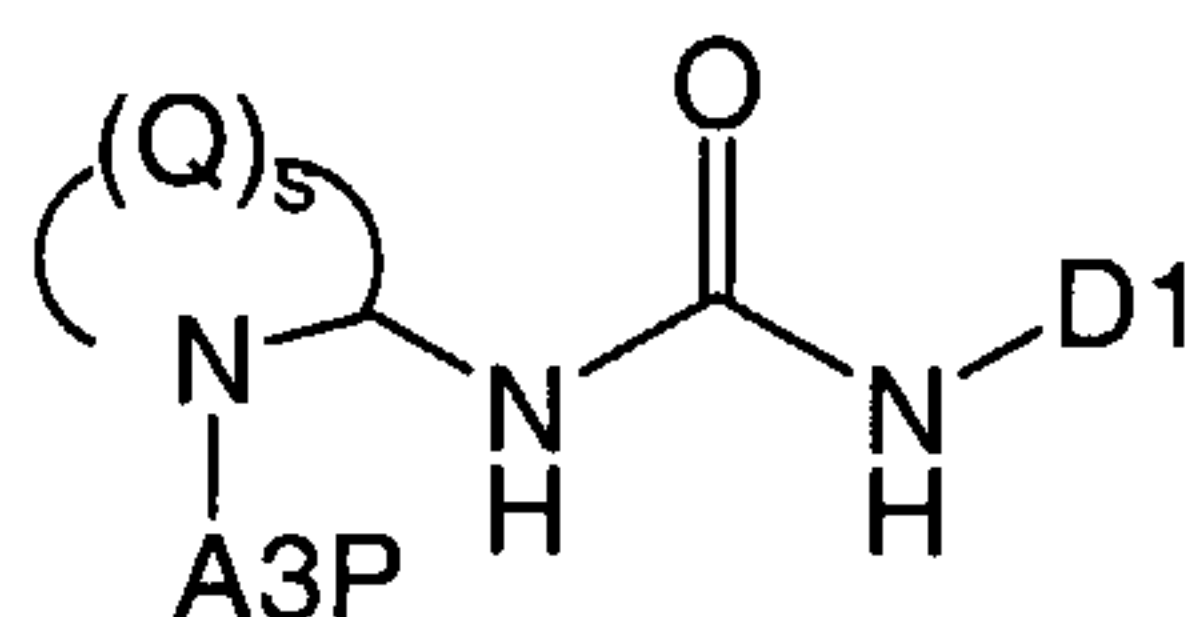
said reaction generating an intermediate compound of the formula



converting said intermediate compound to the carboxylic acid form thereof

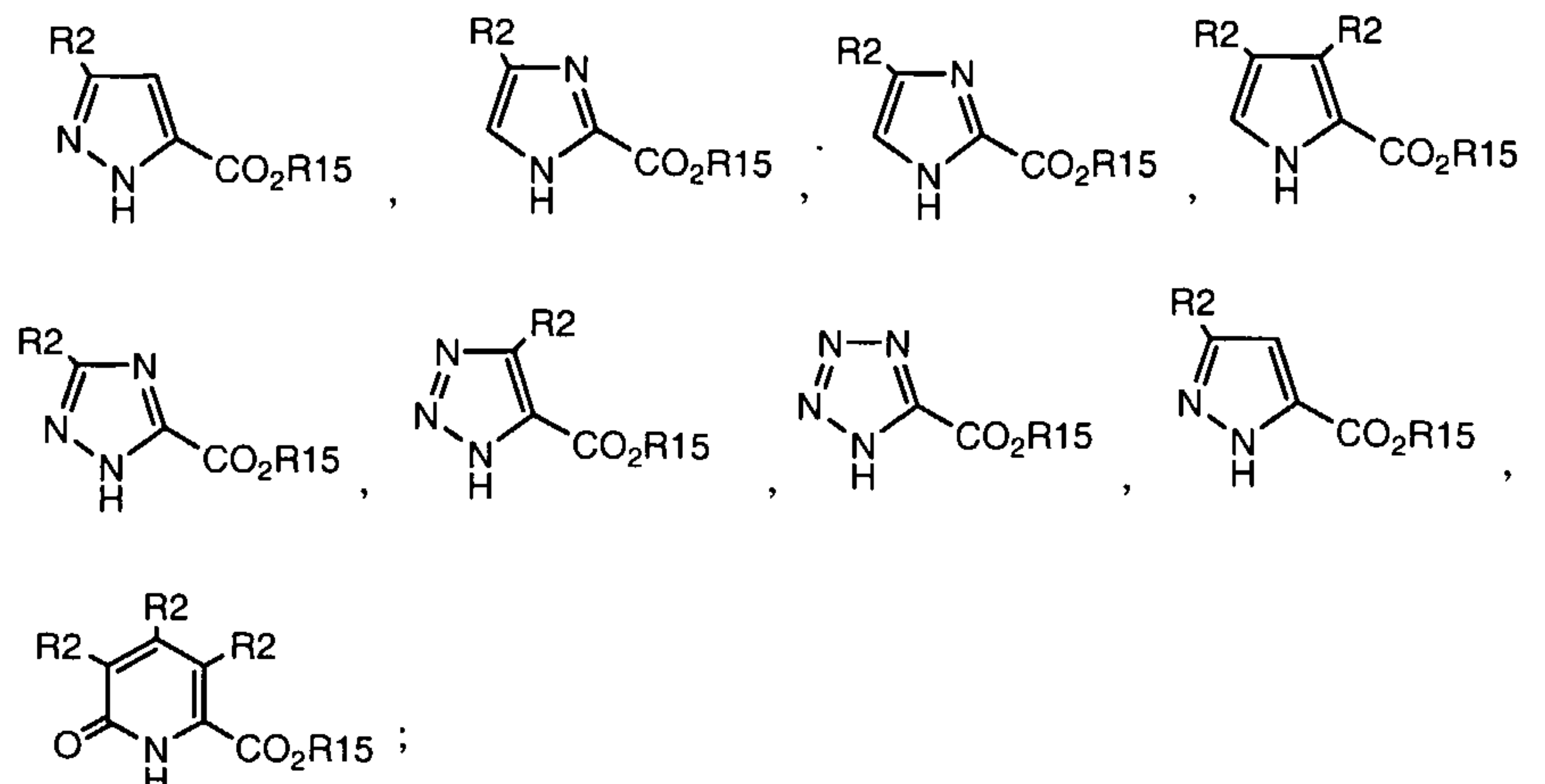


subjecting said carboxylic acid to a Curtius rearrangement in the presence of a compound of formula D1-NH₂, to yield a compound of the formula



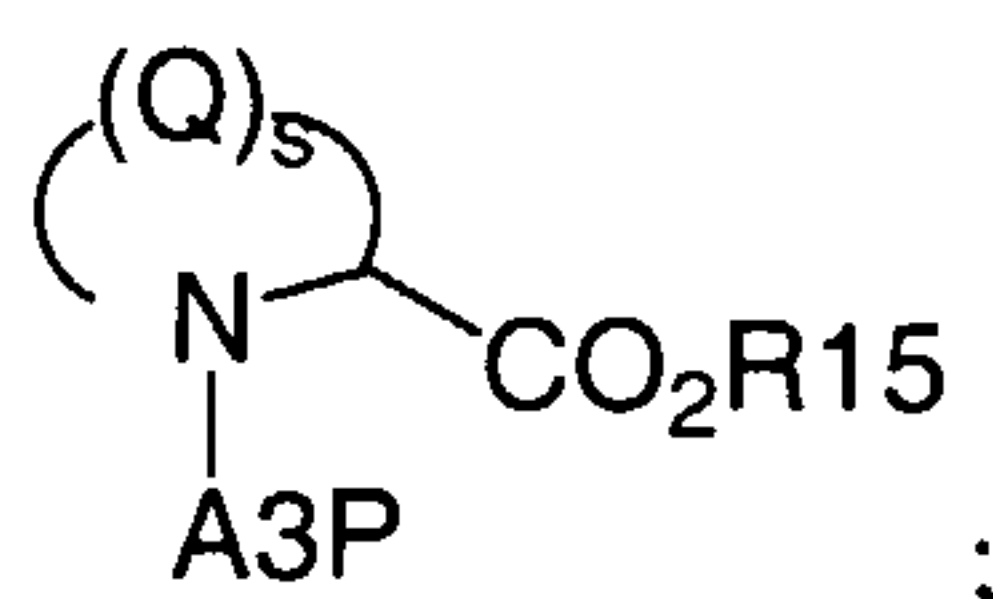
where D1 is selected from the group consisting of mono- and poly-aryl, mono- and poly-heteroaryl, mono- and poly-heterocyclyl.

Preferrably, first step of the method involves using a ring compound taken from the group consisting of



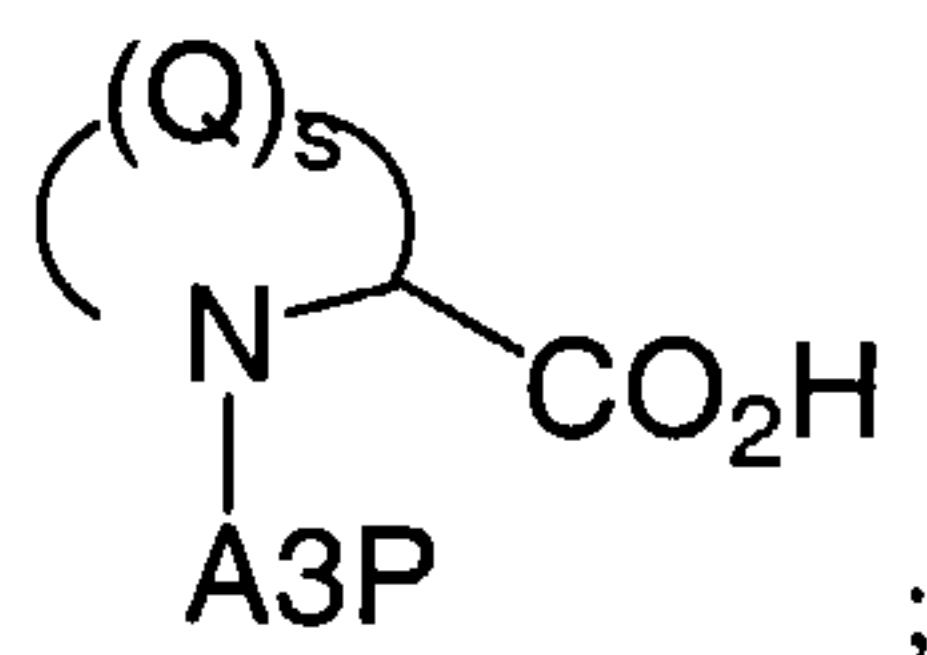
A3P-M is taken from A3P-B(OH)_2 , $\text{A3P-B(OR}_{16}\text{)}_2$, or boroxines $(\text{A3PBO})_3$;

said reaction generating an intermediate compound of the formula

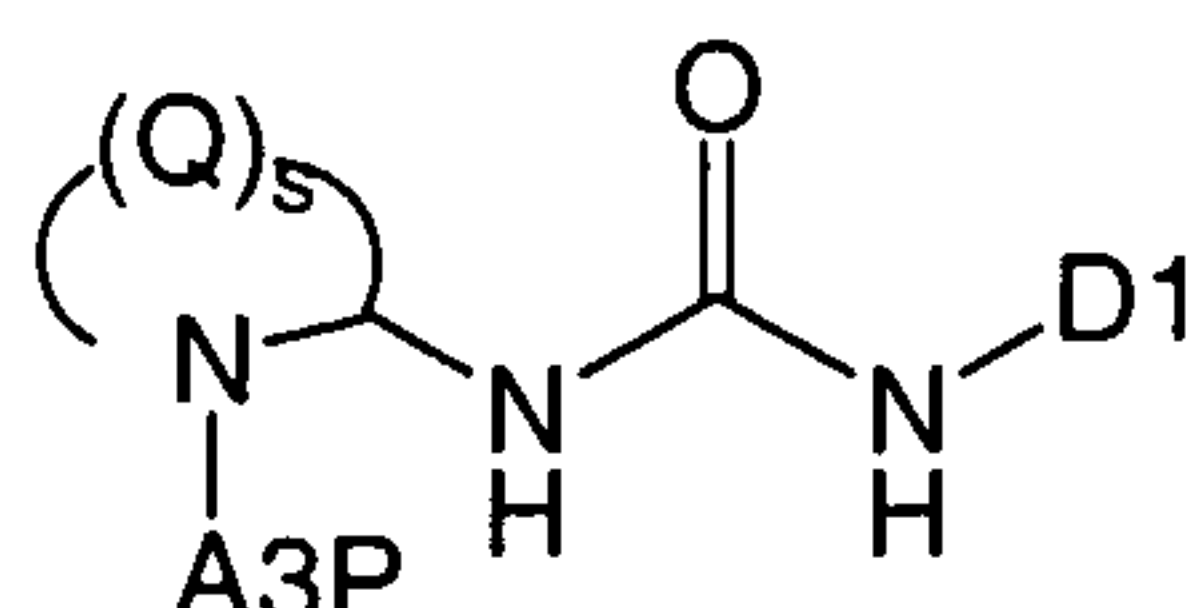


and being catalyzed by a copper(II) catalyst, in an inert solvent taken from the group consisting of dichloromethane, dichloroethane, and N-methylpyrrolidinone, in the presence of a base taken from the group consisting of triethylamine and pyridine, at temperatures ranging from ambient to about 130°C , wherein the reaction is exposed to an atmosphere containing oxygen;

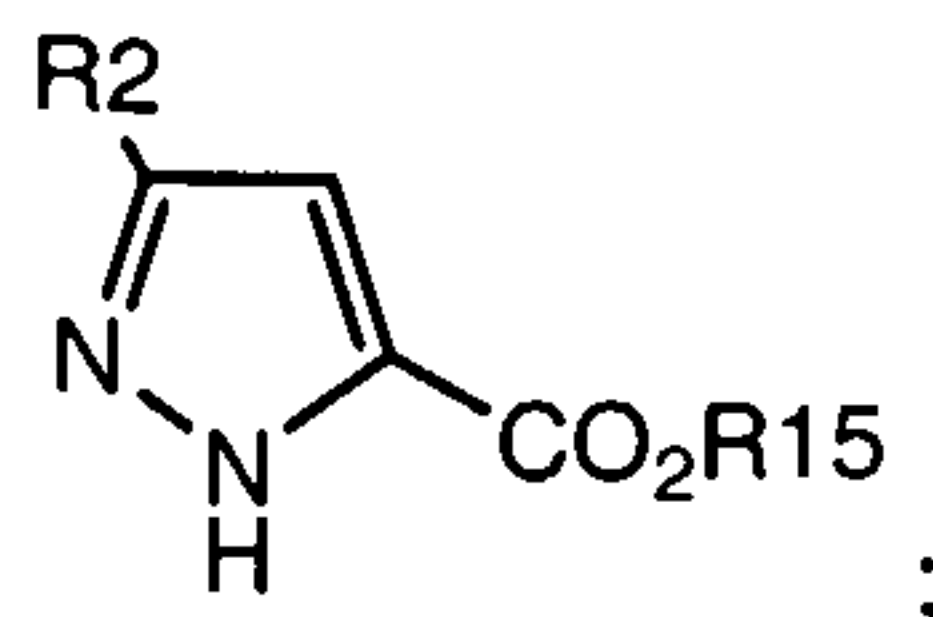
Converting said intermediate compound to the carboxylic acid form thereof



and subjecting said acid form compound to a Curtius rearrangement in the presence of a compound of formula D1-NH_2 , such rearrangement mediated by the use of diphenylphosphoryl azide in an inert solvent taken from the group consisting of toluene, tetrahydrofuran, and dimethoxyethane, and in the presence of a base taken from the group consisting of triethylamine, pyridine, and di-iso-propylethylamine, at temperatures ranging from 80°C to 110°C to yield a desired compound of the formula

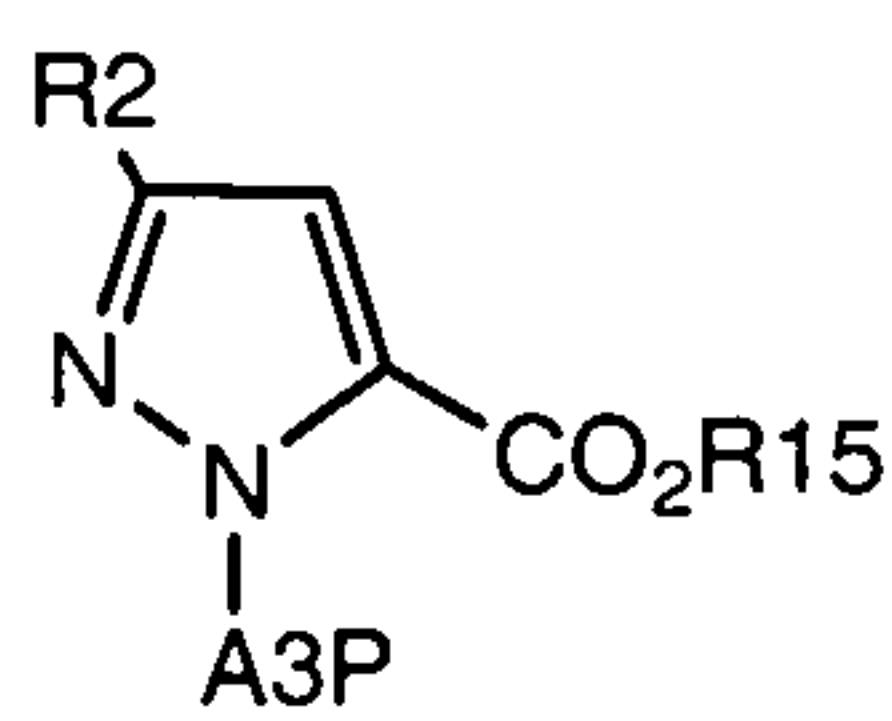


Still more preferably, the starting ring compound is selected from the group consisting of

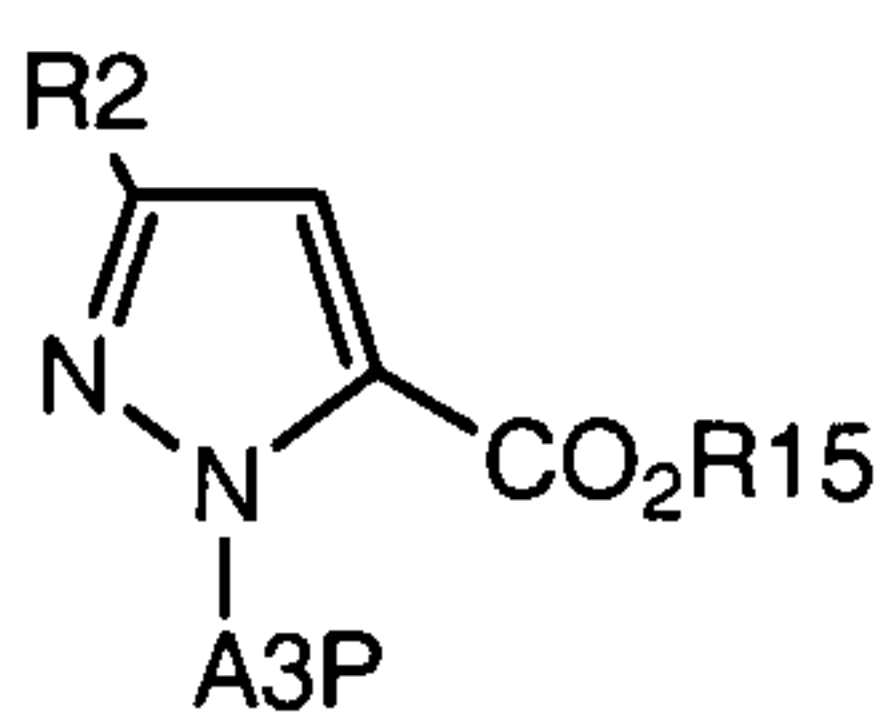


A3P-M is taken from A3P-B(OH)₂, A3P-B(OR₁₅)₂, or boroxines (A3PBO)₃;

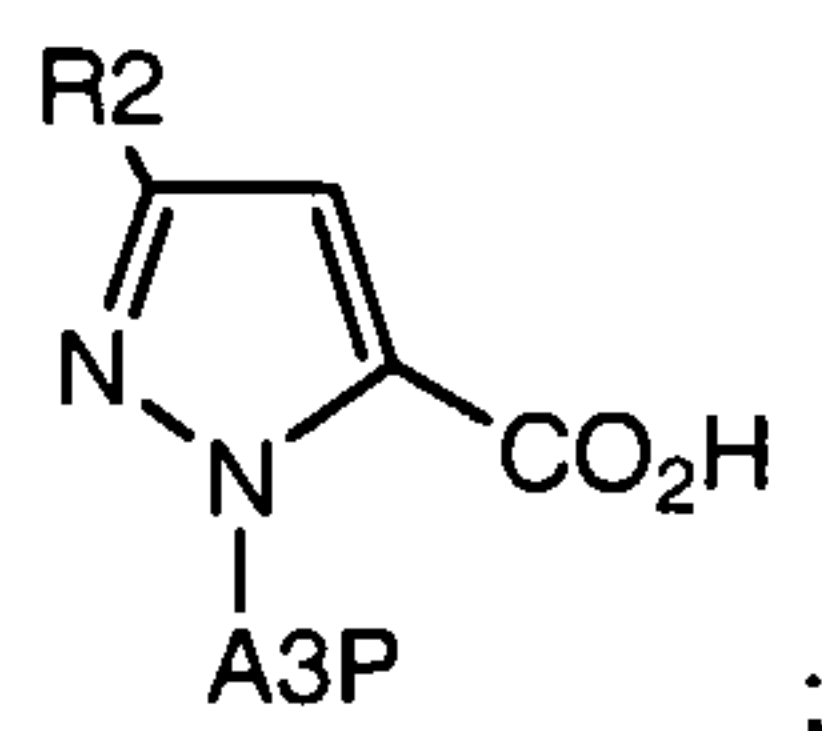
said reaction generating an intermediate compound of the formula



said catalyst comprising copper(II) acetate, said reaction being carried in an inert solvent, selected from the group consisting of dichloromethane, dichloroethane, and N-methylpyrrolidinone, in the presence of a base from the group consisting of triethylamine and pyridine, and in the presence of 4 angstrom sieves at ambient temperature, wherein the reaction is exposed to air, to generate an intermediate compound of the formula



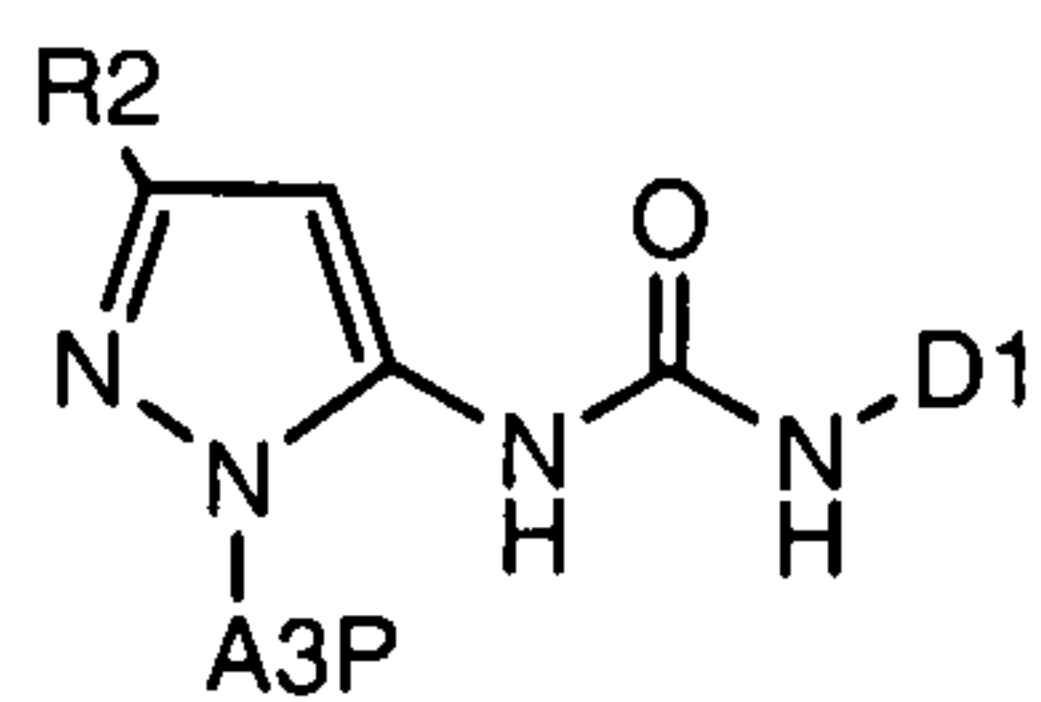
converting said intermediate compound to the carboxylic acid form thereof



subjecting said carboxylic acid form intermediate to a Curtius rearrangement in the presence of a compound of formula D1-NH₂, such rearrangement mediated by the use of diphenylphosphoryl azide in an inert solvent taken from the group consisting of toluene, and in the presence of triethylamine at temperatures ranging from 80°C to 110°C to yield a desired compound of the formula.

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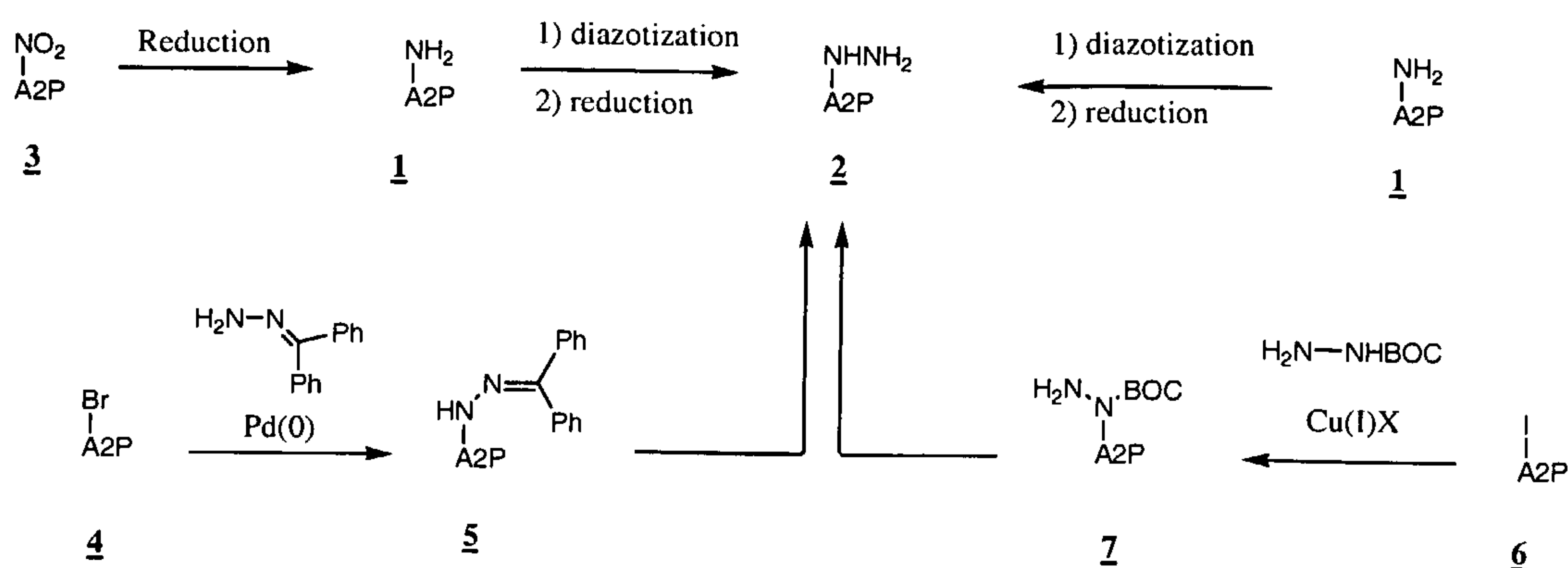


5.2 Other syntheses

The preparation of intermediates containing A1 rings and their subsequent conversion into compounds of Formula I is illustrated in the following schemes. Throughout this specification, A2P refers to a protected form of A2, as defined above, wherein the Z1, Z2, Z3, or Z4 moieties or heteroatoms attached to A2 are suitably protected to allow their use in multi-step chemistry.

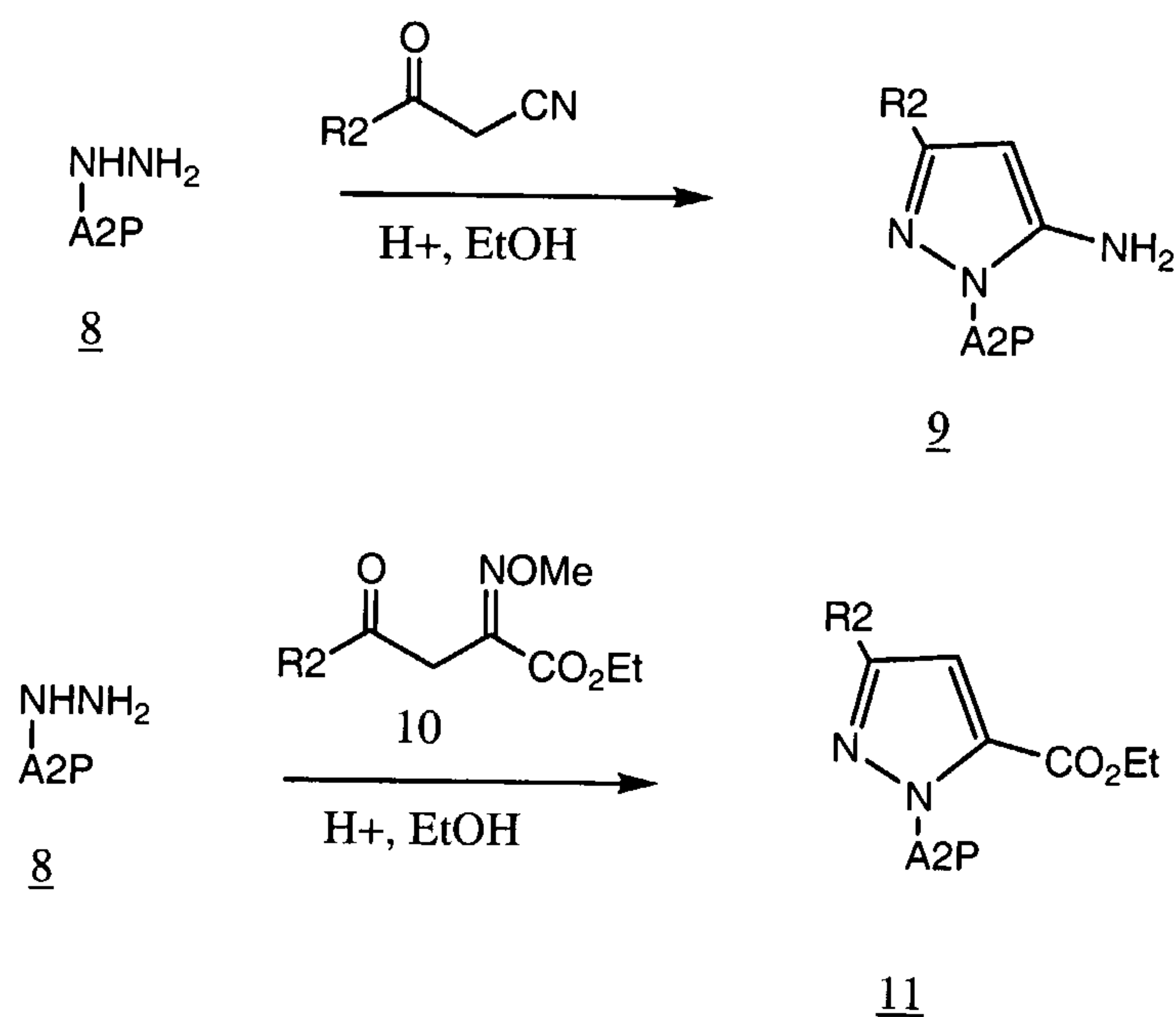
The preparation of intermediates wherein A1 is taken from pyrazolyl A1-1 is illustrated in Schemes 1 through 4. Scheme 1 illustrates the preparation of hydrazines 2. If the amine precursors 1 are readily available, they are converted to the hydrazines 2 by a diazotization/reduction sequence. Preferred conditions react 1 with NaNO₂ in aqueous HCl to form the diazonium salt at about 0C in aqueous solvent or an aqueous/organic cosolvent. The diazonium salt is not isolated, but directly reduced by reaction with SnCl₂.2H₂O under acidic conditions, preferably aqueous HCl at between about 0C and room temperature. The hydrazines 2 are isolated as the HCl addition salts. If the amine precursors 1 are not directly available, they can be formed from the nitro-substituted A2P precursors 3 by reduction, preferably with iron/HCl, SnCl₂.2H₂O, or catalytic hydrogenation, to give the requisite amines 1. Conversion to the hydrazines 2 is accomplished as described above. Alternatively, reaction of the aryl or heteroaryl bromides 4 with benzophenone hydrazone and a palladium catalyst, preferably with Pd(OAc)₂ and DPPF as ligand, can afford the protected hydrazines 5, which are deprotected under acidic conditions, preferably *p*-toluenesulfonic acid or ethanolic HCl, to give rise to the desired hydrazines 2 (Hartwig, J.F., *et al*, *Angew. Chem. Int. Ed.* (1998) 37: 2090; Haddad, N., *et al*, *Tetrahedron Letters* (2002) 43: 2171-2173). Alternatively, reaction of the aryl or heteroaryl iodides 6 with *t*-butylcarbazate and a copper (I) catalyst, preferably CuI in DMF at about 80C with Cs₂CO₃ base and a ligand such as 1,10-phenanthroline, can afford the BOC-protected hydrazines 7, which are converted to the desired hydrazines 2 by treatment with acid (M. Woltor *et al*, *Organic Letters* (2001) 3: 3803-3805).

Scheme 1



Preparation of pyrazoles 9 and 11 are illustrated in Scheme 2. Reaction of hydrazines 8 with *beta*-ketonitriles in an alcoholic solvent, preferably EtOH, and an acid catalyst, preferably HCl or p-toluenesulfonic acid, at about 80C gives aminopyrazoles 9. Analogous treatment of hydrazines 8 with the ethyl 2-(methoxyimino)-4-oxobutanoates 10 affords the pyrazole ethyl esters 11 (Lam, P.Y.S., *et al*, *Journal of Medicinal Chemistry* (2003) 46: 4405-4418).

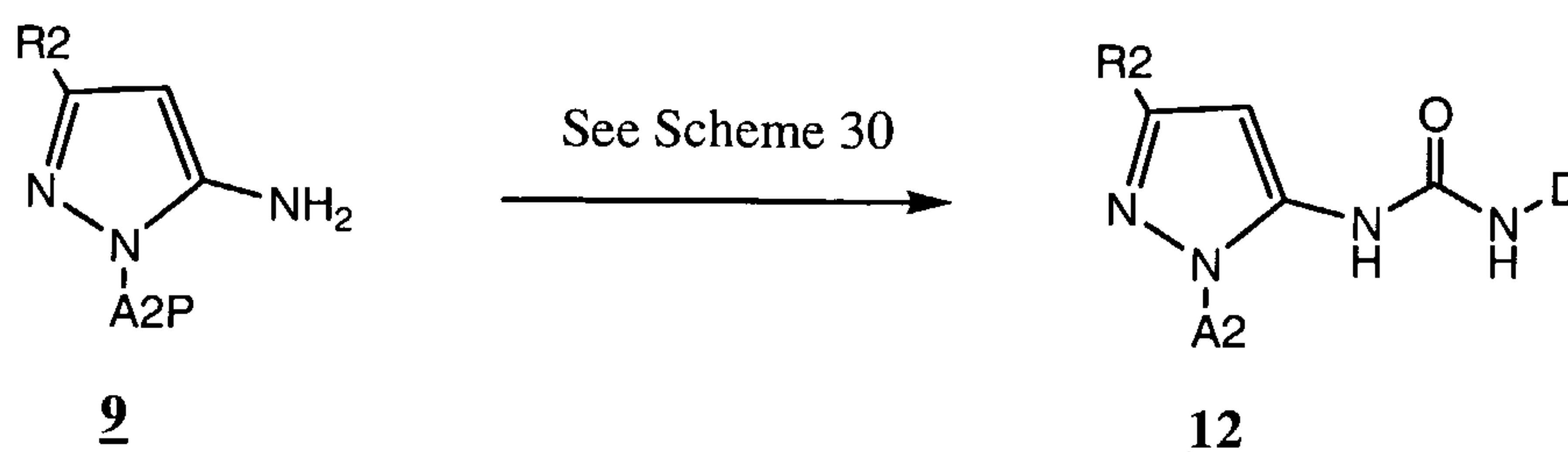
Scheme 2



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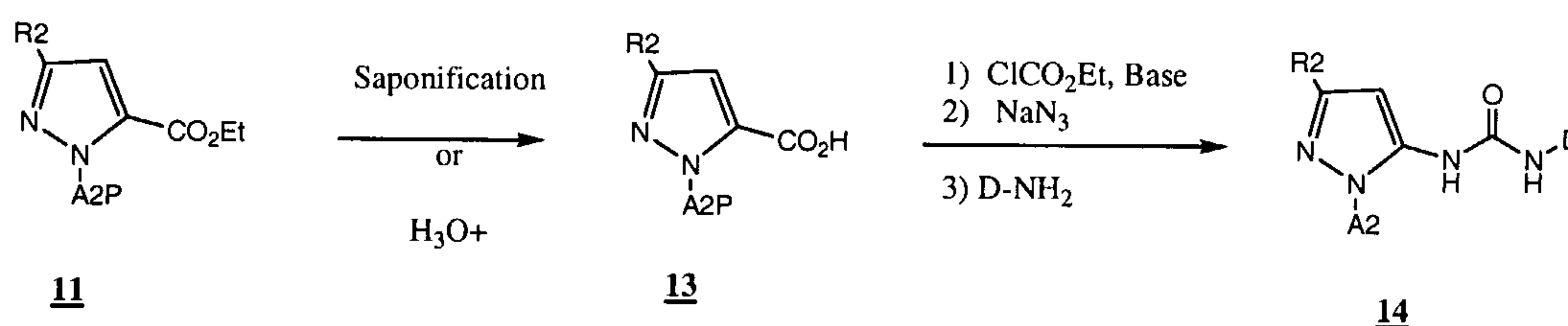
The aminopyrazoles 9 are converted into the desired pyrazole ureas 12 of Formula I (see Scheme 3) by methods described in Scheme 30 for the conversion of the aminothiophene into ureas of Formula I.

Scheme 3



Alternatively, pyrazole ureas of Formula I can be formed from the pyrazole ethyl esters 11 by a sequence illustrated in Scheme 4. Conversion of esters 11 to the carboxylic acids 13 is accomplished by saponification or by treatment with aqueous acid. Curtius-type rearrangement of 13, preferably by treatment with ethyl chloroformate and base, preferably triethylamine, in an organic solvent, preferably THF at about 0°C, and then forming the acyl azide by reaction with sodium azide, and quenching of the *in situ* rearranged isocyanate with D-NH₂ gives rise to the desired pyrazole ureas 14 of Formula I (El Haddad, M. *et al*, *Journal of Heterocyclic Chemistry* (2000) 37: 1247-1252).

Scheme 4



The synthesis of pyrazoles of formula I wherein A1 is A1-2 is exemplified in Scheme 5. Aryl halide 15 (bromo or iodo (preferred)) is reacted with acetylene 16 [CAS 22537-06-0] under standard palladium cross-coupling conditions to yield 17. As described by Coispeau *et. al* (Bull. Chem. Soc. France, 1970, 689-696), 17 reacts monosubstituted hydrazines in the presence of catalytic mineral acid to yield pyrazole 18, which is readily nitrated under

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

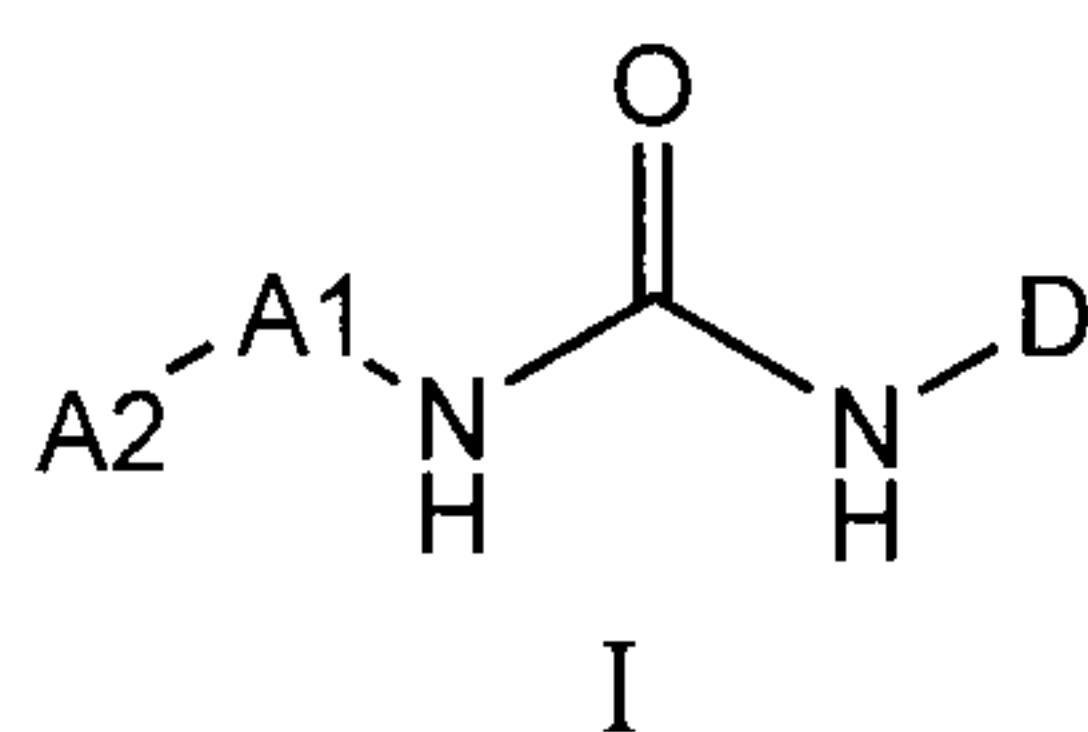
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THAN ONE VOLUME.**

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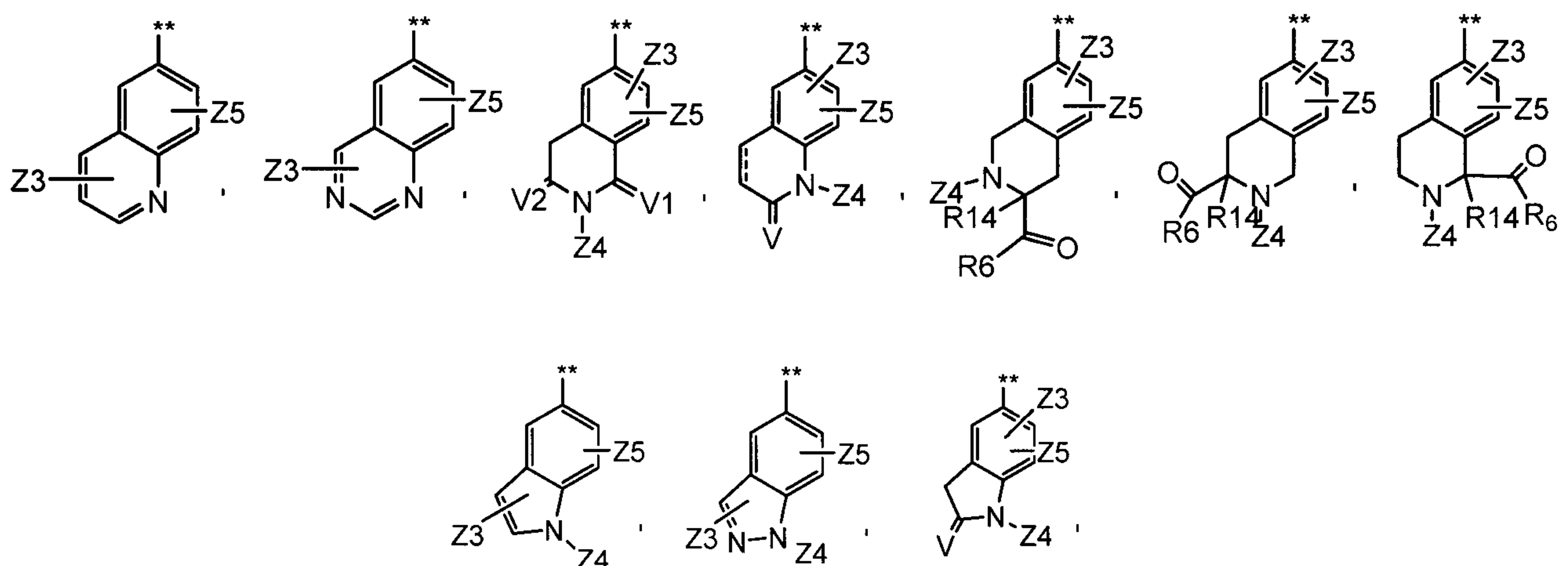
NOTE: For additional volumes please contact the Canadian Patent Office.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A compound of the formula



wherein A2 is a bicyclic fused heteroaryl selected from the group consisting of



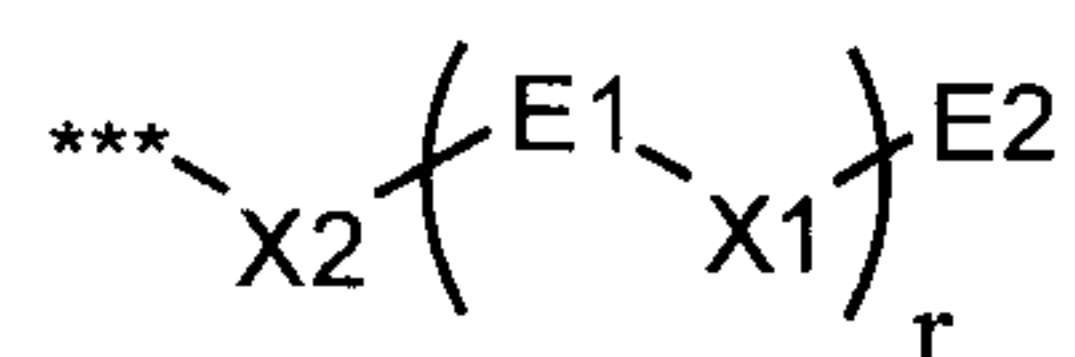
and wherein the symbol (**) is the point of attachment to the A1 ring of formula I;

and wherein ----- indicates either a saturated or an unsaturated bond;

wherein each Z3 and Z5 may be independently attached to either of the rings making up the foregoing bicyclic structures;

A1 is R2-substituted monocyclic 5-membered ring heteroaryl selected from pyrazole or thiophene;

D is a moiety of the formula



wherein E1 is phenyl;

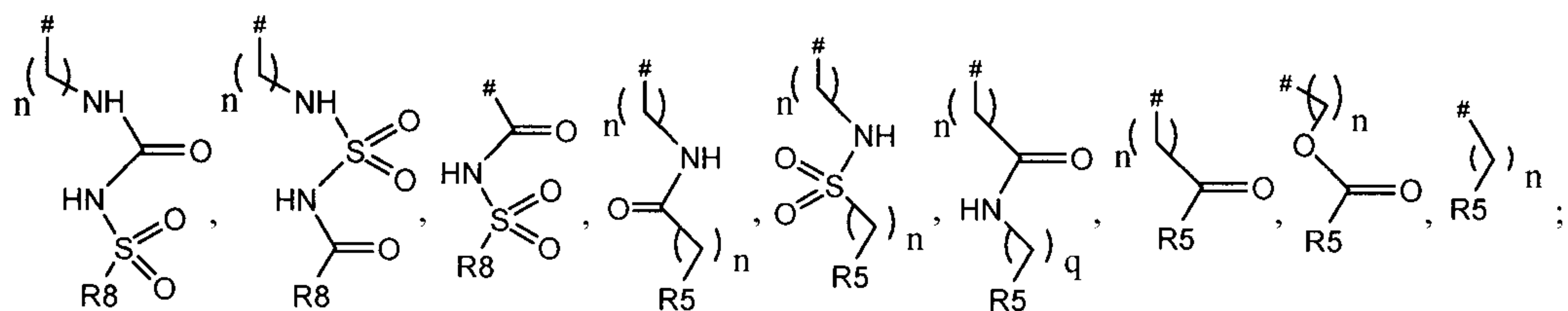
wherein the symbol (***) is the point of attachment to the NH moiety of formula I;

X1 is O;

X2 is a direct bond wherein E1 is directly linked to the NH moiety of formula I;

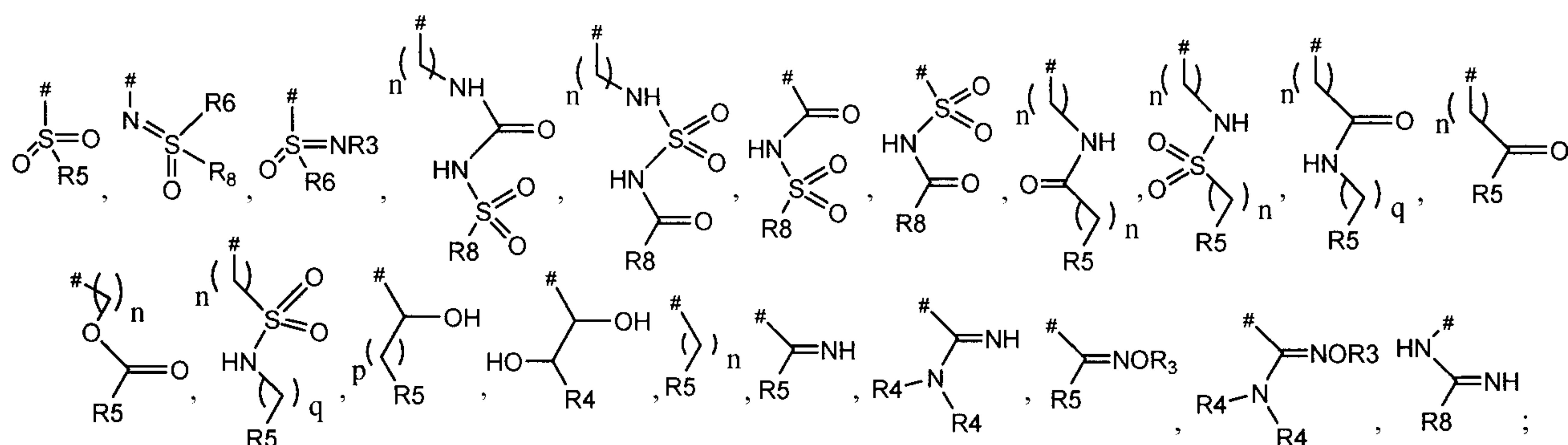
and wherein the E2 ring is Z5- and/or Z6-substituted pyridinyl, pyrimidinyl;

each Z2 is independently and individually selected from the group consisting of hydroxyl, hydroxyC1-C6alkyl, cyano, (R3)₂N-, (R4)₂N-, (R4)₂NC1-C6alkyl, (R4)₂NC2-C6alkylN(R4)-(CH₂)_n, (R4)₂NC2-C6alkylO-(CH₂)_n, (R3)₂N-C(=O)-, (R4)₂N-C(=O)-, (R4)₂N-CO-C1-C6alkyl, carboxyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R3)₂NSO₂, (R4)₂NSO₂, -SO₂R5-, -(CH₂)_nN(R4)C(O)R8, =O, =NOH, =N(OR6), heteroarylC1-C6alkyl, heterocyclylC1-C6alkyl, heteroaryloxyC1-C6alkyl, heterocyclyloxyC1-C6alkyl, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocyclylaminoC1-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z2 moiety to the A2 ring of formula I; in the event that Z2 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

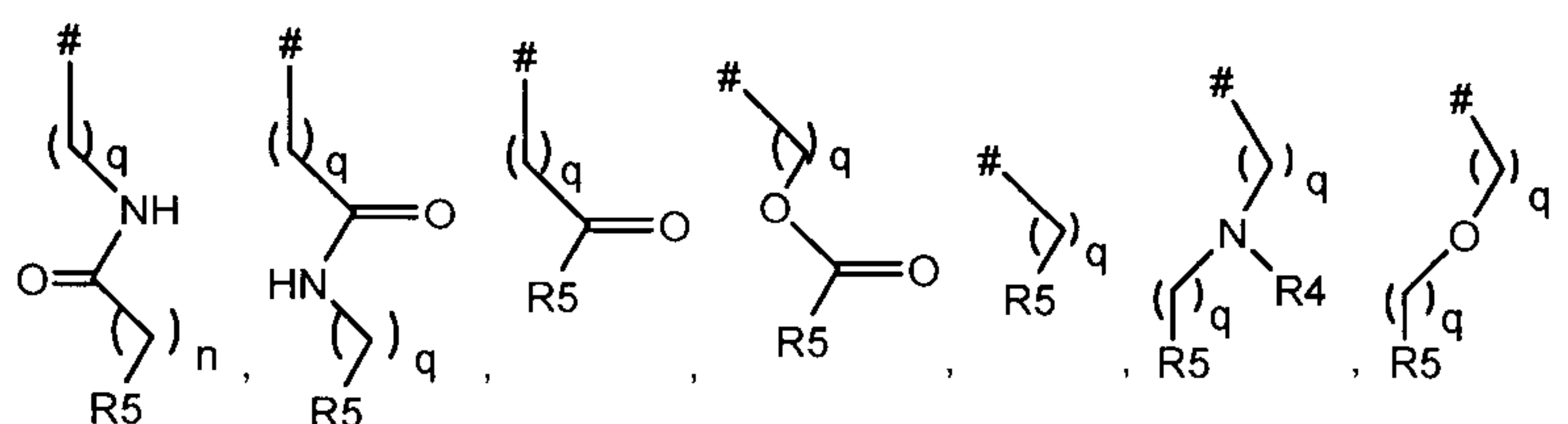
each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyl, hydroxyC1-C6alkyl, cyano, C1-C6alkoxy, C1-C6alkoxyC1-C6alkyl, halogen, CF₃, (R₃)₂N-, (R₄)₂N-, (R₄)₂NC1-C6alkyl, (R₄)₂NC2-C6alkylN(R₄)-(CH₂)_n, (R₄)₂NC2-C6alkylO-(CH₂)_n, -R₈C(=O)-, (R₄)₂N-CO-C1-C6alkyl, carboxyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R₃)₂NSO₂, -SO₂R₃, SOR₃, (R₄)₂NSO₂, -SO₂R₄, -SOR₄, -(CH₂)_nN(R₄)C(O)R₈, -C=(NOH)R₆, -C=(NOR₃)R₆, heteroaryl, heterocyclyl, heteroarylC1-C6alkyl, heterocyclylC1-C6alkyl, heteroaryloxy, heterocyclyloxy, heteroaryloxyC1-C6alkyl, heterocyclyloxyC1-C6alkyl, arylamino, heteroarylamino, heterocyclylamino, arylaminoC1-C6alkyl, heteroarylaminoC1-C6alkyl, heterocyclylaminoC1-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z3 moiety to the A2 ring of formula I;

in the event that Z3 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

each Z4 is a substituent attached to a ring nitrogen and is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl, C1-C6alkoxyC2-C6alkyl, (R4)₂N-C2-C6alkyl, (R4)₂N-C2-C6alkylN(R4)-C2-C6alkyl, (R4)₂N-C2-C6alkyl-O-C2-C6alkyl, (R4)₂N-CO-C2-C6alkyl, carboxyC2-C6alkyl, C1-C6alkoxycarbonylC2-C6alkyl, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, -SO₂R8, -COR8, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, heterocyclylaminoC2-C6alkyl, and moieties of the formulae



wherein the symbol (#) indicates the point of attachment of the Z4 moiety to the A2 ring for formula I;

in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

each Z5 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, halogen, fluoroalkyl, cyano, hydroxyl, alkoxy, oxo, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, -N(R3)₂, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-N(R4)₂, -R5, -O-(CH₂)_q-O-Alkyl, -O-(CH₂)_q-N(R4)₂, -N(R3)-(CH₂)_q-O-Alkyl, -N(R3)-(CH₂)_q-N(R4)₂, -O-(CH₂)_q-R5, and -N(R3)-(CH₂)_q-R5;

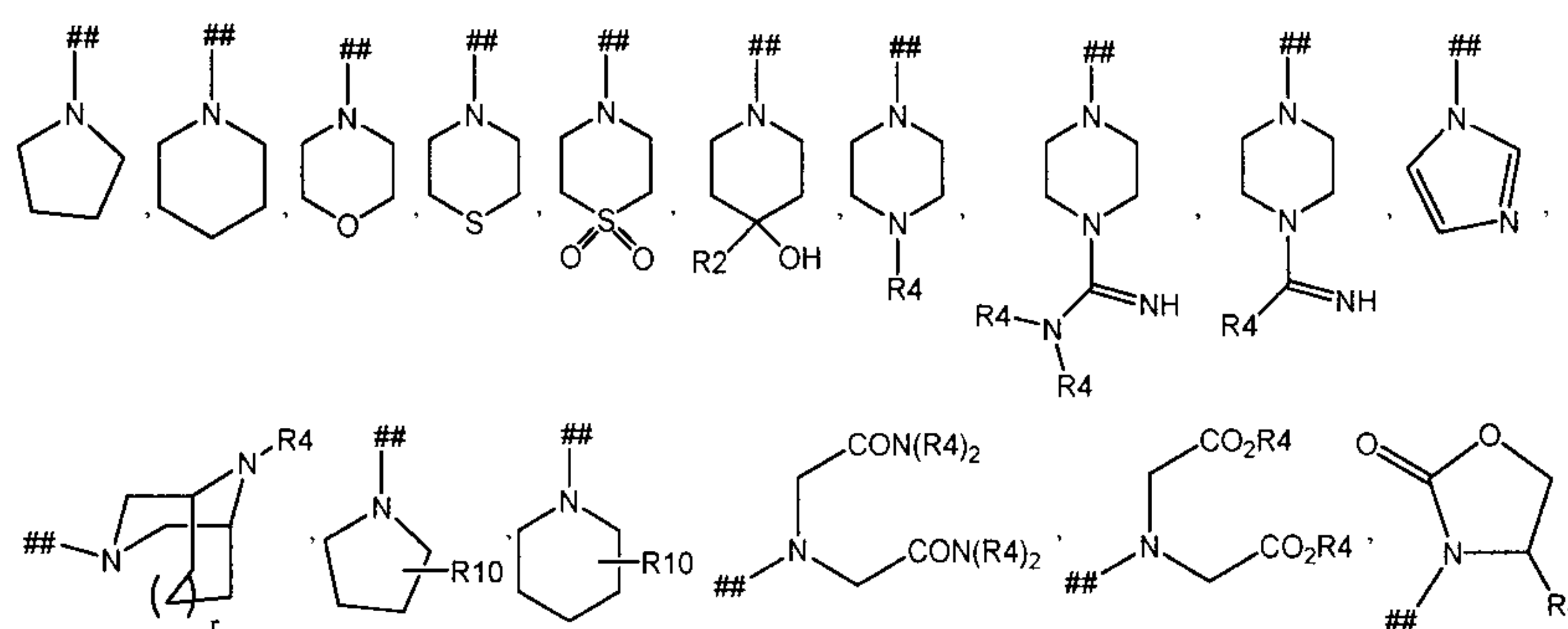
each Z6 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, hydroxyl, C1-C6alkoxy, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyloxy, arylamino, heteroarylamino, and heterocyclylamino, (R3)₂N-, -N(R3)COR8, (R4)₂N-, -R5, -N(R4)COR8, -N(R3)SO₂R6-, -CON(R3)₂, -CON(R4)₂, -COR5, and -SO₂NHR4;

each R2 is selected from the group consisting of monocyclic heteroaryl, C1-C6alkyl, branched C3-C7alkyl, R19 substituted C3-C8carbocyclyl wherein R19 is H or C1-C6alkyl, C1-C6fluoroalkyl wherein the alkyl group is partially or fully fluorinated, phenyl wherein the phenyl group is optionally substituted by one or more fluorine substituents and chlorine;

each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C7carbocyclyl, and phenyl;

each R4 is selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6alkyl, dihydroxyC1-C6alkyl, C1-C6alkoxyC1-C6alkyl, branched C3-C7alkyl, branched hydroxyC1-C6alkyl, branched C1-C6alkoxyC1-C6alkyl, branched dihydroxyC1-C6alkyl, carbocyclyl, hydroxyl substituted carbocyclyl, alkoxy substituted carbocyclyl, dihydroxy substituted carbocyclyl, phenyl, heteroaryl, heterocyclyl, phenylC1-C6alkyl, heteroarylC1-C6alkyl, and heterocyclylC1-C6alkyl;

each R5 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R8, R10, Z2, or Z3 moieties containing a R5 moiety;

each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, phenyl, heteroaryl, and heterocyclyl;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, fluoroalkyl wherein the alkyl moiety is partially or fully fluorinated, carbocyclyl, phenyl, phenylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, OH, C1-C6alkoxy, N(R3)₂, N(R4)₂, and R5;

each R10 is independently and individually selected from the group consisting of CO₂H, CO₂C1-C6alkyl, CO-N(R4)₂, OH, C1-C6alkoxy, and -N(R4)₂;

each R13 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, carbocyclyl, hydroxyC2-C7alkyl, C1-C6alkoxyC2-C7alkyl, (R4)₂N-CO,

(R₄)₂N-CO-C1-C6alkyl, carboxyC1-C6alkyl, C1-C6alkoxycarbonyl, C1-C6alkoxycarbonylC1-C6alkyl, (R₄)₂N-C2-C6alkyl, (R₄)₂N-C2-C6alkylN(R₄)-(CH₂)_q, R₅-C2-C6alkylN(R₄)-(CH₂)_q, (R₄)₂N-C2-C6alkylO-(CH₂)_q, R₅-C2-C6alkyl-O-(CH₂)_q, -(CH₂)_qN(R₄)C(O)R₈, aryl, arylC1-C6alkyl, heteroaryl, heteroarylC1-C6alkyl, heterocyclyl, heterocyclylC1-C6alkyl, aryloxyC2-C6alkyl, heteroaryloxyC2-C6alkyl, heterocyclyloxyC2-C6alkyl, arylaminoC2-C6alkyl, heteroarylaminoC2-C6alkyl, and heterocyclylaminoC2-C6alkyl;

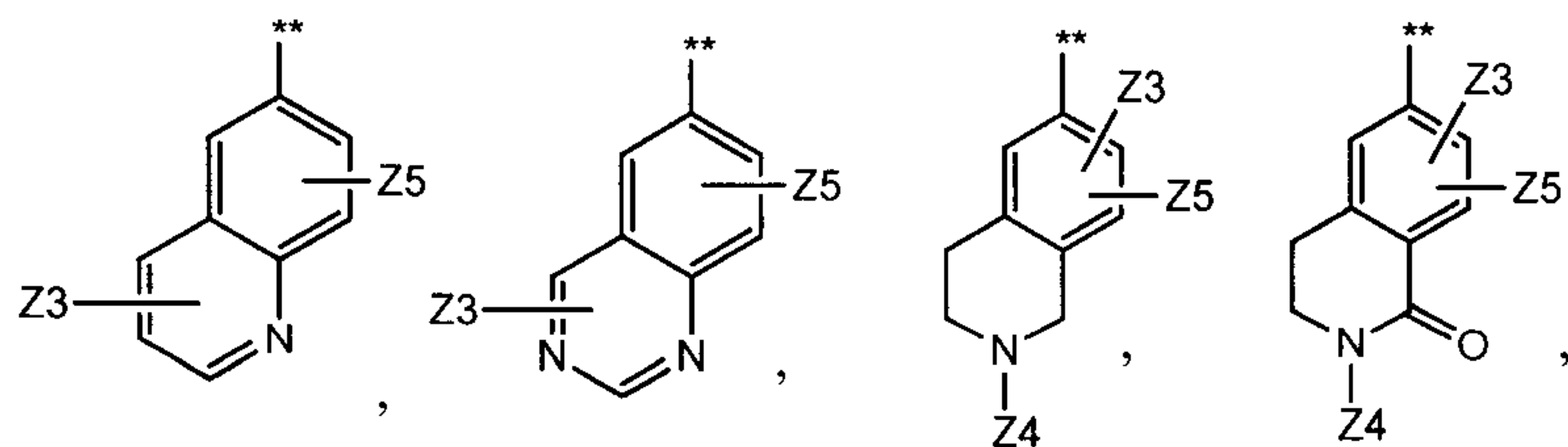
V, V1, and V2 are each independently O or represent two hydrogens connected to the methylene carbon to which the V, V1, or V2 is attached;

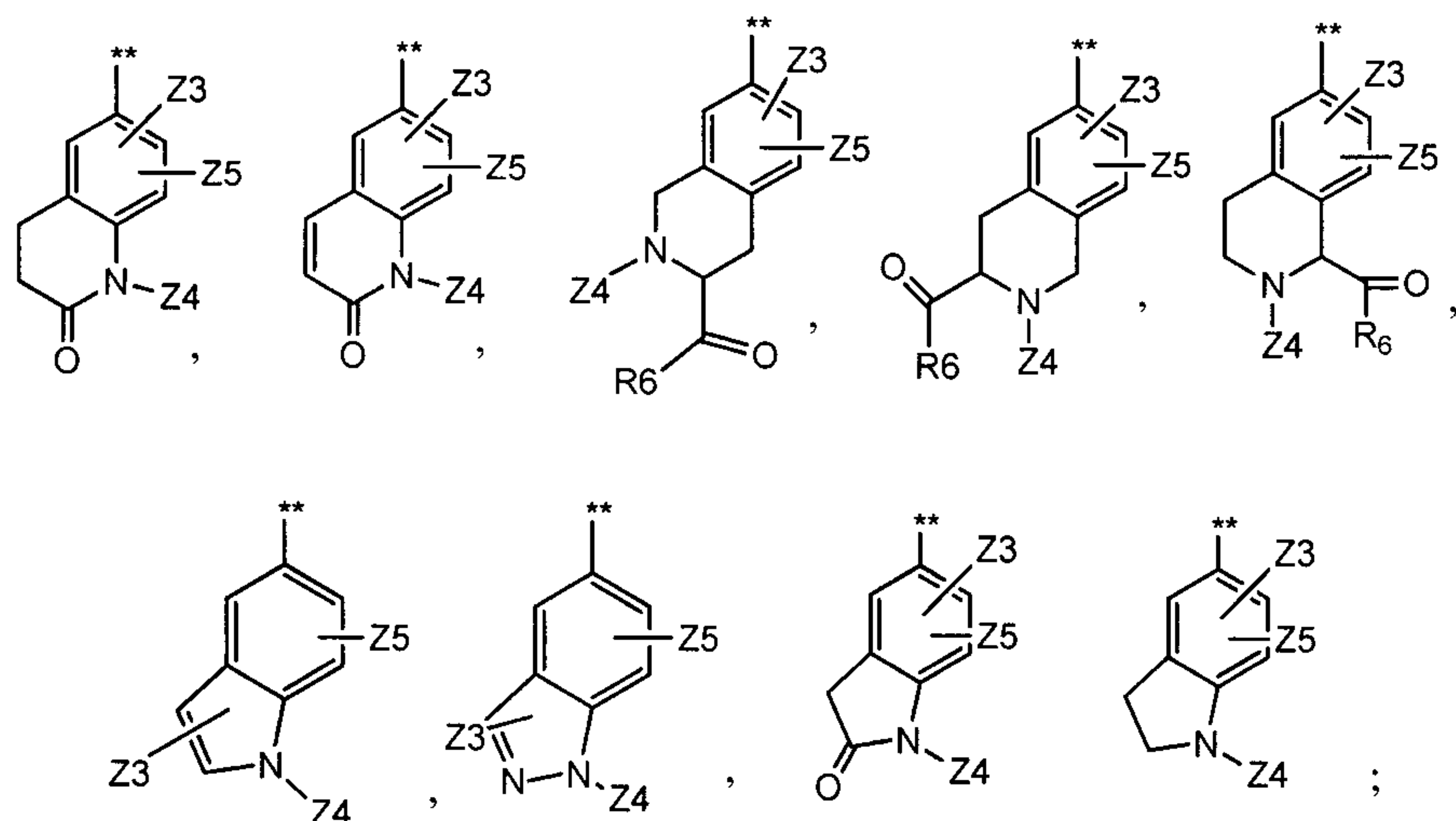
wherein two R₃ or R₄ moieties are independently and individually taken from the group consisting of C1-C6alkyl and branched C3-C6alkyl, hydroxyalkyl, and alkoxyalkyl and are attached to the same nitrogen atom, said moieties may cyclize to form a C3-C7 heterocyclyl ring;

n is 0-4; p is 1-4; q is 2-6; r is 1; and v is 1 or 2;

or a tautomer, diastereomer, enantiomer, or salt of any of the foregoing.

2. The compound of claim 1 wherein A₂ is selected from the group consisting of

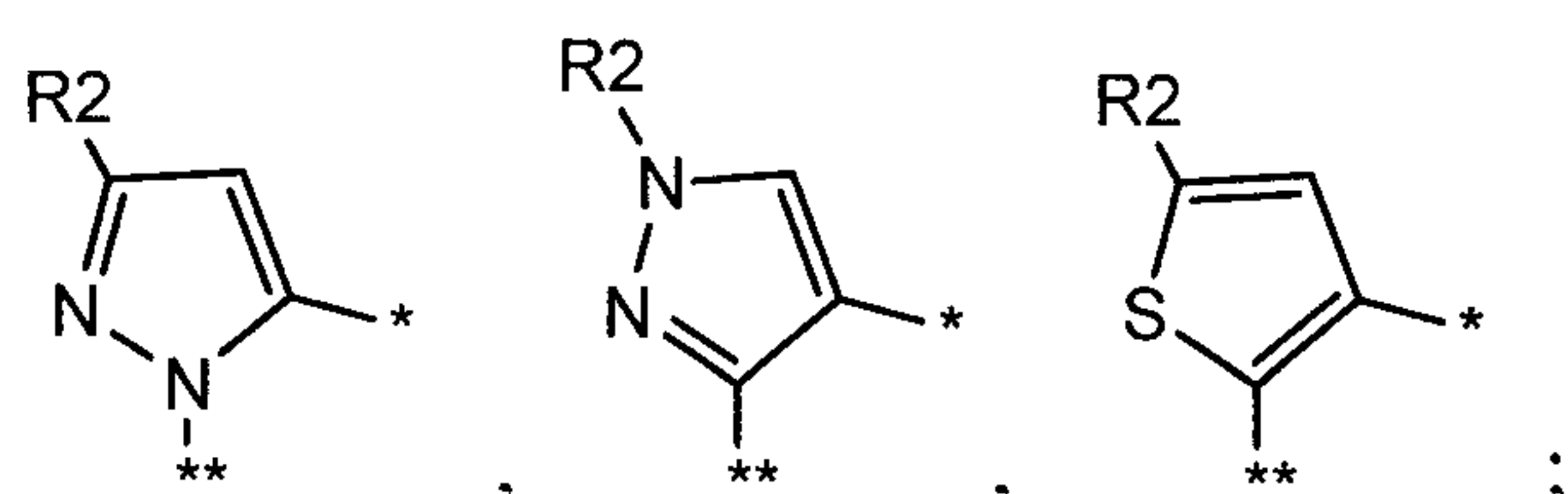




and wherein the symbol (**) is the point of attachment to the A1 ring of formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring.

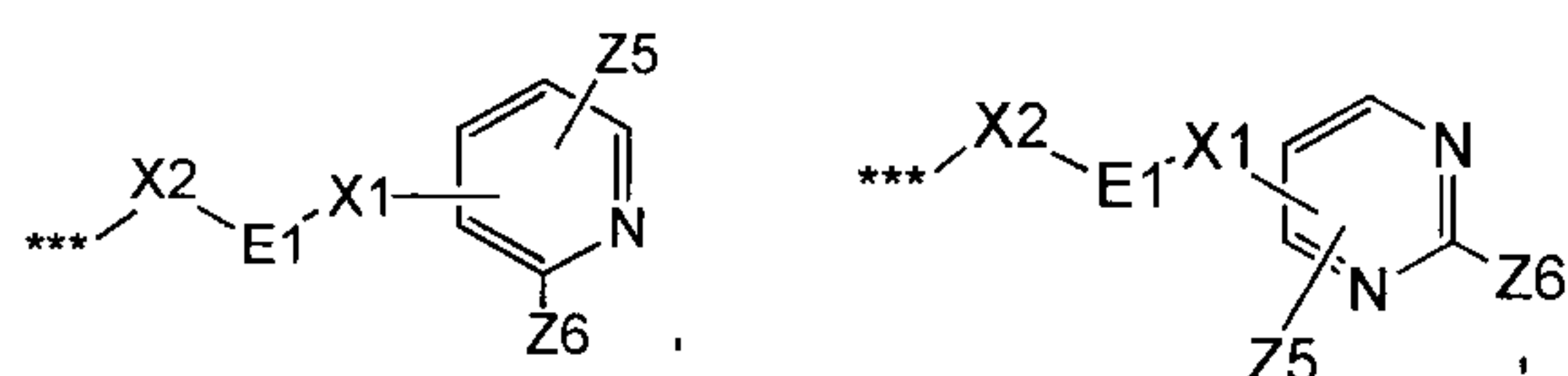
3. The compound of claim 2, wherein A1 is selected from the group consisting of



wherein the symbol (*) denotes the attachment to the NH moiety of formula I and the symbol (**) denotes the attachment to the A2 moiety of formula I.

4. The compound of claim 3 wherein

D is selected from the group consisting of

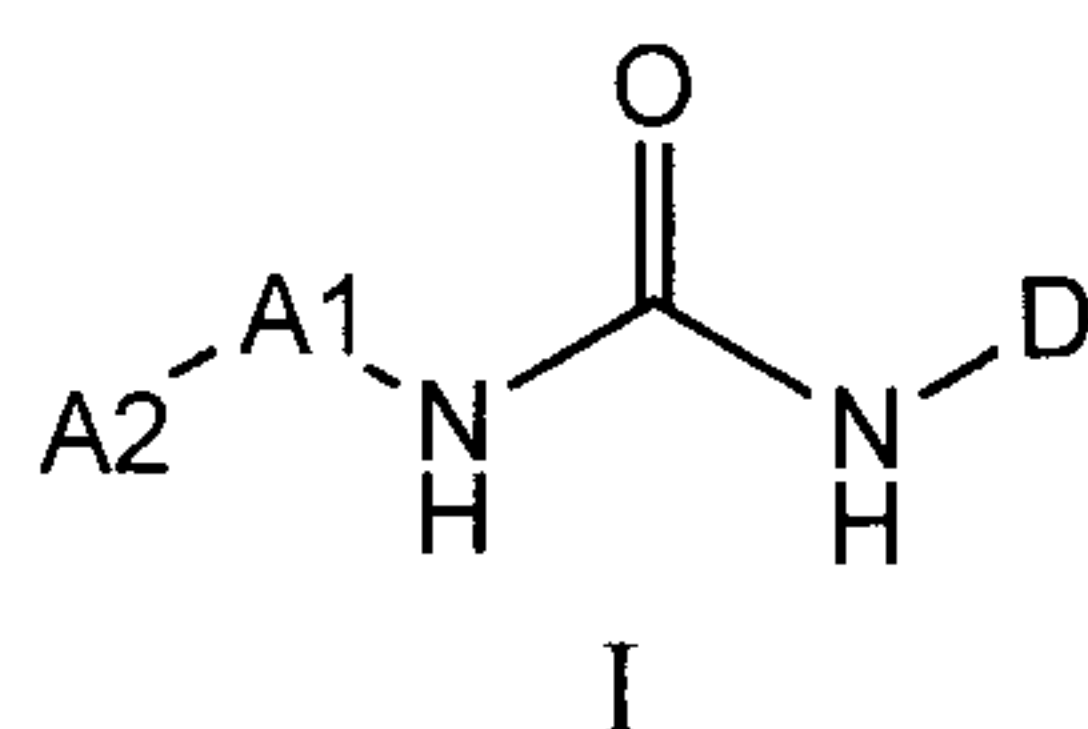


wherein E1 is phenyl;

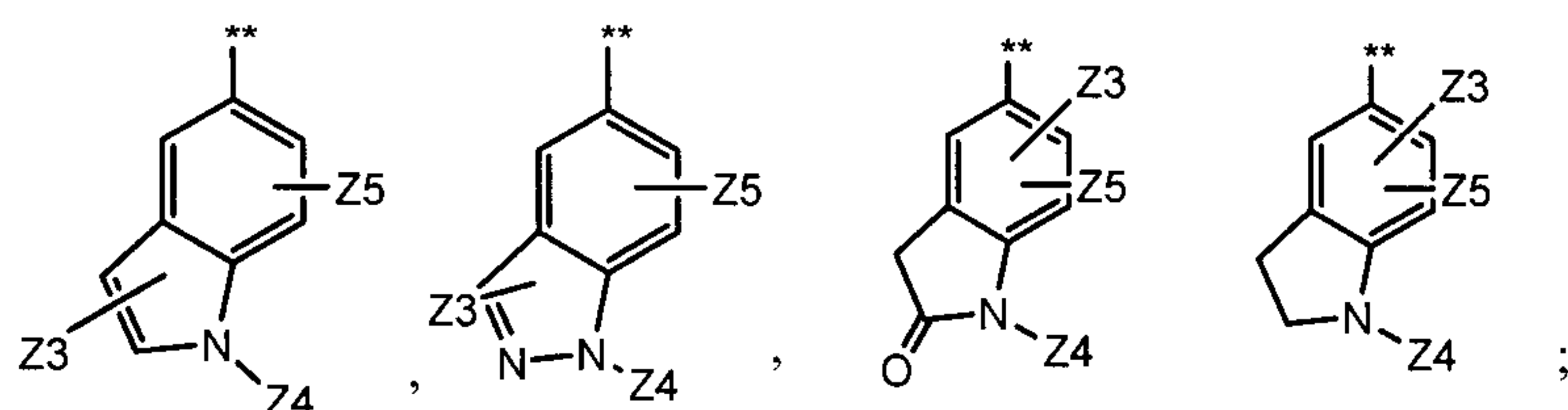
X1 is selected from the group consisting of O; and

X2 is a direct bond wherein E1 is directly linked to the NH moiety of formula I.

5. The compound of claim 4 having the formula I



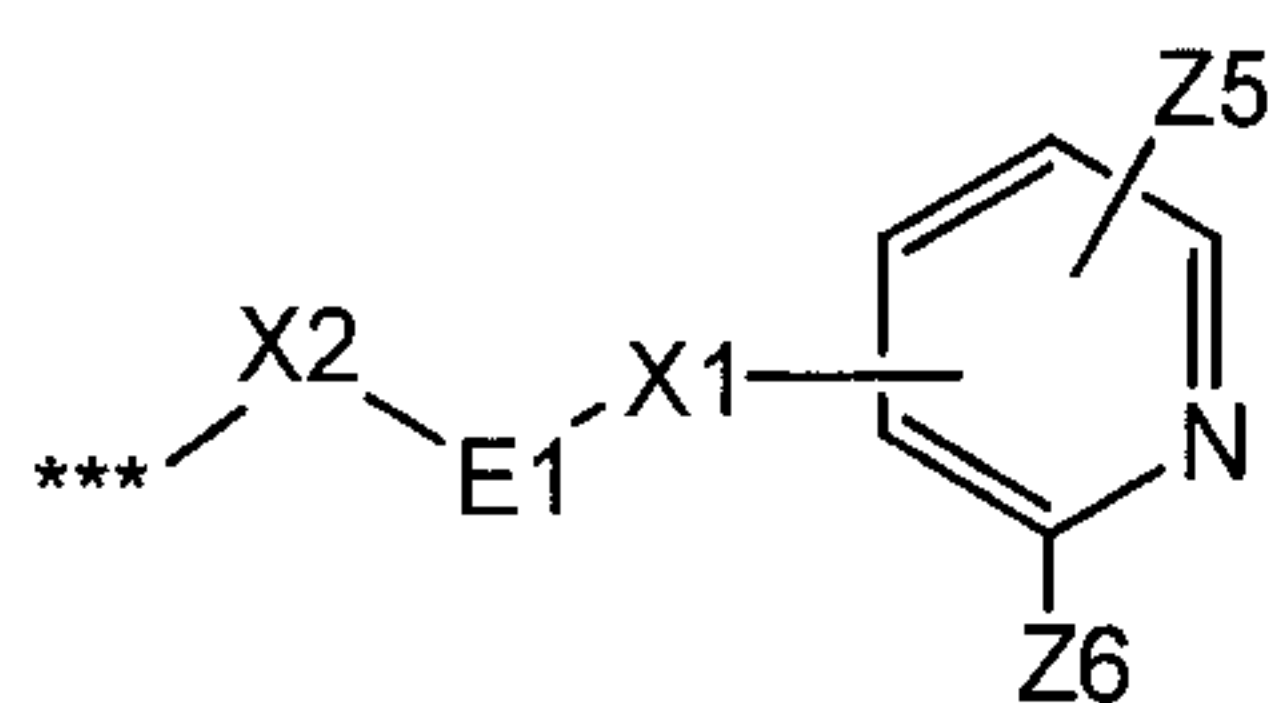
wherein A2 is selected from the group consisting of



wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring;

wherein D is



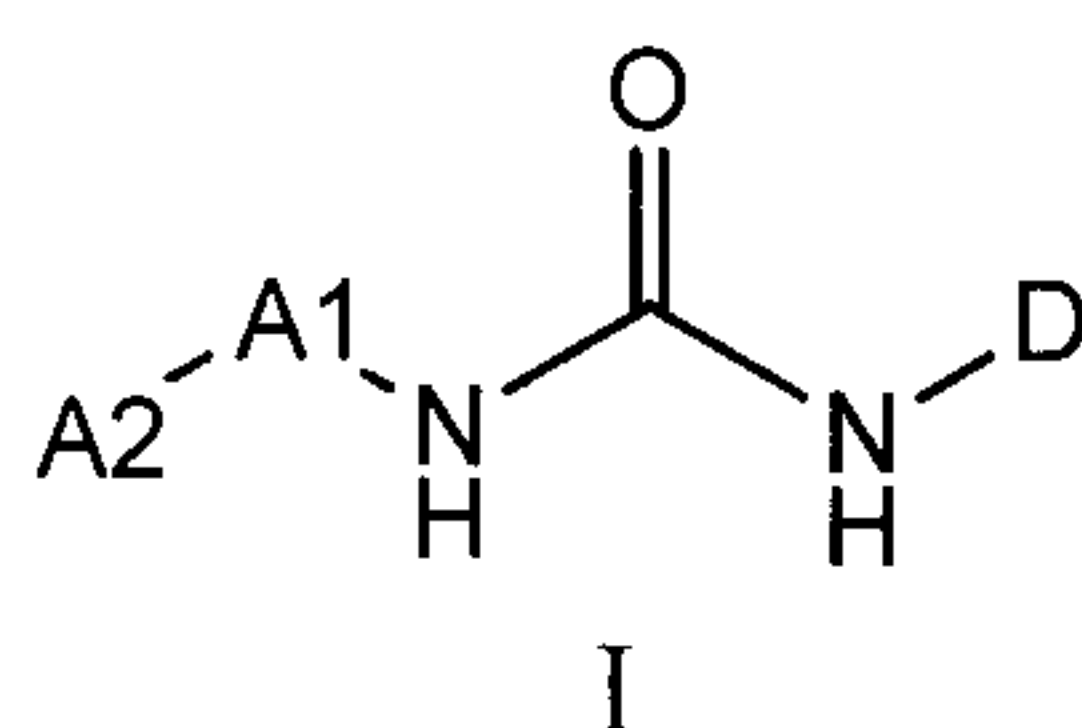
wherein the symbol (***) denotes the attachment to the NH moiety of formula I;

wherein E1 is phenyl;

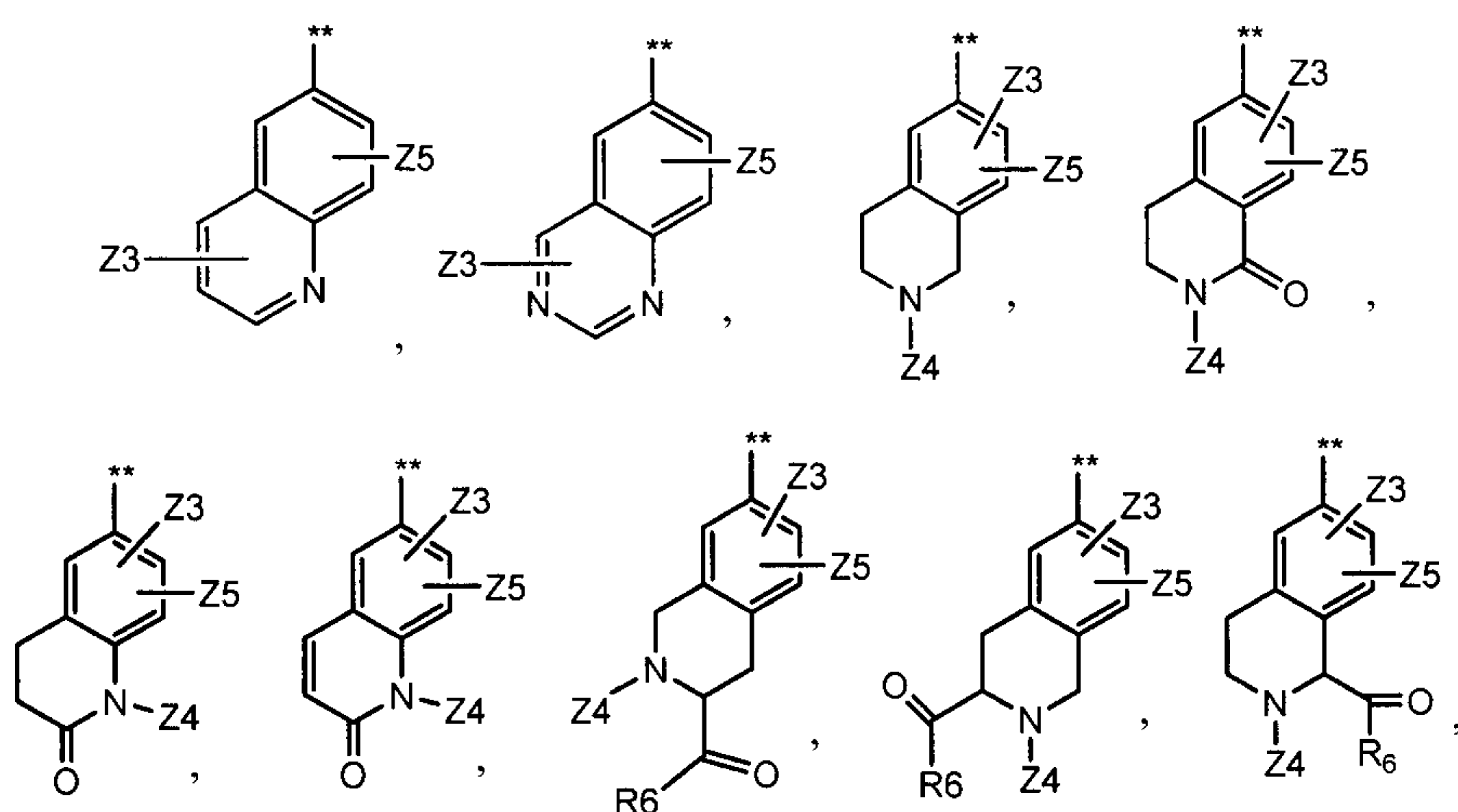
wherein X1 is selected from the group consisting of O; and

wherein X2 is a direct bond.

6. The compound of claim 4 having the formula I



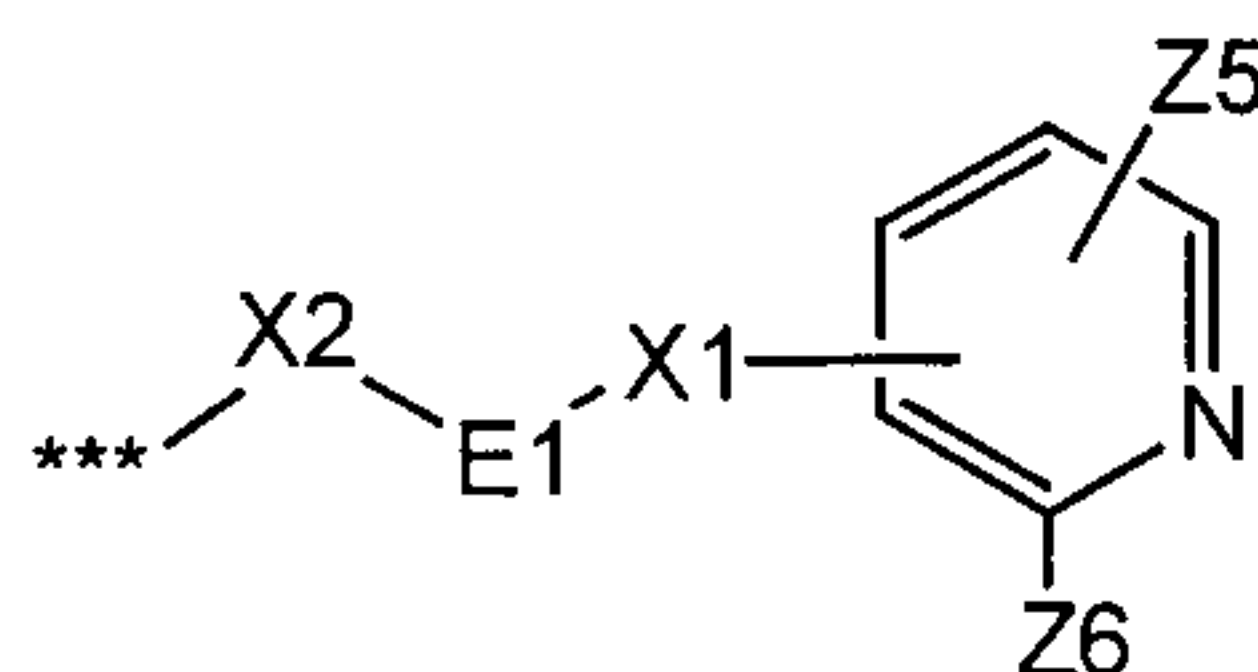
wherein A2 is selected from the group consisting of



wherein the symbol (**) denotes the attachment to the A1 moiety of formula I;

wherein each Z3 and Z5 is independently attached to either aryl or heteroaryl ring of the A2 bicyclic ring;

wherein D is



wherein the symbol (***) denotes the attachment to the NH moiety of formula I;

wherein E1 is phenyl;

wherein X1 is selected from the group consisting of O; and

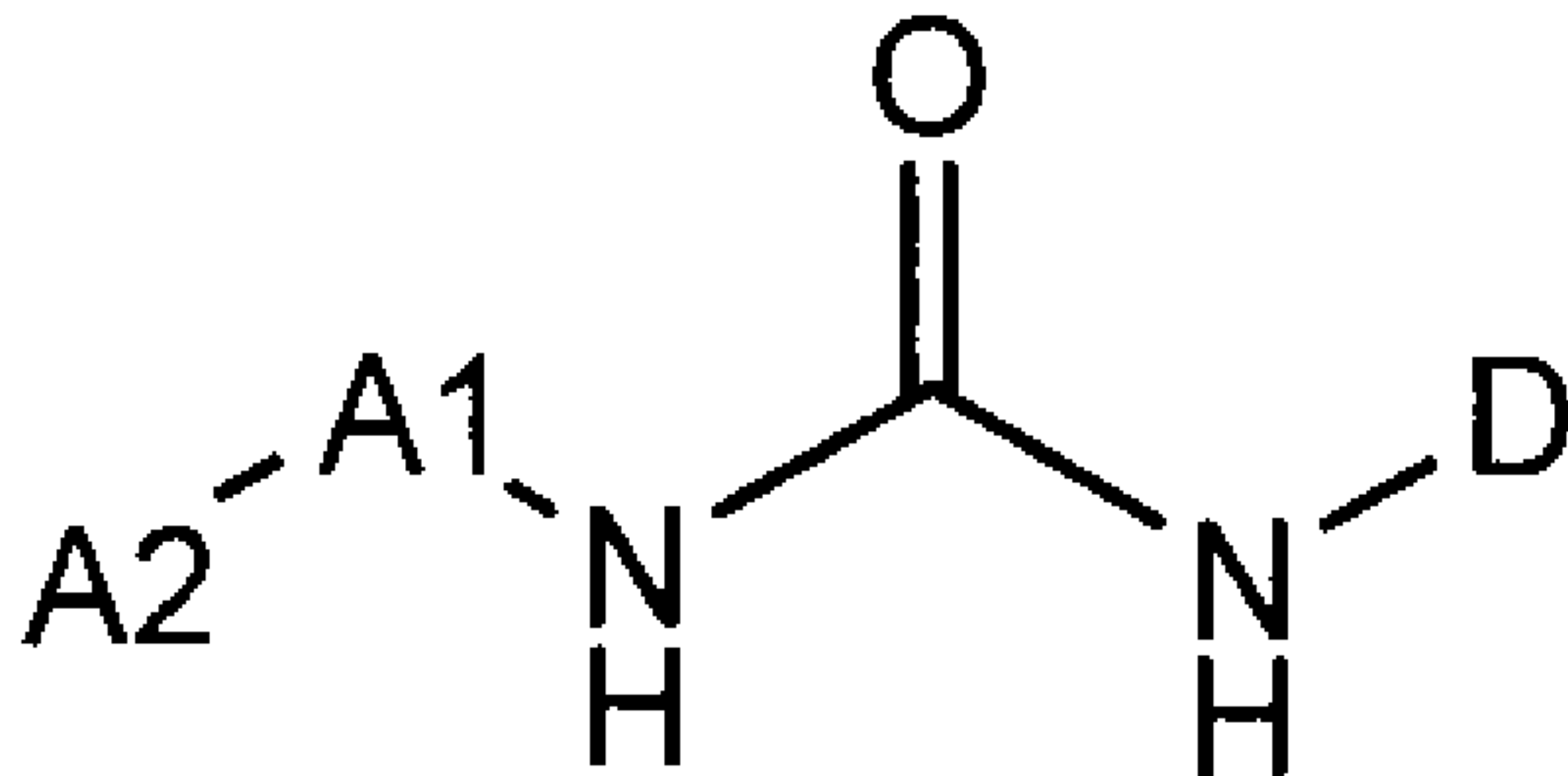
wherein X2 is a direct bond.

7. The compound of claim 1 selected from the group consisting of
 - 1-(3-tert-butyl-1-(quinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,
 - 1-(3-tert-butyl-1-(1H-indol-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,
 - 1-(3-tert-butyl-1-(indolin-5-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,
 - 1-(3-tert-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,
 - 1-(3-tert-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,
 - 1-(3-tert-butyl-1-(1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(5-chloropyridin-3-yloxy)phenyl)urea,
 - 1-(3-tert-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,
 - 1-(3-tert-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,
 - 1-(3-tert-butyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,
 - 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,
 - 1-(3-cyclopentyl-1-(2-oxo-1,2-dihydroquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,
 - 1-(3-tert-butyl-1-(2-(piperazin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,

1-(1-(2-(2-aminoethylamino)quinolin-6-yl)-3-tert-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,
 1-(3-tert-butyl-1-(2-((R)-3-(dimethylamino)pyrrolidin-1-yl)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,
 1-(3-tert-butyl-1-(2-(methylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,
 1-(3-tert-butyl-1-(2-(dimethylamino)quinolin-6-yl)-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,
 1-(1-(2-aminoquinolin-6-yl)-3-tert-butyl-1H-pyrazol-5-yl)-3-(4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)urea,
 1-(3-tert-butyl-1-(3-carbamoyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,
 1-(3-tert-butyl-1-(1-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,
 1-(1-(3-((2,3-dihydroxypropyl)carbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-3-tert-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea,
 6-(3-tert-butyl-5-(3-(3-(pyridin-3-yloxy)phenyl)ureido)-1H-pyrazol-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,
 1-(3-tert-butyl-1-(3-(methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea, and
 1-(1-(1-((2,3-dihydroxypropyl)carbamoyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-3-tert-butyl-1H-pyrazol-5-yl)-3-(3-(pyridin-3-yloxy)phenyl)urea.

8. A pharmaceutical composition comprising the compound of any one of claims 1 or 4 to 7, together with a pharmaceutically acceptable carrier.

9. The pharmaceutical composition of claim 8 wherein the pharmaceutically acceptable carrier is selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.



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